# Ultrasonography for diagnosis, monitoring and treatment of tenosynovitis in patients with rheumatoid arthritis

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**THE 4 ORIGINAL PAPERS ARE**

1. Mads Ammitzbøll-Danielsen, Iustina Janta, Søren Torp-Pedersen, Esperanza Naredo, Mikkel Østergaard, Lene Terslev
   3D Doppler Ultrasound findings in healthy wrist and finger tendon sheaths - Can feeding vessels lead to misinterpretation in Doppler-detected tenosynovitis?
   Arthritis Research and Therapy. 2016, 18 Mar
2. Mads Ammitzbøll-Danielsen, Daniel Glinatsi, Søren Torp-Pedersen, Jakob M Møller, Esperanza Naredo, Mikkel Østergaard, Lene Terslev
   Tenosynovitis evaluation using Image Fusion and B-flow - A pilot study on new imaging techniques in rheumatoid arthritis patients
   Ultraschall in Med. 2017, 16 May
3. Mads Ammitzbøll-Danielsen, Mikkel Østergaard, Esperanza Naredo, Lene Terslev
   Validity and sensitivity to change of the semi-quantitative OMERACT ultrasound scoring system for tenosynovitis in patients with rheumatoid arthritis
   Rheumatology (Oxford) 2016. 10 Sep
4. Mads Ammitzbøll-Danielsen, Mikkel Østergaard, Viktoria Fana, Daniel Glinatsi, Uffe Møller Døhn, Lykke Midtbøll Ørnbjerg, Esperanza Naredo, Lene Terslev
   Intramuscular versus ultrasound guided intratenosynovial glucocorticoid injection for tenosynovitis in patients with rheumatoid arthritis - A randomised, double-blind, controlled study
   Annals of Rheumatic the Diseases 2016. 7 Sep

## INTRODUCTION

Swollen and tender joints were for the first time described by Guillaume de Baillou in 1611 as arthritis. The term rheumatoid arthritis (RA) was introduced in 1858 by Sir Alfred Baring Garrod. This term was later adopted by the British Ministry of Health in 1922 and by the American Rheumatism Association in 1941, replacing the term atrophic arthritis.
RA is a chronic systemic autoimmune disease with ongoing inflammation that potentially will lead to permanent and serious disability due to joint destruction, but also tendon and ligament ruptures. However, better therapeutic options and improved treatment strategies have reduced these serious disabilities. Despite of better treatment, RA still has huge social economic cost due to lost working capacity. The key to further improvement is not only new therapeutics but also to use them correctly.
Clinical management of RA has traditionally been supported by biochemical and radiographic findings. However, imaging modalities like ultrasound (US) and magnetic resonance imaging (MRI) have improved the possibility for better management of RA patients, due to higher sensitivity and specificity for detecting ongoing inflammation.
The focus in the present thesis has been optimisation of US as a tool for diagnosis, monitoring and treatment of tenosynovitis, in order to improve management of RA patients, and thereby increase quality of life, functional ability and working capacity.

## AIMS

The overall aim of this study was to further develop and validate US as a tool for diagnosis, monitoring and treatment of tenosynovitis. This aim was investigated in four studies:
I) an observational, cross-sectional study of 40 healthy controls (3D)
II) an observational, cross-sectional study of 15 RA patients (Image fusion)
III) an observational, longitudinal study of 53 RA patients (USB cohort)
IV) an interventional, longitudinal randomised double-blind placebo controlled trial of 50 patients (Sultan cohort)

This overall aim involved the following specific aims

### Specific aims

1. To investigate the presence of feeding vessels in or in close proximity to extensor and flexor tendon sheaths at the wrists level and in finger flexor tendon sheaths in healthy controls, using 3D ultrasound (Study I).
2. To investigate the discrepancy of US and MRI visualization of tenosynovitis in RA patients and how the newly proposed OMERACT scoring systems of tenosynovitis by US and MRI correspond with each other using image fusion technique (Study II).
3. To investigate whether US BFI is a valid alternative to Doppler US when assessing tenosynovitis. (Study II).
4. To validate the semi-quantitative US OMERACT tenosynovitis scoring system by assessing intra-and interreader reliability and sensitivity to change in a follow-up study of RA patients with tenosynovitis, who were scheduled for treatment optimization (Study III).
5. To evaluate and validate a novel US scoring system by assessing intra-and interreader reliability and sensitivity to change in a follow-

up study of RA patients with tenosynovitis, who were scheduled for treatment (Study III).

6. To compare the metric properties of semi-quantitative and quantitative US assessment methods (Study III).
7. To investigate whether US-tenosynovitis assessment is more sensitive to change than DAS28, CRP, Patient Global VAS, Health Assessment Questionnaire (HAQ), clinical tenosynovitis assessment and a patient reported tendon sheath pain score (VAS-patient tenosynovitis score) in a follow-up study of RA patients with tenosynovitis, who were scheduled for treatment optimization (Study III).
8. To investigate differences in achievement of US tenosynovitis remission, defined as US tenosynovitis GS score ≤ 1 and Doppler score = 0 between US-guided glucocorticoid injection in the tendon sheath and *intramuscular (*im) glucocorticoid injection among RA patients with tenosynovitis (Study IV).
9. To investigate whether change in clinical assessment, patient reported outcome and US parameters are different between US-guided glucocorticoid injection in the tendon sheath and im. glucocorticoid injection among RA patients with tenosynovitis (study IV).

## BACKGROUND

### Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common chronic autoimmune inflammatory synovial disease, with a large influence on the patient's daily living[1], characterised by pain, fatigue and functional impairment. Genetic and environmental factors have been linked to RA, but the ethology is largely unknown[2]. The prevalence is approximately 1 % of the population[3] and the disease has an incident peak between 45 and 75 years and a female/male ratio of 2-4/1[4-7]

### Disease manifestations

The hallmark of RA is symmetric joint inflammation in hands and feet, leading to decreased physical function and joint destruction (erosions)[8]. Since this thesis is focusing on tenosynovitis it is important to know that recent studies have confirmed that inflammation in tendon sheaths, i.e. tenosynovitis, is a very common manifestation of RA[9-14] and may often be mistaken for synovitis and therefore is an underestimated aspect of the disease. As in other autoimmune diseases fatigue is a common systemic symptom and may have a restricted effect on the cognitive and/or physical functioning[15]. Further, an increased risk of several comorbidities as cancer, cardiovascular events, depression and osteoporosis are well-known[8]. These comorbidities are the main explanation for a decreased survival time among RA patients, compared to the average population.

### Clinical assessment

Tender and swollen joint counts, C-reactive protein (CRP) or erythrocyte sedimentation and patient reported outcomes are recommended for monitoring of RA in daily clinical practice. In Denmark the use of the composite Disease Activity Score for 28 joints (DAS28) is widely used [16 17]. This score consists of a combination of tender and swollen joint counts, patient global assessment of disease activity on a visual analogue scale (VAS global) and CRP and is graded as follows; DAS28 value >5.1 indicates high disease activity, ≤ 5.1 and 3.2> moderate disease activity, between ≤3.2 to 2.6> low disease activity, and ≤2.6 remission[18]. Other composite scores as simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) are likewise commonly used in daily clinical care[19]. However, none of these composite cores includes assessment of tenosynovitis, despite it is known to be a common aspect of RA[9-14].

### Predictors for early RA and disease course

Since the introduction of 2010 American College of Rheumatology/ European League Against Rheumatism rheumatoid arthritis classification criteria [20], there has been an increased focus on early diagnosis of RA, but also on early disease course predictors. Due to the aim of this thesis, only the imaging perspective of early disease prediction and erosive development are presented below.

A recent study has shown that ultrasound (US) detected wrist synovitis in combination with anti-cyclic citrullinated peptide (anti-CCP) positivity in patients without clinical synovitis predict progression to RA[21]. On the other hand, Freeston, et al has reported that only seronegative patients with early inflammatory arthritis had added value of routine US assessment for prediction of RA development[22]. Several studies have however found that tenosynovitis is a strong and better predictor for early RA than synovitis [9 23 24], but no study has investigated the combination of anti-CCP positive patients and tenosynovitis as predictors for early RA. Another recent study has reported that tenosynovitis among healthy volunteers is very rare in comparison with synovitis, bone marrow edema and erosion, which indicates a possible importance of tenosynovitis for predicting early RA[25].

Bone marrow edema on magnetic resonance imaging (MRI) has in several studies shown to be the strongest single predictor for erosive progression in early RA [26-29]. A recent study has reported predictive value also of extensor carpi ulnaris tenosynovitis [30].

### The role of tenosynovitis in RA

Tenosynovitis is a common aspect of RA, and a new study has reported that US detected tenosynovitis may be the best imaging predictor for flares[31]. However, very little interest has been given with respect to monitoring and treatment. No large RA treatment strategy studies are dealing with tenosynovitis, which is likely explained by poor capabilities to clinically distinguish between synovitis and tenosynovitis, but also the fact that tendon rupture is less common than joint destruction and therefore considered as less important aspect of RA. However, even though the modern treatment strategy has reduced disease activity and degree of joint destruction, pain and function loss is still common among RA patients. Therefore, a wider disease focus is required in order to further optimise RA treatment, including tenosynovitis.

Treatment

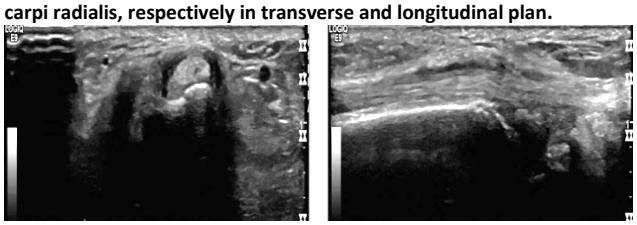
The therapeutic treatment possibilities and strategy have changed fundamentally over the last 20 years. New treatment possibilities such as the introduction of biological disease-modifying anti-rheumatic drug (bDMARD), but also a better understanding of the use of conventional synthetic (csDMARDs) and glucocorticoid steroids, in combination with a more aggressive treatment, have changed RA patient outcome dramatically[32-35]. There is however, still need for improvement and many new therapeutic treatment possibilities are upcoming, as Janus kinases inhibitors[36] or Toll-like receptors inhibititors[37].

Regarding treatment of tenosynovitis, the response to DMARDs treatment is reported in one study to be similar to synovitis[38]. It is common that patients have flares in joints or tendon sheaths, despite stable and effective DMARD treatment, however, only few studies have investigated treatment of tenosynovitis flares in RA [39 40].

### Basic ultrasound physics

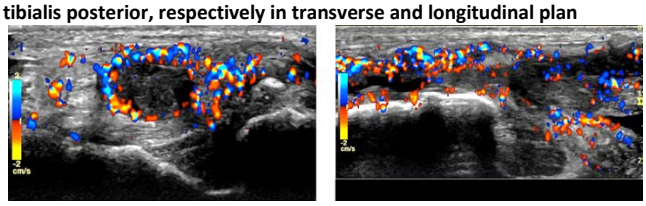
The US images are formed when the emitted ultrasound waves are reflected by the tissue when a difference in impedance occurs. The degree of reflection is depending on the strength of the returning echoes and the echogenicity of the tissue. Each layer of tissue reflects and absorbs the US pulse to some extent when passing through. This reduces the strength of the reflected US pulse when a deeper layer of tissue is reached. Fluid and cartilage are a very weak reflectors (appears black) in contrast to bony structures which are good reflectors and appear white in the US image. This type of US modality is named grey scale (GS) and provides the assessor with detailed information about the anatomy and morphology.

**Figure 1. Illustration of a grey scale detected tenosynovitis in extensor carpi radialis, respectively in transverse and longitudinal plan.**



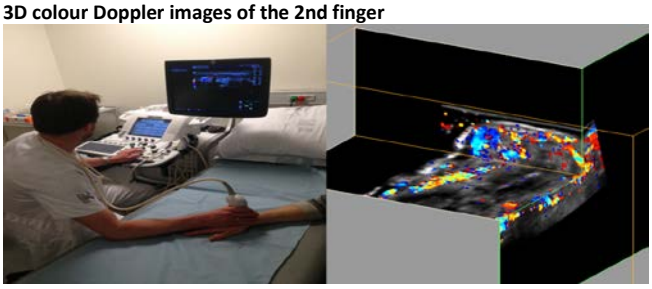
If additional information about the flow in the investigated structures is required, Doppler US is needed. Doppler US is based on the changes in the transmitted waves' reflection by erythrocytes in motions. The difference of the emitted waves and the received waves is translated into colour information, which is applied to the grey scale image showing the flow in the region of interest.
The inflammatory flow differentiates from physiological flow by a lower mean energy/velocity of the moving erythrocytes. In order to depict this slow flow, Doppler settings with the lowest possible wall filter and pulse repetition frequency (PRF) without causing noise are needed. Also the Doppler frequency and gain setting will have an impact on the ability to detect slow flow.
Two different Doppler modalities can be used for slow flow measurement: power Doppler, which displays the energy of all moving erythrocytes, and colour Doppler (CD), which displays the mean velocity of all moving erythrocytes. The most sensitive Doppler modality varies from machine to machine, and is highly dependent on adjustments of the machine factory Doppler settings[41].

**Figure 2. Illustration of a Colour Doppler detected tenosynovitis in tibialis posterior, respectively in transverse and longitudinal plan**



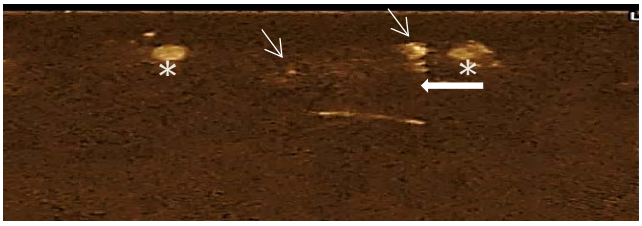
3D Doppler is a relatively new US technique where a volume is created from a motorized sweep by the transducer inside the transducer housing. When the colour Doppler is active during the sweep, the vessels will be outlined with colour inside the volume. After the volume has been created it is possible to step through the volume in 2D.

**Figure 3. Illustration of a 3D ultrasound examination with corresponding 3D colour Doppler images of the 2nd finger**



US B-flow imaging (BFI) is a new technique for vascular imaging, based on US grey scale (GS) physics[42-44]. In the B-flow images the blood cells (weak flow reflectors) are highlighted and signals from the surrounding stationary tissue are suppressed. The advantages of B-flow are that Doppler artefacts such as blooming, reverberations and aliasing are not seen, and theoretically also that it offers higher spatial resolution for vascular anatomy. Whether BFI is an alternative to Doppler for depicting tenosynovitis in RA is unknown

**Figure 4. Illustration of B-flow tenosynovitis at the flexor tendons ([T]) of the 4th finger.**



*The pathological flow/enhancement is marked with thin arrows and an intratenosynovial effusion is marked with a thick arrow. Interdigital arteries are marked with an (*) asterisk.*

**Doppler artifacts**

Knowledge of the most common Doppler US artefacts is essential when it is used for diagnosis and monitoring of RA patients as they may be a cause for misinterpretation of flow information. The most common artefacts are listed below:

**Random noise**

Random noise is seen as colour dots appearing random in the US images, when the gain setting is too high. This artefact can be avoided by adjusting the gain correctly[45].

**Motion**

Motion artefact is when Doppler shifts are generated by movement between transducer and tissue. This artefact is often presented as randomly occurring short flashes of colour and is easily separated from normal blood flow, since it is not pulsating and infrequently reoccur in the same position.
Motion artefacts can be decreased by keeping the probe steady, having the patient sitting still but also by adjusting the wall filter correctly though this may have an impact on Doppler sensitivity [45].

**Blooming**

Blooming artefact is when the colour reaches beyond the vessel wall making it appear larger than it really is, and is related to the Doppler gain setting. Even if gain setting is adjusted according to published recommendations[45], blooming is an unavoidable consequence in order to have a high sensitivity for slow flow.

**Reverberation**

Reverberation artefact is when Doppler signals from a vessel are repeated lower in the images. This repeated signal may be presented deeper inside synovium and lead to misinterpretation of the pathological flow. This artefact cannot be avoided, but if the Doppler box is placed in the top of the image all vessels localised above and outside of the region of interest will be displayed. This gives all essential information to evaluate a possible reverberation artefact.

**Mirror**

Mirror artefact is a well-known GS artefact, where a highly reflecting surface, such as the bone, act as an acoustic mirror. Mirror artefact is however, also seen for Doppler and is simply recognized when the vessel is mirrored around a reflecting surface such as below an intact bone surface.

**Aliasing**

Aliasing artefact is when the Doppler shift of the moving blood is higher than half of the pulse repetition frequency (PRF) and therefor showing false velocity of the displayed flow. Aliasing is only seen for CD and arises when adjusting the PRF for slow flow, and is therefore unavoidable. The incorrect flow velocity has no relevance for the detection of slow flow in arthritis.

**Use of ultrasound in RA**

Musculoskeletal US has undergone a major technological development over the last decades and is now offering a high resolution image of the morphology in the synovium, bones, ligaments, tendons and additional information about increased perfusion in the synovium, reflecting inflammation. These qualities are demonstrated in several studies[46-50] and furthermore, US is shown to be more sensitive for detection of inflammatory change than conventional radiography (x-ray) and clinical evaluation[46-50]. US detected inflammatory change has been evaluated by different scoring systems using either binary, semi-quantitative or quantitative US scoring systems[51-59]. The Outcome Measures in Rheumatology Clinical Trials (OMERACT) US group has therefore in 2009 reviewed[60] all used US scoring systems for synovitis and concluded that no consensus exists for one scoring system, though for Doppler the published semi-quantitative scoring system by Szkudlarek, et al[61] is the most commonly used. The OMERACT US task force is presently validating a new semi-quantitative

scoring system for synovial hypertrophy and Doppler alone and in combination as presented in the APPRAISE study from 2015[62]. Quantitative Doppler assessment of synovitis was proposed in 2003 by Qvistgaard et al[59], since it potentially will be more objective and without ceiling effect (has the possibility to detect change within the same semi-quantitative Doppler score). Terslev et al has reported a better reliability of this method than the semi-quantitative synovitis score in a cross sectional study design [63].

For tenosynovitis assessment the OMERACT US group has in 2012 defined tenosynovitis as presence of at least one of the following [64].
•An abnormal hypoechoic synovial sheath widening, caused by an abnormal effusion and/or tenosynovial hypertrophy.
•An abnormal hypoechoic area in the synovial sheath, either located by or totally surrounding the tendon, which is displaceable and can been seen in two planes.
• Synovial hypertrophy in the synovial sheath defined as the presence of abnormal hypoechoic tissue, which is not displaceable and is poorly compressible, seen in two planes.
• Intratenosynovial Doppler signal in two planes, excluding signals from feeding vessels. It is required that the synovial sheath is widened in grey scale.
In the same paper a new scoring system was validated based on a 4-grade semi quantitative scoring system.
•B-mode: grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe.
•Intratenosynovial Doppler: grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe.
A high intra- and moderate interobserver reproducibility in both grey-scale and Doppler on flexor and extensor tendons in the hand was found.

No quantitative Doppler assessment of tenosynovitis has to our knowledge been reported.

**Magnetic resonance imaging for tenosynovitis.**
MRI is excellent imaging modality for visualization of tenosynovitis, but also other structures as synovitis, erosion and bone marrow edema[65 66]. Tenosynovitis assessment is based on intratenosynovial effusion and/or post-contrast tenosynovial enhancement. The OMERACT MRI in arthritis working group has proposed a four-grade semi-quantitative scoring system based on tenosynovial enhancement on axial T1-weighted pre- and post-contrast MR images (i.e. grade 0, no intratenosynovial effusion or post-contrast tenosynovial enhancement ; grade 1, >0 but <1.5 mm; grade 2, ≥1.5 but <3 mm; grade 3, ≥3 mm intratenosynovial effusion or post-contrast tenosynovial enhancement )[67].

**Definitions of Validity:**
It is crucial to test validity for outcome measures. Validity criteria have in the past been described by Tugwell and Bombardierl[68] and Felson et al[69] and more recently in relation to US by Østergaard and Wiell [70]. The validity definitions used in this thesis are listed below.

**Face validity**
This is the credibility of an outcome measure, i.e. whether the assessment method measures what it is supposed to measure.

**Content validity**
This is the comprehensiveness of the outcome measure, i.e. does it cover all important aspects of the disease activity.

**Criterion validity**
This is the accuracy of the outcome measure. Criterion validity is often subdivided into two. Concurrent validity: does the measure reflect the same degree of inflammation, applied at the same time, as the gold standard**.** Predictive validity: does the measure have predictive value for future gold standard outcome, such as erosive radiographic progression or functional loss.

**Construct validity**
This is the consistency of the outcome measure with other substituted measures, e.g. how US measured synovitis reflects clinical assessed synovitis.

**Discriminant validity**
This is the degree of change that the outcome measure can detect. Both after initiation of new treatment (sensitivity to change), but also the reproducibility of the measure, i.e. the reliability of the measurement when change are detected.

## PATIENTS AND METHODS
The present PhD study thesis is based on four, studies, which are described below, and in further detail in appendices I-IV, respectively.

*Study I*
*3D Doppler Ultrasound findings in healthy wrist and finger tendon sheaths - Can feeding vessels lead to misinterpretation in Doppler-detected tenosynovitis?*
Healthy participants without prior history of arthritis or tendon diseases and without pain in their fingers or wrists were included from June 2014 to December 2014. Twenty participants had 3D Doppler US examination of the 2nd and 3rd finger and 20 participants of the wrist on the right hand.

*Study II*
*Ultrasound and magnetic resonance imaging fusion of images and B-flow evaluation of tenosynovitis - A pilot study on new imaging techniques in rheumatoid arthritis patients*
RA patients >18 years were eligible for inclusion if they had US-verified tenosynovitis in the wrist/hand. All patients were recruited from the rheumatology outpatient clinic at Rigshospitalet, Denmark, from July 2015 to May 2016 by one physician, with experience in musculoskeletal US. If tenosynovitis was confirmed by US, an MRI scan was performed, with subsequent image fusion and US BFI (maximal three days after MRI).
Patients were excluded if they had initiated or changed dosage of csDMARDs and/or bDMARDs between the MRI scan and the image fusion or if they had glucocorticoid treatment within the last four weeks prior to the MRI scan and image fusion.

*Study III*
*Validity and sensitivity to change of the semi-quantitative OMERACT ultrasound scoring system for tenosynovitis in patients with rheumatoid arthritis*
RA patients with active disease requiring treatment intensification with csDMARDs and/or bDMARDs and with US verified tenosynovitis were included from the rheumatology outpatient clinic at Rigshospitalet, from October 2013 to June 2015.
US assessments of the flexor and extensor tendon sheaths of the clinically most affected hand or foot were performed at baseline and seen for follow-up at 3 months and 6 months. In 20 patients, US were performed independently and blinded by two investigators at baseline and 6 months to assess the interobserver agreement. Each investigator saved representative video clips for each tendon sheath's pathology, and after a minimum of one month, the video clips were re-evaluated for assessing intraobserver agreement at baseline and 6 months.

*Study IV*
*IM versus ultrasound guided intratenosynovial glucocorticoid injection for tenosynovitis in patients with rheumatoid arthritis - A randomised, double-blind, controlled study*
RA patients >18 years were eligible for inclusion if they had tenosynovitis in the hand or ankle region, both on clinical examination, defined as pain on movement localised to the affected tendon sheath, and on US, according to the definition by the OMERACT US group[64]. All patients were recruited from the rheumatology outpatient clinic at Rigshospitalet, Denmark, from December 2013 to September 2015 by study independent physicians. All recruited patients were screened, i.e. clinical and US exam-

inations were performed of the study investigators. One or two tendon sheaths were chosen for intervention. If more than two tendons fulfilled the predefined definition for tenosynovitis, the patients were not randomised due to ethical considerations.

Patients were excluded if they had intiated csDMARDs and/or bDMARDs within the last 12 weeks prior to inclusion, changed dosage of csDMARDs and/or bDMARDs and/or glucocorticoid treatment within the last 6 weeks. During the follow-up period, patients were excluded if the DMARD treatment was changed.

RA patients with tenosynovitis were randomised into two groups. An "im group", receiving im injection of 14 milligrams (2 ml) of betamethasone (BM) (e.g. glucocorticoid) in the gluteal muscles and US guided isotonic saline injection in up to two tendon sheaths (maximum 1 ml for each tendon sheath); and a "intratenosynovial group" receiving 2 ml of im isotonic saline and US guided BM injection in up to two tendon sheaths (maximum 7 milligrams (1 ml) for each tendon sheath). Follow-up was performed at 2, 4 and 12 weeks (+/- 3 days) after injections.

**Imaging**

In Study I, II, III and IV, US was performed at Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup and additionally at Department of Radiology, Rigshospitalet, Glostrup in study II. The equipment and settings were identical in both departments. MRI was performed at Department of Diagnostic Radiology, Copenhagen University Hospital Herlev-Gentofte in study II.

**Ultrasonography**

All ultrasound examinations were performed on a General Electric Logiq E9. In study II, III and IV a a high frequency linear ML 6-15 probe was used, and in study I a 3D ultrasound probe. CD was used in all studies as it is the most sensitive Doppler modality on this machine[41]. In study II, III and IV a Doppler frequency of 7.5 megahertz (MHz), pulse repetition frequency of 0.4 and gain just below the noise limit were applied. For the 3D probe in study I a Doppler frequency of 8.3 MHz, pulse repetitions frequency of 0.4, wall filter at 66, Gain at 20 db, and colour priority at 100% were applied. The Doppler settings were made according to published recommendations[45] and the same Doppler settings were used for all examinations in studies, respectively.

Tenosynovitis was assessed by GS and CD using the semi-quantitative scoring systems proposed by the OMERACT US group[64]. This scoring system includes a four-grade semiquantitative scale for GS (i.e., grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) and Doppler (i.e., grade 0, no intratenosynovial Doppler signal; grade 1, focal intratenosynovial Doppler activity; grade 2, multifocal intratenosynovial Doppler activity; grade 3, diffuse intratenosynovial Doppler activity). If abnormal intratendinous Doppler signal, addition of 1 score point (however, with a maximum of 3 in total Doppler score). Furthermore, a quantitative Doppler evaluation was performed for each tendon sheath, using Q-analysis software program on the Logic E9, calculating the fraction of colour pixels in the region of interest: pixel index (PI)= 0-100%. The PI was made on a transverse 5-second video clip of the most affected part of the tendon sheath with an average time consumption of 36 seconds.

BFI settings were adjusted to maximal sensitivity of 50 units, frequency at 12 MHz and dynamic range at 66. The tendon sheath flow was scored using a non-validated scoring system. The score was defined as, 0: No flow, 1: Focal flow, 2: Multifocal flow, 3: Diffuse flow.

The majority of all US examinations has been performed by Dr Mads Ammitzbøll Danielsen after a pre-trial phase training in US examinations and participation in musculoskeletal US courses. Dr Mads Ammitzbøll Danielsen mastering US tenosynovitis diagnostic has further been confirmed in study III, where a high intra- and interreader reliability was found.

Three experts in musculoskeletal US have assisted in the studies: Dr Iustina Janta has assisted with US assessment in study I, Dr Søren Torp-Pedersen in studies I and II, and Dr, phd Lene Terslev in studies III, and IV.

**Magnetic resonance imaging**

In study II, axial T1-weighted pre- and post-contrast fat-saturated MR image sets (0.8mm slice thickness) were obtained using a Philips 1.0 Tesla MRI scanner. MR images were scored by one trained reader of MRI tenosynovitis[67] using a four-grade semi-quantitative scoring system (i.e. grade 0, no intratenosynovial effusion or post-contrast tenosynovial enhancement; grade 1, >0 but <1.5 mm; grade 2, ≥1.5 but <3 mm; grade 3, ≥3 mm intratenosynovial effusion or post-contrast tenosynovial enhancement) as proposed by the OMERACT MRI in arthritis working group.

For tendon measurement on MRI, two measures were applied in order to investigate the effect of the partial volume artefacts (figure 1), as follows; Area 1, the area of the black tendon (i.e. excluding the volume averaging area, see below). Area 2, the area of the black tendon plus the grey band that surrounds the black tendon, marking the transition to enhancing tendon sheath due to volume averaging/partial volume artefact (i.e. area 2 includes voxels containing two types of tissue). The assessment of MR images were performed by the trained assessor, Dr Glinatsi.

**Clinical assessment and patient reported outcomes**

The blinded clinical assessment of tenosynovitis in study III and IV was made according to published recommendations[71]. A binary score for clinical tendon sheath involvement (absent/present) was performed in the involved hand(s) or ankle(s). Clinical signs of tenosynovitis were scored as being present if there was pain on movement localized at the examined tendon sheath(s) and if the pain could be reproduced by resisted active movement of the affected tendons, with the forearm or lower leg stabilised. Further, findings such as crepitus, tenderness or swelling over the affected tendon sheaths supported the scoring, but were not mandatory.

DAS28, Patient Global visual analogue scale (VAS) and Assessment Questionnaire (HAQ) were evaluated for each visit in study III and at baseline in study II and IV. Additionally, a patient reported tendon sheath pain score (VAS-patient tenosynovitis score) from 0-100 was performed in study III and IV at each visit.

Furthermore, the patients perception of treatment effect was evaluated after 2, 4 and 12 weeks on a 5 point scale (1. Markedly aggravated, 2. Slightly aggravated, 3. Unchanged, 4. Slightly improved, 5. Markedly improved) and was applied in study IV.

**Statistical analysis**

Statistical analyses were performed using SAS Enterprise Guide 6.1 and IBM SPSS statistics 22.0 and the main analyses used for the specific aims are present below. Further details are found in papers I-IV.

For analysing the presences of feeding vessels and the discrepancy of US and MRI visualization of tenosynovitis in study I and II simple descriptive statistics were used. The results within the studies were compared by the use of non-parametric statistics (Mann Whitney U test with a p-value less than 0.05 considered as significant).

Differences for measurement of the tendon and tendon sheath areas on US and MRI were expressed as medians and 25/75 percentiles and were analysed two-sided using Wilcoxon's test for paired data with a p-value less than 0.05 considered as significant . Descriptive statistics were used to present the results of the different tenosynovitis scorings. Further, agreement between the US and MRI scorings on tendon sheath level were expressed as the percentage of exact agreement (PEA) and percentage of close agreement (PCA). The PCA is the fraction of tendon sheaths where the readers differ by ≤1.0.

For validation of US OMERACT tenosynovitis scoring and the quantitative US scoring in study II, intra- and interobserver agreement on the patient level was assessed for 20 patients at baseline and 6 months for each

reader's sum scores by using single measure intraclass correlation coefficients (ICC), smallest detectable change (SDC; 1.96 x standard deviation (SD) on change scores (i.e. the change in scores between baseline and follow-up) divided by the square root of the number of readers) and smallest detectable difference (SDD; 1.96 x SD on baseline scores divided by the square root of the number of readers)[72 73].

The agreement between the two readers at tendon sheath level was expressed as PEA and PCA. The PCA is the fraction of tendon sheaths where the readers differ by ≤1.0 for GS and CD scores and ≤10.0 for PI. The threshold for PCA for PI was chosen referring to our experience in the study, where all scores except two were between 0-40.
Change in scores/values during the study were assessed by a two-sided Wilcoxon's test for paired data with a p-value less than 0.05 considered as significant. Sensitivity to change was estimated using the standardized response mean (SRM), calculated as the mean change score divided by the standard deviation (SD) of the change.

In study IV tenosynovitis remission was calculated as a binary outcome and analysed by Fisher's exact test and relative risks between the groups at 2, 4 and 12 weeks. A non-responder imputation (NRI) was used for missing data in these analyses.
Further, differences in tenosynovitis treatment response, assessed by use of US assessment, pain VAS-score and clinical assessment within and between groups, were expressed as medians and 25/75 percentiles and were analysed two-sided using Wilcoxon's test for paired data and Mann Whitney's test for unpaired data, with a p-value less than 0.05 considered as significant. Missing data was analysed as last observation carried forward in these analyses.

## RESULTS

The main results from the 4 studies reflecting the specific aims are presented below and in appendix I, II, III and IV.

### Study cohorts

A summary of selected baseline characteristics are presented in table 1.

**Table 1 Baseline characteristics**

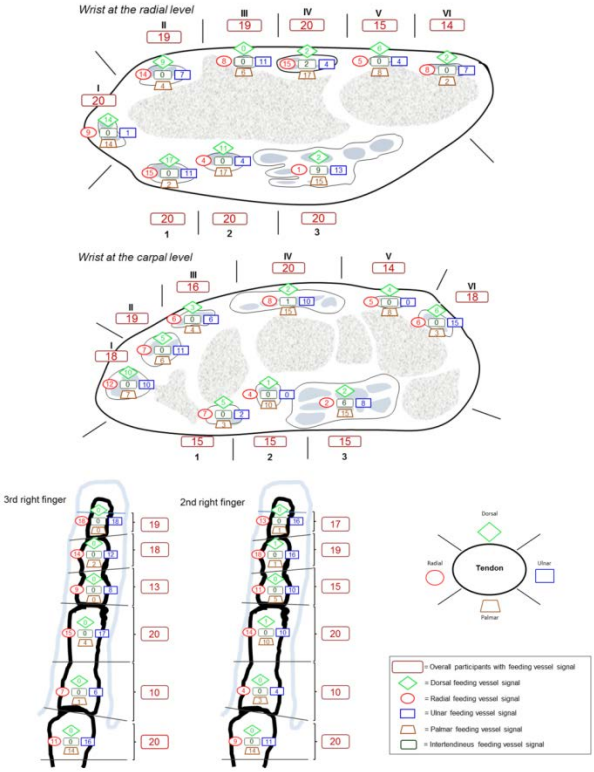
| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| **Age (years)** | 30 [23;59] | 52 [41;67] | 55 [46;68] | 57 [47;66] |
| Women (%) | 50 | 67 | 84 | 90 |
| Disease duration (months) | - | 2.0 [1;67] | 4.0 [1;96] | 35 [16;94] |
| IgM-RM positive (%) | - | 67 | 61 | 70 |
| Anti-CCP (%) | - | 73 | 67 | 78 |
| DAS28 | - | 4.6 [4.0;5.4] | 4.6 [3.8;5.4] | 3.0 [2.5;3.5] |
| VAS global | - | 71 [34;91] | 66 [49;79] | 33 [20.5;51.5] |
| CRP (mg/l) | - | 14 [6;21] | 11 [5;19] | 7.5 [5;11.5] |
| HAQ score | - | 1.0 0.5;1.625] | 1.0[0.75;1.5] | 0.75 [0.5;1.0] |
| GS score (tendon level) | - | 2.0 [1.0;2.0] | 3.0 [2.0;4.0]* | 2.0 [2.0;2.0.0] |
| CD score (tendon level) | - | 2.0 [1.0;3.0] | 3.0 [1.0;4.0]* | 2.0 [2.0;3.0] |
| Pixel index (tendon level) | - | 18 [11;21] | 16 [4;31]* | 12 [4;23] |
| Concomitant csDMARDs (%) | - | 53 | 98 | 82 |
| Concomitant bDMARDs (%) | - | 33 | 20 | 35 |

Values are the median (25;75 pctl) except where indicated otherwise; anti-CCP, anticyclic citrullinated peptide; IgM-RM, IgM rheumatoid factor; DAS28, Disease Activity Score for 28 joints, using CRP, C-reactive protein; VAS global, patient global visual analogue scale; HAQ, health assessment questionnaire; GS, grey scale; CD, Colour Doppler; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; bDMARDs, biological DMARDs; * tenosynivits sum score from the wrist or ankle

### The presence of feeding vessels in or in close proximity to extensor and flexor tendon sheaths at the wrist level and in finger flexor tendon sheaths in healthy controls (Specific aim 1, Study I)

None of the healthy controls had tenosynovitis according to the the semi-quantitative scoring system proposed by the OMERACT US group[64]. Feeding vessels were common at the wrist and the 2nd and 3rd finger, except for the proximal segment at the proximal interphalangeal bone. The distribution of feeding vessels for the wrist and fingers is illustrated in figure 5.

**Figure 5 Number of participants with feeding vessel signal at different location**




Distribution of feeding vessel signals in relation to the flexor tendon sheaths of the 2nd and 3rd right finger and the wrist. The bordeaux coloured boxes represent the overall number of participants who had feeding vessel signal in the marked area, calculated as presence/absence. The other colour boxes represent the number of participants who had feeding vessel signals at a specific location for the marked area (explained in the schematic drawing, in the lower right corner of the figure) I; abductor pollicis longus and extensor pollicis brevis, II; extensor carpi radialis longus and extensor carpi radialis brevis, III: extensor pollicis longus, VI; extensor indicis and extensor digitorum communis, V; extensor digiti minimi, IV; extensor carpi ulnaris, 1; flexor carpi radialis 2; flexor pollicis longus 3; flexor digitorum superficialis and profundus.

Feeding vessels at the wrist were common at both the radial and carpal level. Superficial feeding vessels seem to be more common than profound feeding vessels (the feeding vessels closest to the bone) for the extensor tendons, except for the 4th compartment and the 1st and 2nd compartment at the carpal level. Intertendinous feeding vessels were mainly seen in the tendon sheath of flexor digitorum superficialis and profundus, but also in the 4th compartment. Intratendinous Doppler signal was seen in the extensor carpi ulnaris (ECU) tendon twice. No other intratendinous Doppler signals were seen.
For the 2nd and 3rd finger the overall segmental distribution (calculated as +/- for each segment) of feeding vessels did not differ significantly (Mann Whitney U test; p=0.84). The median was respectively 5.00 (25th;75th percentile, 4.75;6.00) and 5.00 (4,75;6.00) for the 2nd and 3rd finger. The feeding vessels were predominantly seen at the ulnar and radial aspects of the tendon sheath, compared to the dorsal and palmar location (p <0.01), except at the distal part of the metacarpal bones, where the palmar location was common. Vessels at the dorsal aspect of the flexor tendon were extremely rare, intertendinous feeding vessels and intratendinous signals were not seen.

Discrepancy of US and MRI visualization and scoring of tenosynovitis using image fusion technique (Specific Aim 2, Study II)
All included patients had tenosynovitis both on US and MRI when image fusion was used for comparison. However, image fusion also revealed some differences between the imaging modalities. It is especially worth

mentioning that Doppler signals within the tendon sheath corresponded in most cases to enhancement of the tendon sheath on MRI, but Doppler signals were only seen in a fraction of the enhanced tendon sheaths. Further, it was difficult for US to distinguish between an effusion and tenosynovial hypertrophy inside the tendon sheath, in contrast to MRI. In some cases the tendon and tendon sheath were slightly flattened on US, despite applying only a very light probe pressure, in order not to miss Doppler signals. Additionally, US showed limitation in separating tendons when they were in close proximity, as in compartment 4 or in proximal part the finger flexor tendon sheath (at the metacarpophalangeal joint level).

We also noted that tendons inside the tendon sheath by eyeballing seemed to be smaller on MRI than US when compared with image fusion. The area of the tendons on US had a median of 0.16 cm2 (25;75 pctl: 0.10;0.25) in comparison with MRI area 1 (the area of the black tendon); 0.09 cm2 (0.06-0.18) and area 2 (the area of the black tendon including the grey band surrounding it); 0.13 cm2 (0.10;0.25). If US was used as reference, there was a statistically significant difference for area 1 (Wilcoxon's test; p<0.01), but not for area 2 (p=0.47). Please see appendix II for further details about the difference between the imaging modalities. Overall agreement between US and MRI tenosynovitis scoring systems was good, however the agreement was slightly higher when using MRI measure 2, please see table 2.

**Table 2 Tenosynovitis scores and corresponding delta scores on tendon level for all imaging modalities**

| Patient no | Tendon sheath | CD | BFI | ΔCD;BFI | MRI_1 | MRI_2 | ΔCD;MRI_1 | ΔCD;MRI_2 | GS | ΔGS;MRI_1 | ΔGS;MRI_2 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Extensor carpi ulnaris | 3 | 1 | 2 | 3 | 3 | 0 | 0 | 3 | 0 | 0 |
| 2 | Flexor pollicis longus | 2 | 0 | 2 | 1 | 2 | 1 | 0 | 2 | 1 | 0 |
| 3 | Flexor carpi radialis | 2 | 1 | 1 | 3 | 3 | -1 | -1 | 2 | -1 | -1 |
| 4 | Flexor tendon of the 4th digit | 3 | 2 | 1 | 3 | 3 | 0 | 0 | 2 | -1 | -1 |
| 5 | Flexor tendons of the 5th digit | 3 | 0 | 3 | 3 | 3 | 0 | 0 | 2 | -1 | -1 |
| 6 | Flexor tendon of the 2nd digit | 2 | 1 | 1 | 2 | 1 | 0 | 1 | 2 | 0 | 1 |
| 7 | Extensor carpi ulnaris | 3 | 1 | 1 | 3 | 3 | 0 | 0 | 3 | 0 | 0 |
| 8 | Extensor carpi ulnaris | 0 | 0 | 0 | 1 | 1 | -1 | -1 | 1 | 0 | 0 |
| 9 | Extensor carpis radialis brevis/longus | 2 | 0 | 2 | 3 | 2 | -1 | 0 | 1 | -2 | -1 |
| 10 | Extensor pollicis longus | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 |
| 11 | Extensor digitorum communis/indicis proprius | 2 | 1 | 1 | 3 | 3 | -1 | -1 | 3 | 0 | 0 |
| 12 | Flexor tendon of the 3rd digit | 0 | 0 | 0 | 2 | 1 | -2 | -1 | 1 | -1 | 0 |
| 13 | Extensor digiti minimi | 1 | 0 | 1 | 2 | 1 | -1 | 1 | 1 | -1 | 0 |
| 14 | Flexor carpi radialis | 2 | 0 | 2 | 2 | 2 | 0 | 0 | 2 | 0 | 0 |
| 15 | Extensor carpi ulnaris | 3 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 |
| | The percentage of exact agreement (PEA) | | | 13 | | | 40 | 47 | | 40 | 53 |
| | The percentage of close agreement (PCA) | | | 40 | | | 93 | 100 | | 93 | 100 |

Tenosynovitis scores on tendon level (0-3) for colour Doppler (CD), grey scale (GS), B-flow imaging (BFI) and MRI area 1 and 2. Delta scores are calculated for BFI, MRI area 1 and 2 with CD as reference and for MRI area 1 and 2 with GS as reference. Further, the percentage of exact agreement (PEA) and the percentage of close agreement (PCA) used for comparing the agreement between the scores.
No, number; MRI_1, the area of the black tendon; MRI_2, the area of the black tendon plus the grey band that surrounds the black tendon; PEA, expresses the percentage of the patients receiving the same score; PCA, is the percentage of the patients where the score differ no more than 1.0.

In contrast, the agreement between BFI and CD US was poor, since the quality of the BFI images and flow sensitivity was low, as illustrated in figure 4. For further details please see appendix II.

**Validation of the semi-quantitative US OMERACT tenosynovitis scoring system (Specific Aim 3, study III)**

Intra- and interreader agreement for the 20 selected patients was very good for GS (all ICCs ≥0.82) and CD (all ICCs ≥0.89) for both baseline and change scores. The SDC of both GS and CD was below 1 at all sites, i.e. below the increment of the scoring system. SDCs expressed as the percentages of the maximal observed score and percentage of the maximal possible score for the interreader scores were for GS and CD below 20% (reflecting a high potential to detect changes) (see table 3).

**Table.3 Intrareader and Interreader Intraclass correlation coefficients (ICC), smallest detectable change (SDC), smallest detectable difference (SDD), SDC as percentage of the maximal observed score (PMOS) and percentage of the maximal possible score (PMPS)**

| | Intrareader-baseline | | | | Intrareader-change | | | | Interreader-baseline | | Interreader-change | | SDC as % of the max observed score | SDC as % of the max possible score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ICC reader 1 | SDD | ICC reader 2 | SDD | ICC reader 1 | SDC | ICC reader 2 | SDC | ICC | SDD | ICC | SDC | PMOS | PMPS |
| Grey scale | 0.91 | 1.1 | 0.82 | 1.7 | 0.89 | 0.69 | 0.86 | 0.76 | 0.89 | 1.3 | 0.89 | 0.97 | 7.5 | 2.5 |
| Colour Doppler | 0.96 | 0.75 | 0.94 | 0.98 | 0.95 | 0.42 | 0.96 | 0.42 | 0.95 | 0.9 | 0.9 | 0.93 | 5.5 | 2.4 |
| Pixel index | 0.99 | 5.1 | 0.97 | 17.1 | 0.94 | 4.5 | 0.99 | 3.1 | 0.67 | 21.7 | 0.41 | 30.1 | 25.7 | 2.3 |

Intrareader and Interreader agreement score is calculated by total tendon sum score for each patient and is expressed as single measure ICC with a 95% CI. ICC ≥ 0.50 is considered good and ICC ≥ 0.80 is considered very good. SDC is calculated for Intrareader and Interreader change scores and SDD for Intrareader and Interreader baseline scores. PMOS and PMPS are calculated for Interreader change score.

**Validate of novel quantitative US method for assessment of tenosynovitis, Pixel index (Specific Aim 4, Study III)**

The intrareader agreement for PI was very good (ICC≥0.94). However, the interreader agreement was only good for baseline (ICC=0.67) and moderate for change score (ICC=0.41). The SDC for PI intrareader change was 4.5, which is considered as acceptable, but low for change, i.e. 30.1. Interreader SDC expressed as the percentage of the maximal observed score was 25.7%, opposite the percentage of the maximal possible score was 2.3 (see table 2).

**Table 4. Percentage of exact agreement (PEA) and percentage of close agreement (PCA) for tenosynovitis assessment of tendon sheath on patient level**

| | Intrareader baseline | | Intrareader change | | Interreader baseline | | Interreader change | |
|---|---|---|---|---|---|---|---|---|
| | Mean PEA | Mean PCA | Mean PEA | Mean PCA | PEA | PCA | PEA | PCA |
| GS overall (mean) | 96.7 | 99.7 | 95.0 | 99.5 | 93.4 | 99.4 | 89.1 | 99.1 |
| CD overall (mean) | 95.0 | 98.9 | 94.5 | 98.8 | 94.4 | 99.4 | 93.8 | 98.8 |
| PI overall (mean) | 90.6 | 98.6 | 88.1 | 98.0 | 86.3 | 98.1 | 85.9 | 97.5 |

Interreader PEA expresses the percentage of patients receiving the same score by the two readers and the interreader PCA is the percentage of the patients where the score difference is no more than 1.0 for GS and CD and 10.0 for PI; GS, grey scale (0-3); CD, Colour Doppler (0-3); PI, pixel index (0-100)

However, SRM was higher for the semi-quantitative scoring system after 6 months (GS=0.9, CD=0.8) than for the quantitative assessment (PI=0.7).

**Whether US-tenosynovitis assessment is more sensitive to change than other disease markers of tenosynovitis and RA (Specific Aim 6, Study III)**
All parameters decreased significantly from baseline to 6 months and the SRM was good for GS, CD and VAS-patient tenosynovitis score; moderate for PI, clinical evaluation, DAS28 and VAS-Global; and low for HAQ and CRP, between baseline and 6 months (see table 5)

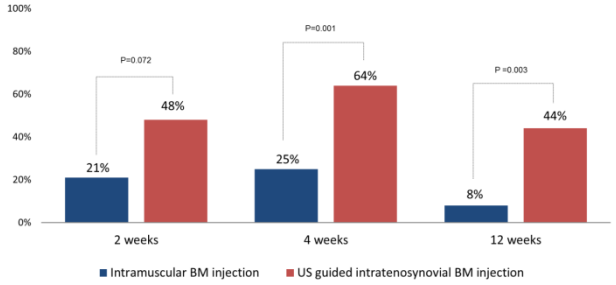
**Table 5. Change in outcome score/index over 6 months and standardized response mean (SRM) for each score/index**

| | | | Baseline | | Δ 0-3 months | | | Δ 0-6 months | | | SRM 0-6 months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Grey scale | *Mean* | *(Std. Dev)* | 3.5 | (2.64) | -1.4 | (2.23) | | -2.1 | (2.35) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.9 |
| | *Median* | *[25;75 pctl]* | 3.0 | [2;4] | 1.0 | [-2;0] | | -2.0 | [-3;-1] | | |
| Colour Doppler | *Mean* | *(Std. Dev)* | 3.4 | (3.46) | -2.0 | (3.28) | | -2.6 | (3.35) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.8 |
| | *Median* | *[25;75 pctl]* | 3.0 | [1;4] | -1.0 | [-3;0] | | -2.0 | [-3;0] | | |
| Pixel index | *Mean* | *(Std. Dev)* | 22.4 | (24.05) | -14.2 | (23.60) | | -16.7 | (24.59) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.7 |
| | *Median* | *[25;75 pctl]* | 16.0 | [4;31] | -9.0 | [-22;0] | | -14.0 | [-27;0] | | |
| Clinical TS As | *Mean* | *(Std. Dev)* | 2.4 | (1.94) | -0.8 | (1.93) | | -1.4 | (2.39) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.6 |
| | *Median* | *[25;75 pctl]* | 2.0 | [1;3] | 0.0 | [-2;0] | | -1.0 | [-3;0] | | |
| VAS-patient TS | *Mean* | *(Std. Dev)* | 47.7 | (23.5) | -20.9 | (30.1) | | -31.3 | (29.2) | | |
| | | | | | | | P <.01 | | | P <.01 | 1.1 |
| | *Median* | *[25;75 pctl]* | 51.0 | [26;68] | -25.0 | [-75;5] | | -32.0 | [-55;-11] | | |
| DAS28 | *Mean* | *(Std. Dev)* | 4.6 | (0.9) | -1.2 | (1.43) | | -1.3 | (1.76) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.7 |
| | *Median* | *[25;75 pctl]* | 4.6 | [3.8;5.4] | -1.1 | [-1.7;0.1] | | -1.2 | [-2.2;-0.1] | | |
| CRP | *Mean* | *(Std. Dev)* | 15.3 | (14.1) | -2.5 | (15.69) | | -5.9 | (13.5) | | |
| | | | | | | | P=0.05 | | | P <.01 | 0.4 |
| | *Median* | *[25;75 pctl]* | 11.0 | [5;19] | 0.0 | [-8;0] | | -2.0 | [-8;0] | | |
| VAS Global | *Mean* | *(Std. Dev)* | 61.5 | (22.4) | -14.5 | (28.1) | | -20.3 | (27.7) | | |
| | | | | | | | P <.01 | | | P <.01 | 0.7 |
| | *Median* | *[25;75 pctl]* | 66.0 | [49;79] | -7.0 | [-31;6] | | -19.0 | [-41;-1.0] | | |
| HAQ | *Mean* | *(Std. Dev)* | 1.1 | (0.6) | 0.2 | (0.4) | | 0.2 | (0.7) | | |
| | | | | | | | P <.01 | | | P =0.03 | 0.3 |
| | *Median* | *[25;75 pctl]* | 1.0 | [0.8;1.5] | 0.3 | [0;0.4] | | 0.3 | [-0.25;0.63] | | |

SRM is considered trivial, <0.20; small, 0.20-0.49; moderate, 0.50-0.79; good, ≥0.80; P, Wilcoxon Signed Ranks Test; TS, tenosynovitis score; As, assessments; VAS TS, patient reported visual analogue scale (0-100 mm) for pain tenosynovitis; CRP, C-reactive protein; VAS global, patient global visual analogue scale(0-100 mm) for assessment of disease activity; HAQ, health assessment questionnaire

**Differences in achievement of US tenosynovitis remission, between US-guided glucocorticoid injection in the tendon sheath and im. glucocorticoid injection (Specific Aim 7, Study IV)**
US tenosynovitis remission at week 4 was achieved in 25% (6/24) of the patients in the "im group" and in 64% (16/25) in the "intratenosynovial group". This difference was highly statistically significant, Fisher exact test p=0.001, i.e. a difference of -39 percentage point (pp) (CI -65pp to -13pp). At week 12, US tenosynovitis remission was achieved in 8% (2/24) of the patients in the "im group" and in 44% (11/25) of the patients in the "intratenosynovial group", i.e. a difference of -36 pp (CI -58pp to -13pp), p=0.003. At 2 weeks, US tenosynovitis remission was achieved in 21% (5/24) of the patients in the "im group" and in 48% (13/25) of the patients in the ""intratenosynovial group", i.e. a difference of -27pp (CI -53pp to -2pp), p=0.072. The treatment responses for each group at each visit are illustrated in figure 6.

**Figure 6 Proportions of patients with ultrasound tenosynovitis remission at weeks 2, 4 and 12**




US, ultrasound; US tenosynovitis remission defined as US tenosynovitis grey scale score ≤1 and colour Doppler score = 0; p, Fisher exact test (p); BM, betamethasone. The primary endpoint was at week 4

**Are changes in clinical assessment, patient reported outcome and US parameters different between US-guided glucocorticoid injection in the tendon sheath and im. glucocorticoid injection? (Specific Aim 8, Study IV)**
In both groups statistically significant decreases in all assessed US parameters (GS, CD and PI) were observed between baseline and 12 weeks, which is in contrast to VAS tenosynovitis and clinical assessment where significant change were found only in the "intratenosynovial group", see table 6.

**Table 6 Tenosynovitis outcome values: At baseline, change within patients receiving the intramuscular BM injection group ("im group") and patients receiving the US-guided intratenosynovial BM injection ("intratenosynovial group"), and differences between groups**

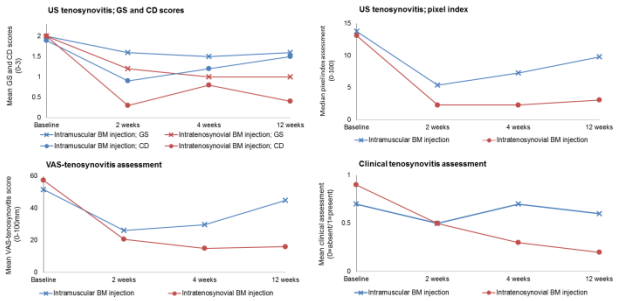
| | Baseline | | Δ 0-2 weeks^ | | | Δ 0-4 weeks^ | | | Δ 0-12 weeks^^ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median [25;75 pctl] | Mean (SD) | Median [25;75 pctl] | Mean (SD) | p | Median [25;75 pctl] | Mean (SD) | p | Median [25;75 pctl] | Mean (SD) | p |
| Grey scale – intramuscular | 2 [2;2] | 2.0 (0.4) | 0* [-1;0] | -0.4 (0.4) | | -0.5** [-1;0] | -0.6 (0.7) | | -0.5* [-1;0] | -0.4 (0.8) | |
| | | | | | =0.02 | | | <0.01 | | | =0.01 |
| Grey scale – intratenosynovial | 2 [2;2] | 2 (0.6) | -1**[-1;0] | -0.8 (0.6) | | -1** [-2;-1] | -1.2 (0.8) | | -1** [-2;0] | -1.0 (0.8) | |
| Colour Doppler – intramuscular | 2 [1.5;2.5] | 1.9 (0.9) | -1** [-2;0] | -1.0 (1.0) | | 0* [-1;0] | -0.7 (1.0) | | 0* [-1;0] | -0.4 (0.8) | |
| | | | | | =0.02 | | | <0.01 | | | <0.01 |
| Colour Doppler - intratenosynovial | 2 [2;3] | 2.0 (1.0) | -2** [-2;-1] | -1.6 (1.1) | | -2** [-2;-1] | -1.6 (1.0) | | -2** [-2;-1] | -1.6 (1.1) | |
| Pixel Index – intramuscular | 14 [4;20] | 13.8 (10.4) | -5** [-17;0] | -8.4 (9.9) | | -3** [-120;-6] | -6.5 (7.9) | | -2* [-9;0] | -4.0 (8.1) | |
| | | | | | =0.57 | | | =0.18 | | | =0.05 |
| Pixel Index – intratenosynovial | 9 [3;24] | 13.1 (12.2) | -8** [-16;-5] | -11.0 (11.0) | | -8** [-16;-13] | -10.8 (11.1) | | -8** [-14;-1] | -10.1 (10.7) | |
| VAS-patient TS - intramuscular | 51 [37;74.5] | 51.6 (24.2) | -19.5** [-48;-1.5] | -25.5 (30.0) | =0.15 | -26* [-42.5;8.5] | -20.3 (34.9) | =0.02 | -8.5 [-40.5;5] | -6.8 (53.7) | <0.01 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| VAS-patient TS-intratenosynovial | 65 [44.;71] | 57.4 (22.2) | -39** [-53;-17] | -36.5 (24.2) | | -42** [-58;-34] | -42.6 (19.0) | | -44** [-62;-24] | -41.1 (24.6) |
| Clinical As – intramuscular | 1 [0.5;1] | 0.7 (0.4) | -1* [-1;0] | -0.2 (0.5) | | 0 [-1;0] | -0.2 (0.6) | | 0 [-0.5;0] | -0.2 (0.6) |
| | | | | | =0.23 | | | =0.04 | | <0.01 |
| Clinical As – intratenosynovial | 1 [1;1] | 0.9 (0.3) | 0* [-1;0] | -0.4 (0.5) | | -1** [-1;0] | -0.6 (0.5) | | -1** [-1;-0] | -0.6 (24.6) |

P,p-value for Mann Whitney U test of difference between change from baseline between "im group" and "intratenosynovial" group; *p<0.05,**p<0.01, Wilcoxon Signed Rank test of change within groups ; ^1 missing value calculated as last observation carried forward; ^^ 16 missing values calculated as last observation carried forward; BM, betamethasone; US, ultrasound; TS, tenosynovitis; VAS TS, patient reported visual analogue scale (0-100 mm) for pain tenosynovitis; As, assessments

Change in values in the "im group" and the "intratenosynovial group" were compared for week 2, 4 and 12, a statistical significantly higher change were observed for all GS and CD scores in the "intratenosynovial group", see table 6. Similar results were seen for VAS-tenosynovitis and clinical tenosynovitis assessment at week 4 and 12, illustrated in figure 3. However, the PI was only able to show a borderline significance after 12 weeks between the "im group" and the "intratenosynovial group". These differences between the two groups are illustrated in figure 7.

**Figure 7 Tenosynovitis exact values (mean) between intramuscular BM injections and US guided intratenosynovial BM injections at baseline, and at weeks 2, 4 and 12**




BM, betamethasone; US, ultrasound; GS, grey scale score; CD, colour Doppler score; VAS tenosynovitis, patient reported visual analogue scale (0-100 mm) for pain tenosynovitis

## Discussion

The methodological considerations in this thesis will be discussed in the first part of the discussion. Thereafter, a discussion of the specific aims from the four studies will be presented.

### Methodological considerations

US has gone through major technological developments over the last two decades and has obtained an important role in the management of RA patients, including tenosynovitis assessment. Despite this, US is often perceived as being operator dependent and methodological consideration of US validity is therefore highly relevant[70].

The methodological focus of this thesis has been development and validation of US as a tool for monitoring tenosynovitis. Overall, a high validity of a new outcome measure as US is very important before implementing it in clinical trials. However, there have been several examples of insensitive outcome measures in clinical trials[69], including US measurement[74]. In order to obtain a high validity, reliability tests in different patient cohorts and clinical settings are needed. In accordance with the OMERACT filter[75], tenosynovitis US pathologies in 2012 were defined and tested for intra- and interreader reliability among experts in a cross-sectional study of 10 patients , with a moderate to good intra- and interreader agreement for GS and Doppler[64]. Further development and validation of US as a tool for monitoring tenosynovitis was therefore needed when this thesis was planned.

Doppler US may cause erroneous measurement of low grade inflammation due to physiological flow in close proximity to the tendon sheath. Considerations of face validity (i.e. whether the assessment method measures what it is supposed to measure) is therefore relevant when Doppler US is used. Study I was the first to examine the normal vascularisation in relation to the tendon sheaths in the hand and the potential pitfalls it may cause when distinguishing normal flow from pathological flow. The study hereby increased the credibility of US assessed tenosynovitis.

Histopathologic assessment is the gold standard of synovitis measurement[76-78]. However, MRI has in several studies[79-87] shown good agreement with histopathological samples of synovitis and similar agreement has been seen in some US studies[88 89]. Therefore, MRI is often considered as the gold standard for synovitis measurement. In study II we have tested US versus MRI assessment (MRI considered as the gold standard) for concurrent validity (i.e. does the measure reflect the same degree of inflammation, applied at the same time, as the gold standard). US and MR images of tenosynovitis were compared live with image fusion in order to investigate whether the pathological change in the modalities reflect each other. This comparison also further validated the credibility and comprehensiveness of US for tenosynovitis assessment. A similar comparison of US and MRI using image fusion has only been made once previously among RA patients, testing how the imaging modalities reflected erosions[90].

Assessment of US tenosynovitis reproducibility and sensitivity to change (i.e. discriminant validity) is a key criterion for validation of US as a tool for monitoring tenosynovitis and has been tested in study III in this thesis. This study is one of the first to test longitudinal reproducibility and sensitivity to change for US assessment of tenosynovitis [10 38 91] and the first to validate the OMERACT tenosynovitis scoring system[64]. Furthermore, a quantitative assessment method was tested longitudinally. The reproducibility was assessed using several methods including ICC and SDC, as described in the method section. SDC addressed the smallest change between two measurements that can reliable be detected, which is crucial knowledge before applying a scoring system in clinical trials (or daily clinical practice).

Sensitivity to change was investigated as responsiveness to DMARD treatment over 6 months, measured as change values in US assessment parameters, evaluated by SRM. These changes in US parameters were further compared with changes in clinical parameters and patient reported outcomes in order to obtain information of construct validity (i.e. correlation to other disease activity measures). Study IV has in line with the findings in study III, demonstrated that the US tenosynovitis assessment is sensitivity to change.

The capability of US to distinguish between the responses in two groups of RA patients receiving different treatment was demonstrated for the first time in a randomised double blind trial over 3 months in study IV. Furthermore, construct validity was tested, since US assessed tenosynovitis was compared to the standard method of assessment, i.e. clinical assessment for tenosynovitis. An overview of validity components tested in this thesis is presented in table 7.

**Table 7 Assessment of validity components in study I to IV**

| | Face validity | Content validity | Criterion validity | | Construct validity | Discriminant validity | |
|---|---|---|---|---|---|---|---|
| | *Credibility* | *Comprehensiveness* | *Concurrent validity* | *Predictive validity* | | *Reproducibility* | *Sensitivity to change* |
| Study I | + | - | - | - | - | - | - |
| Study II | - | + | + | - | + | - | - |
| Study III | - | + | - | - | + | + | + |
| Study IV | - | + | - | - | + | - | + |

+, validity tested; -, validity not tested

This thesis has added new important information on validity aspects of US as a measurement instrument of tenosynovitis in RA patients, but far are we from implementing it as standard monitoring method in clinical trials? In accordance with the OMERACT filter [75] a measurement instrument, as US assessment of tenosynovitis, needs to fulfill this specific criteria: truthfulness, discriminative validity and feasibility.

As described above this thesis has covered the majority of key elements regarding truthfulness, such as face, content, criterion and construct validity. However, a credibility study of normal vascularization in the ankle may be needed, since several studies[10 92-94] show that tenosynovitis in this region is very common. Likewise, the obtainment of real criterion validity for tenosynovitis, where histopathologic and US assessed changes are compared, would be ideal.
The reproducibility and sensitivity to change (discriminative validity) for tenosynovitis have been tested in a single center study (study III) with positive results. However, it could be desirable also to have tested the sensitivity to change in a longitudinal multicenter study, in order to assess the influence of different cohorts and readers on the measure of US responsiveness. Such a study is ongoing.

The feasibility of US as measurement instrument for tenosynovitis assessment has been demonstrated in this thesis, since it was used in more than 350 visits. The average time consumption of tenosynovitis assessment in study III and IV was about 12 and 36 seconds for the semi-quantitative and quantitative assessments, respectively. These results indicated that the semi-quantitative method is a more feasible method for assessment of tenosynovitis and can be considered to be in line with US joint assessment.

In table 8 this author's rating of US validitystrength for tenosynovitis assessment is presented, taking into consideration all published US studies tenosynovitis.

**Table 8. Validity strength of US tenosynovitis assessment**

| | Face and content validity | | Criterion validity | | Construct validity | Discriminant validity | |
|---|---|---|---|---|---|---|---|
| | *Credibility* | *Comprehensive-ness* | *Concurrent validity* | *Predictive validity* | | *Reproducibil-ity* | *Sensitivity to change* |
| US assessment of tenosynovitis | +++ | ++ | ++ | + | ++ | ++ | +++ |

*+++, high validity; ++, intermediate validity; +, low validity; -, none validity*

The credibility of US tenosynovitis assessment is overall rated high, probably slightly better for the wrist and fingers since there is a better knowledge of physiological flow than in other regions. US visualization very well covers the structural change in the tendon and tendon sheath, but has as illustrated in study II some limitations regarding the capability to distinguish between effusion and tenosynovial hypertrophy inside the tendon sheath, but also to separate tendons when they are in close proximity. The comprehensiveness is therefore rated as intermediate.

The concurrent validity is a weak point in US validation, since histopathologic samples are needed. Direct comparison between histopathologic and US assessed signs of tenosynovitis has never been investigated. A few studies have documented close relationship for synovitis between histopathologic and US changes [88 89]. The relation between histopathologic and MRI findings is however better documented[81-87] . Therefore MRI is often considered an acceptable gold standard. The concurrent validity for US tenosynovitis assessment is therefore rated as intermediate. Regarding predictive validity, the rating is low, since only two studies have investigated US assessed tenosynovitis as a predictor for disease development (flares) [31 95].

However, several MRI studies have found that tenosynovitis is a strong and better predictor for early RA than synovitis [9 23 24] and tenosynovitis in ECU predict erosive development[30]. However, a recent study has reported no predictive value of systematic joint assessment by US[96].
Regarding construct validity, study III and IV have contributed with important knowledge, of comparison with clinical examination, which is only reported in a few studies[48 50]. Furthermore, the agreement between US and MRI for tenosynovitis assessment has been reported in study II, but also by Wakefield et al[11]. Based on these studies it is reasonable to give US as high construct validity rating.
The reproducibility rating of tenosynovitis assessment by US is medium and have been tested in two cross sectional multicenter studies[38 64] and longitudinally in study III. To obtain a higher rating further longitudinally studies are needed. Sensitivity to change, using different tenosynovitis US scoring system, is tested in several studies[10 38], including studies III and IV, with great results and are therefore rated as high.

Overall US tenosynovitis assessment is well validated, and can be used in clinical trials. Nevertheless, further validation is recommended (see table 8).

Regarding BFI assessment of slow flow, there is to my knowledge no published study testing the validity. In study II we have tested concurrent validity and found important limitations, mainly explained by the poor imaging quality. Therefore B-flow is currently not credible as an outcome measure for tenosynovitis.

**Validation results for US assessed tenosynovitis**
This thesis (study I) demonstrated that 3D Doppler US examination is an ideal imaging modality for systematic assessment of physiological flow, since a volume video clip of the whole tendon sheath can be produced, just as with MRI and computed tomography, i.e. the reading of the US examination can be standardized and reproduced. On the other hand, it is unavoidable that the setting will be less sensitive for slow flow in order to reduce movement artifacts when using 3D, due to the movement of the transducer during the sweep[97-100]. However, the 3D probe was used for assessing physiological flow which is slightly faster than pathological flow and therefore less affected by the slightly different Doppler adjustments. Overall there are more advantages of 3D Doppler than disadvantages when physiological flow is assessed. Physiological flow in relation to the wrist and finger joints has previously been assessed with 2D Doppler US examination, however, with considerable variation[101-103], illustrating the well-known reproducibility difficulties with 2D US. A 3D US approved assessment of physiological flow in relation to the wrist and finger joints, including vessel channels[104], could therefore be highly relevant, also seen in relation to the upcoming OMERACT joint scoring system "GLOSS" . Possibly other joint regions such as elbow, knee, ankle and foot could be included, but knowledge of 3D Doppler US capabilities in these regions is limited.

Study I demonstrated that Doppler findings in or in close proximity to the tendon sheaths were common in wrists and fingers in healthy participants and may be a source of misinterpretation because they seem to be located inside the tendon sheath, not only due to their location but because of blooming and/or reverberations artefacts. Therefore this thesis has shown high agreement between US and MRI assessments of tenosynovitis (study II) when knowledge of the distribution and specific patterns of Doppler findings in wrists and fingers were taken into account.

To our knowledge only two studies have compared tendons visualized by MRI and US using image fusion[105 106]. However, study II in this thesis was the first to make a quantitative comparison of US and MRI tendon size. This measurement revealed that the tendon area was smaller on MRI, due to the partial volume artefact and this artefact should be included in the tendon measurement, when scoring tenosynovitis on MRI.

Partial volume artefact is possibly an underestimated error when measurement on MRI is used for scoring of inflammation as reported by study II. Due to a higher spatial resolution on US, but also that semi-quantitative scoring is not based on measurement, this problem is less significant for

US. However, study II has shown that the tendon and tendon sheath in some cases were slightly flattened on US, despite applying very light probe pressure in order not to miss Doppler signals. Normally a too high probe pressure is one of the most common mistakes for beginners of musculoskeletal US, but study II revealed that it could also be the case for experts in musculoskeletal US.

The agreement for scoring between the two imaging modalities was quite good, despite of different methods, i.e. MRI scoring based on the thick (most enhanced) part of the tendon sheath, while US scoring is including the synovitis incidence of the whole tendon sheath. However, the results illustrate that both imaging modalities have excellent abilities to assess tenosynovitis. Results from study II further showed that BFI is not an alternative to CD. Even in patients with pronounced Doppler signals, BFI only showed sparse signs of flow and further development of this modality, including improvement of the anatomical visualisation, is required in order to increase the sensitivity and clinical applicability.

In study III the OMERACT US tenosynovitis scoring system was tested by two investigators in a longitudinal study. The intra- and interreader results were overall excellent and slightly better than previously demonstrated [64]. The good results may have been facilitated by the fact that it was a single centre study and only two readers were involved, which had trained together prior to the study. The calculated SDC was below the increment of scoring system (SDC ≤1 per patient) for both GS and CD assessments, illustrating the scoring system's excellent capability to detect change over time.

A semi-quantitative scoring system will always include the risk of a ceiling effect, opposite a quantitative evaluation method and we therefore tested the use of pixel analysis (Q Analysis®). However, the reliability performance for the quantitative US pixel evaluation was disappointing, clearly reflected by ICC of 0.41 and a SDC of 30.1, meaning that PI is only reliable (sensitivity to change) when tenosynovitis is severe(PI >30% ). Why the evaluation of the most inflamed part of the tendon sheath (i.e. quantitative US pixel evaluation) performed less good than the overall assessment of the whole tendon sheath (i.e. semi-quantitative assessment) is unknown.

The interreader reliability for PI was also considerably lower than previously reported for joints[107]. This thesis has shown good correspondence between semi-quantitative US and MRI assessment, where MRI scoring likewise was based on the most affected part of the tendon sheath, so similarity between semi-quantitative and quantitative assessment will be expected. A possible explanation could be that the range of the quantitative US pixel evaluation method was far from being fully used, illustrated by the considerable difference between the SDC percentage of the maximal observed score (25.7%) and percentage of the maximal possible score (2.3%). Since quantitative US pixel evaluation is more time consuming than the OMERACT scoring system, this study (study III) demonstrated no advantages of quantitative US pixel evaluation compared to the semi-quantitative OMERACT scoring system.

If these results are compared with similar MRI tenosynovitis reliability studies [65 108] using ICC for intrareader agreement, the ICC values were slightly better. Regarding the interreader agreement the ICC results were comparable for the semi-quantitative US scoring system, but less impressing for the quantitative method.

The response to new treatment was as expected over 6 months decreased significantly in all evaluated parameters. The decreases in GS and CD were mainly seen between baseline and 3 months, but also between 3-6 months (please see appendix III, table 5). In contrast, there was no significant change in DAS28, CRP and HAQ between 3-6 months, which indicates that routine disease monitoring is not fully covering tenosynovitis. This was in line with findings by Hammer et al.[10], using a scoring system based on GS (presence of tenosynovitis and fluid) and power Doppler (presence of vascularization) on a four-point scale: 0 = none, 1 = minor, 2 = moderate or 3 = major presence [10].

The responsiveness of US, as measured by the SRM from 0-6 months for GS and CD scores, was in line with previous studies using different scoring systems [10 38]. GS and CD had a high and numerically slightly higher SRM than clinical assessment of tenosynovitis, DAS28, HAQ, PI, CRP and VAS-global, indicating a high ability to detect small changes in tenosynovitis activity. SRM of CRP and US tenosynovitis score have previously been reported [38] to be similar, which is in contrast to the results from study III and from Hammer et al[10]. This discrepancy is most likely explained by marked difference in baseline levels of CRP. DAS-28 was reported by Hammer et al to be more responsive (higher SRM) than the applied tenosynovitis scoring system, which is different from the results in study III. The most important explanation for this difference is the applied inclusion criteria, giving a lower baseline DAS-28 and a higher tenosynovitis incidence in study III.

There is also the possibility that the OMERACT US group's semi-quantitative tenosynovitis US scoring is a slightly more responsive scoring system, despite of similar SRM means. To fully answer this question a head to head comparison is needed.

In study III VAS-tenosynovitis was the most responsiveness assessment method for tenosynovitis. However, this score was very biased, as all patients had been made aware of having tenosynovitis and therefore inclined to report change in tenosynovitis pain. Whether patients can make this discrimination between tendon sheath pains and overall joint pain in everyday life is doubtful.

**Treatment of tenosynovitis**

This thesis (study IV) is the first to compare IM versus US guided intratenosynovial intratenosynovial BM injection in order to provide disease control after 2, 4 and 12 weeks in RA patients with tenosynovitis. The study was designed as a high level evidence study[109] (a randomised double blind study, level A) in order to have trustworthy results, which can be implemented in daily clinic.

The primary outcome was defined as US tenosynovitis GS score ≤1 and Doppler score = 0 at week 4, i.e. tenosynovitis remission. US GS grade 1 findings may be seen even in healthy individuals[110 111] and this remission definition is therefore very strict. The same outcome was used for weeks 2 and 12 (secondary outcome).

The results clearly showed that RA patients with tenosynovitis, as assessed 4 and 12 weeks after treatment benefitted from local BM injection compared to IM administered BM. The explorative patient-reported outcome showed similar results, demonstrating that the difference in treatment outcome is also clinically meaningful for the patient. Thus, the result showed that US guided BM intratenosynovial injections are superior to im injections of BM, not only assessed by imaging, but also seen from the patient's point of view.

In the planning of the study it was expected that the use of PI would provide a higher sensitivity to change, since PI includes all changes in colour information. This means that change within the same semi-quantitative score can be detected, e.g. if the grade 3 score was given at baseline and follow-up, PI could theoretically detect a difference. The results, however, showed no clinical importance of PI, and this result was in line with quantitative joint assessment by Ellegaard et al[107] and previous result from study III, demonstrating no advantages of PI compared to the semi-quantitative OMERACT scoring system.

The small sample size of the study was a relative limitation, due to increasing the risk of a type 2 error. However, the results were convincing, with a statistically significant difference between groups. The analysis was done using data imputations (intention to treat; non-responder imputation or last observation carried forward), and we found similar

results with and without the use of these imputations, supporting the reliability of our results.

US guided injections in order to ensure correct placement of the BM in the tendon sheath[112 113] were used for all patients and were well tolerated, but we have not evaluated whether US guided injections are better than blinded local injections. This question has been addressed for joints by Cunnington et al[112] in a randomised double blind study and has failed to prove a difference.
However, a recent study has reported better short term effect of US guided intratenosynovial injections compared to blinded injections of corticosteroid [40]. The primary and secondary outcome was, however, patient reported pain, which is a very biased outcome, since the injection method was not blinded for the patients. On the other hand, the US assessment was blinded for the treatment method, and showed a significant lower Doppler score in the US guided group after 4 weeks. For GS score there was no difference between the groups. Despite of some methodological weaknesses in this study, it is still indicating a relevance of using US guided intratenosynovial injections for local treatment of tenosynovitis in RA patients.
A previous study has shown long-lasting remission of injected joints and minimal side effects of intraarticular BM injection[114], which is in accordance with the findings in study IV and support that this finding has potential to improve the treatment of tenosynovitis in RA patients

## CONCLUSIONS

In relation to the specific aims of this thesis, the conclusions were:

- Doppler findings in or in close proximity to the tendon sheaths were common in wrists and fingers in healthy participants. These feeding vessels can be a source of error, not only due to their presence but also because they may be interpreted as being inside the tendon sheath due to blooming and reverberations artefacts (aim 1).
- US and MRI had high agreement using image fusion for assessment of tenosynovitis when partial volume artefacts were taken into account (aim 2).
- BFI was not a valid alternative to CD for measurement of slow flow as seen in tenosynovitis (aim 3)
- The OMERACT US scoring system for tenosynovitis had an excellent intra- and interreader agreement between trained investigators and a high ability to detect change over time (aim 4).
- Quantitative tenosynovitis assessment by pixel index had a very good intrareader agreement and moderate to good interreader agreement, but a moderate ability to detect change over time (aim 5).
- Quantitative tenosynovitis assessment demonstrated no advantages compared to the semi-quantitative OMERACT tenosynovitis scoring system (aim 6).
- The high responsiveness of both GS and CD scores indicated that the OMERACT US scoring system was useful for diagnosing and monitoring tenosynovitis among RA in clinical trials and practice (aim 7).
- Tenosynovitis remission was achieved significantly more frequently in the US guided intratenosynovial intratenosynovial glucocorticoid injection group than in the IM glucocorticoid injection group, both at 4 and 12 weeks follow-up (aim 8).
- RA patients with tenosynovitis responded significantly better clinically and by US assessment when treated with US guided intratenosynovial glucocorticoid injection compared to im glucocorticoid injection, both at 4 and 12 weeks (aim 9).

In conclusion, it is this author's opinion that US tenosynovitis assessment, especially if the OMERACT US group's semi-quantitative US scoring system is used, is well validated and can be used for monitoring in clinical trials and practice and that US guided glucocorticoid injection is a useful therapeutic option for the treatment of tenosynovitis.

### Future perspectives

The present thesis has added new knowledge on US impact on modern diagnosis, monitoring and treatment of tenosynovitis. This, combined with high availability of US in daily clinical practice, calls for further US studies of tenosynovitis in RA. Moreover the clinical utility of glucocorticoid US-guided injections at different locations, needs further studies.

Therefore, several important research questions remain to be addressed. These include the following;

- To investigate the presence of feeding vessels in or in close proximity to extensor and flexor tendon sheaths in the ankle and possible other joints.
- To compare US assessed tenosynovitis with histopathological changes
- To investigate if US assessed tenosynovitis in early undifferentiated arthritis predicts development of RA
- To investigate if a treat to target treatment including local treatment of tenosynovitis leads to a faster and deeper remission among RA patients
- To investigate if routine US assessment and treatment of tenosynovitis can lead to less erosive progression
- To investigate differences in treatment response of IM versus ultrasound guided glucocorticoid injection in joints.
- To further investigate the predictive value of US tenosynovitis for treatment response in RA

**ABBREVIATIONS (Alphabetic order)**

| | |
|---|---|
| Anti-CCP | Anti-cyclic citrullinated peptide |
| bDMARD | Biological disease-modifying anti-rheumatic drug |
| BFI | B-flow imaging |
| CDAI | Clinical Disease Activity Index |
| CD | Colour Doppler |
| csDMARDs | Conventional synthetic disease-modifying anti-rheumatic drug |
| CRP | Serum C-reactive protein |
| DAS28 | Disease Activity Score for 28 joints |
| GS | Grey scale |
| ICC | Intraclass correlation coefficients |
| MRI | Magnetic resonance imaging |
| NRI | Non-responder imputation |
| OMERACT | Outcome Measures in Rheumatology Clinical Trials |
| PCA | Percentage of close agreement |
| PEA | Percentage of exact agreement |
| PRF | Pulse repetition frequency |
| RA | Rheumatoid arthritis |
| SDAI | Simplified Disease Activity Index |
| SD | Standard deviation |
| SDC | Smallest detectable change |
| SRM | Standardized response mean |
| VAS | Visual analogue scale |
| VAS global | Patient global assessment of disease activity |
| VAS- tenosynovitis | A patient reported tendon sheath pain score on a visual analogue scale |


### English summary

Rheumatod arthritis is a chronic systemic autoimmune disease, characterized by inflammation in joints and tendon sheaths, which frequently leads to permanent and serious disability due to joint destruction, but also tendon and ligament ruptures. Clinical management of rheumatoid arthritis has traditionally been supported by biochemical and radiographic findings. However, imaging modalities like ultrasound and magnetic resonance imaging (MRI) have improved the possibility for better management of rheumatoid arthritis patients, due to higher sensitivity and specificity for detecting ongoing inflammation, this thesis is focusing on tenosynovitis as recent studies have shown that inflammation in tendon sheaths, i.e. tenosynovitis, is a very common manifestation of rheumatoid arthritis and may often be mistaken for synovitis. Furthermore, presence of ultrasonographic tenosynovitis may predict clinical flare and erosive progression.

The main aim of this PhD thesis was to further develop and validate ultrasound as a tool for diagnosis, monitoring and treatment of tenosynovitis. This was investigated in four studies:

Study I: 3D Doppler Ultrasound findings in healthy wrist and finger tendon sheaths - Can feeding vessels lead to misinterpretation in Doppler-detected tenosynovitis?

Study II: Image fusion of Ultrasound and MRI and B-flow evaluation of tenosynovitis - A pilot study on new imaging techniques in rheumatoid arthritis patients.

Study III: Validity and sensitivity to change of the semi-quantitative Outcome Measures in Rheumatology Clinical Trials (OMERACT) ultrasound scoring system for tenosynovitis in patients with rheumatoid arthritis and for the quantitative scoring system, pixel index.

Study IV: Intramuscular versus ultrasound guided intratenosynovial glucocorticoid injection for tenosynovitis in patients with rheumatoid arthritis - A randomised, double-blind, controlled study with ultrasound and clinical follow up at 4 and 12 weeks.

From the studies presented in the PhD thesis the following was concluded:

- Doppler findings in or in close proximity to the tendon sheaths were common in wrists and fingers in healthy participants. These feeding vessels may be a source of misinterpretation, i.e .wrong diagnosis of a low degree of tenosynovitis, not only due to their presence but also because they may be interpreted as being inside the tendon sheath due to blooming and reverberations artefacts.
- Ultrasound and MRI had high agreement using image fusion for assessment of tenosynovitis when MRI partial volume artefacts were taken into account. In contrast, the agreement between B-flow and ultrasound was poor, since the quality of the b-flow images and the flow sensitivity were low.
- The OMERACT ultrasound scoring system for tenosynovitis had an excellent intra- and interreader agreement between trained investigators and a high ability to detect change over time, similar the quantitative tenosynovitis assessment by pixel index had a very good intrareader agreement and moderate to good interreader agreement, but only a moderate ability to detect change over time. The ultrasound scores had a high responsiveness, indicating that the OMERACT ultrasound scoring system was useful for diagnosing and monitoring tenosynovitis in rheumatoid arthritis patients in clinical trials and practice.
- For treatment of tenosynovitis in rheumatoid arthritis patients, remission (ultrasound tenosynovitis grey scale score ≤1 and Doppler score = 0) was achieved significantly more frequently in the ultrasound guided intratenosynovial glucocorticoid injection group than in the intramuscular glucocorticoid injection group, both at 4 and 12 week follow-ups. Furthermore, tenosynovitis responded significantly better clinically and by ultrasound assessment when treated with ultrasound guided intratenosynovial glucocorticoid injection compared to intramuscular glucocorticoid injection, both at 4 and 12 week follow-ups.

**REFERENCES**


1. Young A, Dixey J, Cox N, et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). Rheumatology (Oxford) 2000;**39**(6):603-11.
2. Gerlag DM, Norris JM, Tak PP. Towards prevention of autoantibody-positive rheumatoid arthritis: from lifestyle modification to preventive treatment. Rheumatology (Oxford) 2016;**55**(4):607-14.
3. Sacks JJ, Luo YH, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. Arthritis care & research 2010;**62**(4):460-4.
4. Di WT, Vergara F, Bertiller E, et al. Incidence and Prevalence of Rheumatoid Arthritis in a Health Management Organization in Argentina: A 15-year Study. The Journal of rheumatology 2016.
5. Pedersen JK, Svendsen AJ, Horslev-Petersen K. Prevalence of rheumatoid arthritis in the southern part of denmark. The open rheumatology journal 2011;**5**:91-7.
6. Eriksson JK, Neovius M, Ernestam S, et al. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis care & research 2013;**65**(6):870-8.
7. Humphreys JH, Verstappen SM, Hyrich KL, et al. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the rheumatic diseases 2013;**72**(8):1315-20.
8. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;**376**(9746):1094-108.
9. Nieuwenhuis WP, Krabben A, Stomp W, et al. Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. Arthritis & rheumatology (Hoboken, NJ) 2015;**67**(4):869-76.
10. Hammer HB, Kvien TK. Ultrasonography shows significant improvement in wrist and ankle tenosynovitis in rheumatoid arthritis patients treated with adalimumab. Scandinavian journal of rheumatology 2011;**40**(3):178-82.
11. Wakefield RJ, O'Connor PJ, Conaghan PG, et al. Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging. Arthritis and rheumatism 2007;**57**(7):1158-64.
12. Rowbotham EL, Freeston JE, Emery P, et al. The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with rheumatoid arthritis. European radiology 2016;**26**(2):444-50.
13. Navalho M, Resende C, Rodrigues AM, et al. Bilateral evaluation of the hand and wrist in untreated early inflammatory arthritis: a comparative study of ultrasonography and magnetic resonance imaging. The Journal of rheumatology 2013;**40**(8):1282-92.
14. Lisbona MP, Maymo J, Perich J, et al. Rapid reduction in tenosynovitis of the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. Annals of the rheumatic diseases 2010;**69**(6):1117-22.
15. Loppenthin K, Esbensen BA, Jennum P, et al. Sleep quality and correlates of poor sleep in patients with rheumatoid arthritis. Clinical rheumatology 2015;**34**(12):2029-39.
16. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Annals of the rheumatic diseases 2009;**68**(6):954-60.
17. Horslev-Petersen K, Hetland ML, Ornbjerg LM, et al. Clinical and radiographic outcome of a treat-to-target strategy using methotrexate and intra-articular glucocorticoids with or without adalimumab induction: a 2-year investigator-initiated, double-blinded, randomised, controlled trial (OPERA). Annals of the rheumatic diseases 2015.
18. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and rheumatism 1995;**38**(1):44-8.
19. Ward MM, Guthrie LC, Alba MI. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. Annals of the rheumatic diseases 2015;**74**(9):1691-6.
20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism 2010;**62**(9):2569-81.
21. Nam JL, Hensor EM, Hunt L, et al. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. Annals of the rheumatic diseases 2016.

22. Freeston JE, Wakefield RJ, Conaghan PG, et al. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Annals of the rheumatic diseases 2010;**69**(2):417-9.
23. Navalho M, Resende C, Rodrigues AM, et al. Bilateral MR imaging of the hand and wrist in early and very early inflammatory arthritis: tenosynovitis is associated with progression to rheumatoid arthritis. Radiology 2012;**264**(3):823-33.
24. Eshed I, Feist E, Althoff CE, et al. Tenosynovitis of the flexor tendons of the hand detected by MRI: an early indicator of rheumatoid arthritis. Rheumatology (Oxford) 2009;**48**(8):887-91.
25. Mangnus L, van Steenbergen HW, Reijnierse M, et al. MR-detected features of inflammation and erosions occur in symptom-free persons from the general population. Arthritis & rheumatology (Hoboken, NJ) 2016.
26. McQueen FM, Benton N, Perry D, et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. Arthritis and rheumatism 2003;**48**(7):1814-27.
27. Haavardsholm EA, Boyesen P, Ostergaard M, et al. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. Annals of the rheumatic diseases 2008;**67**(6):794-800.
28. Hetland ML, Ejbjerg B, Horslev-Petersen K, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). Annals of the rheumatic diseases 2009;**68**(3):384-90.
29. Boyesen P, Haavardsholm EA, Ostergaard M, et al. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. Annals of the rheumatic diseases 2011;**70**(3):428-33.
30. Lillegraven S, Boyesen P, Hammer HB, et al. Tenosynovitis of the extensor carpi ulnaris tendon predicts erosive progression in early rheumatoid arthritis. Annals of the rheumatic diseases 2011;**70**(11):2049-50.
31. Bellis E, Scire CA, Carrara G, et al. Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the Italian Society for Rheumatology. Rheumatology (Oxford) 2016.
32. Rasch LA, van Tuyl LH, Lems WF, et al. Initial high-dose prednisolone combination therapy using COBRA and COBRA-light in early rheumatoid arthritis. Neuroimmunomodulation 2015;**22**(1-2):51-6.
33. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis and rheumatism 2006;**54**(5):1401-9.
34. Horslev-Petersen K, Hetland ML, Junker P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. Annals of the rheumatic diseases 2014;**73**(4):654-61.
35. O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. The New England journal of medicine 2013;**369**(4):307-18.
36. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Annals of the rheumatic diseases 2013;**72 Suppl 2**:ii111-5.
37. Joosten LA, Abdollahi-Roodsaz S, Dinarello CA, et al. Toll-like receptors and chronic inflammation in rheumatic diseases: new developments. Nature reviews Rheumatology 2016;**12**(6):344-57.
38. Vlad V, Berghea F, Micu M, et al. Tenosynovitis US scoring systems follow synovitis and clinical scoring systems in RA and are responsive to change after biologic therapy. Medical ultrasonography 2015;**17**(3):352-60.
39. Di Geso L, Filippucci E, Meenagh G, et al. CS injection of tenosynovitis in patients with chronic inflammatory arthritis: the role of US. Rheumatology (Oxford) 2012;**51**(7):1299-303.
40. Gutierrez M, Di Matteo A, Rosemffet M, et al. Short-term efficacy to conventional blind injection versus ultrasound-guided injection of local corticosteroids in tenosynovitis in patients with inflammatory chronic arthritis: A randomized comparative study. Joint, bone, spine : revue du rhumatisme 2015.
41. Torp-Pedersen S, Christensen R, Szkudlarek M, et al. Power and color Doppler ultrasound settings for inflammatory flow: impact on scoring of disease activity in patients with rheumatoid arthritis. Arthritis & rheumatology (Hoboken, NJ) 2015;**67**(2):386-95.
42. Weskott HP. [B-flow--a new method for detecting blood flow]. Ultraschall in der Medizin (Stuttgart, Germany : 1980) 2000;**21**(2):59-65.
43. Pellerito JS. Current approach to peripheral arterial sonography. Radiologic clinics of North America 2001;**39**(3):553-67.
44. Henri P, Tranquart F. [B-flow ultrasonographic imaging of circulating blood]. Journal de radiologie 2000;**81**(4):465-7.
45. Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Annals of the rheumatic diseases 2008;**67**(2):143-9.
46. Szkudlarek M, Klarlund M, Narvestad E, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. Arthritis research & therapy 2006;**8**(2):R52.
47. Szkudlarek M, Narvestad E, Klarlund M, et al. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. Arthritis and rheumatism 2004;**50**(7):2103-12.
48. Hmamouchi I, Bahiri R, Srifi N, et al. A comparison of ultrasound and clinical examination in the detection of flexor tenosynovitis in early arthritis. BMC musculoskeletal disorders 2011;**12**:91.
49. Backhaus M, Burmester GR, Sandrock D, et al. Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Annals of the rheumatic diseases 2002;**61**(10):895-904.
50. Milosavljevic J, Lindqvist U, Elvin A. Ultrasound and power Doppler evaluation of the hand and wrist in patients with psoriatic arthritis. Acta radiologica (Stockholm, Sweden : 1987) 2005;**46**(4):374-85.
51. Hammer HB, Bolton-King P, Bakkeheim V, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. Annals of the rheumatic diseases 2011;**70**(11):1995-8.
52. Perricone C, Ceccarelli F, Modesti M, et al. The 6-joint ultrasonographic assessment: a valid, sensitive-to-change and feasible method for evaluating joint inflammation in RA. Rheumatology (Oxford) 2012;**51**(5):866-73.
53. Backhaus M, Burmester GR, Gerber T, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Annals of the rheumatic diseases 2001;**60**(7):641-9.
54. Scheel AK, Hermann KG, Kahler E, et al. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis and rheumatism 2005;**52**(3):733-43.
55. Naredo E, Gamero F, Bonilla G, et al. Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: comparison of extended versus reduced joint evaluation. Clinical and experimental rheumatology 2005;**23**(6):881-4.
56. Taylor PC, Steuer A, Gruber J, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. Arthritis and rheumatism 2004;**50**(4):1107-16.
57. Hau M, Schultz H, Tony HP, et al. Evaluation of pannus and vascularization of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis by high-resolution ultrasound (multidimensional linear array). Arthritis and rheumatism 1999;**42**(11):2303-8.
58. Szkudlarek M, Court-Payen M, Jacobsen S, et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis and rheumatism 2003;**48**(4):955-62.

59. Qvistgaard E, Rogind H, Torp-Pedersen S, et al. Quantitative ultrasonography in rheumatoid arthritis: evaluation of inflammation by Doppler technique. Annals of the rheumatic diseases 2001;**60**(7):690-3.
60. Mandl P, Naredo E, Wakefield RJ, et al. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. The Journal of rheumatology 2011;**38**(9):2055-62.
61. Szkudlarek M, Court-Payen M, Strandberg C, et al. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis and rheumatism 2001;**44**(9):2018-23.
62. D'Agostino MA, Wakefield RJ, Berner-Hammer H, et al. Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Annals of the rheumatic diseases 2015.
63. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Spectral Doppler and resistive index. A promising tool in ultrasonographic evaluation of inflammation in rheumatoid arthritis. Acta radiologica (Stockholm, Sweden : 1987) 2003;**44**(6):645-52.
64. Naredo E, D'Agostino MA, Wakefield RJ, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Annals of the rheumatic diseases 2012.
65. Haavardsholm EA, Ostergaard M, Ejbjerg BJ, et al. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Annals of the rheumatic diseases 2007;**66**(9):1216-20.
66. Haavardsholm EA, Ostergaard M, Ejbjerg BJ, et al. Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting. Arthritis and rheumatism 2005;**52**(12):3860-7.
67. Glinatsi D, Bird P, Gandjbakhch F, et al. Reliability of an OMERACT rheumatoid arthritis tenosynovitis scoring system for wrist and hand [Abstract] FRI0521. Ann Rheum Dis 2016; .
68. Tugwell P, Bombardier C. A methodologic framework for developing and selecting endpoints in clinical trials. The Journal of rheumatology 1982;**9**(5):758-62.
69. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis and rheumatism 1993;**36**(6):729-40.
70. Ostergaard M, Wiell C. Ultrasonography in rheumatoid arthritis: a very promising method still needing more validation. Current opinion in rheumatology 2004;**16**(3):223-30.
71. Harrington JM, Carter JT, Birrell L, et al. Surveillance case definitions for work related upper limb pain syndromes. Occupational and environmental medicine 1998;**55**(4):264-71.
72. Bruynesteyn K, Boers M, Kostense P, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Annals of the rheumatic diseases 2005;**64**(2):179-82.
73. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;**1**(8476):307-10.
74. Zufferey P, Brulhart L, Tamborrini G, et al. Ultrasound evaluation of synovitis in RA: correlation with clinical disease activity and sensitivity to change in an observational cohort study. Joint, bone, spine : revue du rhumatisme 2014;**81**(3):222-7.
75. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for Outcome Measures in Rheumatology. The Journal of rheumatology 1998;**25**(2):198-9.
76. Cooper NS, Soren A, McEwen C, et al. Diagnostic specificity of synovial lesions. Human pathology 1981;**12**(4):314-28.
77. Lindblad S, Hedfors E. Intraarticular variation in synovitis. Local macroscopic and microscopic signs of inflammatory activity are significantly correlated. Arthritis and rheumatism 1985;**28**(9):977-86.
78. Smith MD, Baeten D, Ulfgren AK, et al. Standardisation of synovial tissue infiltrate analysis: how far have we come? How much further do we need to go? Annals of the rheumatic diseases 2006;**65**(1):93-100.
79. Takase K, Ohno S, Takeno M, et al. Simultaneous evaluation of long-lasting knee synovitis in patients undergoing arthroplasty by power Doppler ultrasonography and contrast-enhanced MRI in comparison with histopathology. Clinical and experimental rheumatology 2012;**30**(1):85-92.
80. Axelsen MB, Stoltenberg M, Poggenborg RP, et al. Dynamic gadolinium-enhanced magnetic resonance imaging allows accurate assessment of the synovial inflammatory activity in rheumatoid arthritis knee joints: a comparison with synovial histology. Scandinavian journal of rheumatology 2012;**41**(2):89-94.
81. Gaffney K, Cookson J, Blake D, et al. Quantification of rheumatoid synovitis by magnetic resonance imaging. Arthritis and rheumatism 1995;**38**(11):1610-7.
82. Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, et al. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium. Arthritis and rheumatism 1997;**40**(10):1856-67.
83. Ostendorf B, Peters R, Dann P, et al. Magnetic resonance imaging and miniarthroscopy of metacarpophalangeal joints: sensitive detection of morphologic changes in rheumatoid arthritis. Arthritis and rheumatism 2001;**44**(11):2492-502.
84. Tamai K, Yamato M, Yamaguchi T, et al. Dynamic magnetic resonance imaging for the evaluation of synovitis in patients with rheumatoid arthritis. Arthritis and rheumatism 1994;**37**(8):1151-7.
85. Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, et al. Quantification of synovistis by MRI: correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. Magnetic resonance imaging 1998;**16**(7):743-54.
86. Ostergaard M, Stoltenberg M, Henriksen O, et al. Quantitative assessment of synovial inflammation by dynamic gadolinium-enhanced magnetic resonance imaging. A study of the effect of intra-articular methylprednisolone on the rate of early synovial enhancement. British journal of rheumatology 1996;**35**(1):50-9.
87. Konig H, Sieper J, Wolf KJ. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. Radiology 1990;**176**(2):473-7.
88. Koski JM, Saarakkala S, Helle M, et al. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. Annals of the rheumatic diseases 2006;**65**(12):1590-5.
89. Andersen M, Ellegaard K, Hebsgaard JB, et al. Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. Annals of the rheumatic diseases 2014;**73**(4):678-83.
90. Iagnocco A, Perella C, D'Agostino MA, et al. Magnetic resonance and ultrasonography real-time fusion imaging of the hand and wrist in osteoarthritis and rheumatoid arthritis. Rheumatology (Oxford) 2011;**50**(8):1409-13.
91. Haavardsholm EA, Ostergaard M, Hammer HB, et al. Monitoring anti-TNFalpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. Annals of the rheumatic diseases 2009;**68**(10):1572-9.
92. Suzuki T, Okamoto A. Ultrasound examination of symptomatic ankles in shorter-duration rheumatoid arthritis patients often reveals tenosynovitis. Clinical and experimental rheumatology 2013;**31**(2):281-4.
93. Aga AB, Hammer HB, Olsen IC, et al. First step in the development of an ultrasound joint inflammation score for rheumatoid arthritis using a data-driven approach. Annals of the rheumatic diseases 2016;**75**(8):1444-51.
94. Gutierrez M, Pineda C, Salaffi F, et al. Is ankle involvement underestimated in rheumatoid arthritis? Results of a multicenter ultrasound study. Clinical rheumatology 2016.

95. Janta I, Valor L, De la Torre I, et al. Ultrasound-detected activity in rheumatoid arthritis on methotrexate therapy: Which joints and tendons should be assessed to predict unstable remission? Rheumatology international 2016;**36**(3):387-96.
96. Haavardsholm EA, Aga AB, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. Bmj 2016;**354**:i4205.
97. Sreerangaiah D, Grayer M, Fisher BA, et al. Quantitative power Doppler ultrasound measures of peripheral joint synovitis in poor prognosis early rheumatoid arthritis predict radiographic progression. Rheumatology (Oxford) 2016;**55**(1):89-93.
98. Lai KL, Chen DY, Chen YH, et al. Assessment of wrist joint inflammation in patients with rheumatoid arthritis by quantitative two- and three-dimensional power Doppler ultrasonography. Clinical and experimental rheumatology 2014;**32**(5):674-9.
99. Filippucci E, Meenagh G, Delle Sedie A, et al. Ultrasound imaging for the rheumatologist. XX. Sonographic assessment of hand and wrist joint involvement in rheumatoid arthritis: comparison between two- and three-dimensional ultrasonography. Clinical and experimental rheumatology 2009;**27**(2):197-200.
100. Albrecht K, Grob K, Lange U, et al. Reliability of different Doppler ultrasound quantification methods and devices in the assessment of therapeutic response in arthritis. Rheumatology (Oxford) 2008;**47**(10):1521-6.
101. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Doppler ultrasound findings in healthy wrists and finger joints. Annals of the rheumatic diseases 2004;**63**(6):644-8.
102. Millot F, Clavel G, Etchepare F, et al. Musculoskeletal ultrasonography in healthy subjects and ultrasound criteria for early arthritis (the ESPOIR cohort). The Journal of rheumatology 2011;**38**(4):613-20.
103. Carotti M, Salaffi F, Morbiducci J, et al. Colour Doppler ultrasonography evaluation of vascularization in the wrist and finger joints in rheumatoid arthritis patients and healthy subjects. European journal of radiology 2012;**81**(8):1834-8.
104. Finzel S. How to differentiate erosions and vessel channels [Abstract] SP0145. Ann Rheum Dis 2016; .
105. Liu J, Zhan W, Zhou M, et al. The feasibility study of US-MRI virtual navigation in the shoulder. Clinical imaging 2012;**36**(6):803-9.
106. Wong-On M, Til-Perez L, Balius R. Evaluation of MRI-US Fusion Technology in Sports-Related Musculoskeletal Injuries. Advances in therapy 2015;**32**(6):580-94.
107. Ellegaard K, Terslev L, Christensen R, et al. Comparison of discrimination and prognostic value of two US Doppler scoring systems in rheumatoid arthritis patients: a prospective cohort study. Clinical and experimental rheumatology 2014;**32**(4):495-500.
108. Axelsen MB, Eshed I, Horslev-Petersen K, et al. A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. Annals of the rheumatic diseases 2015;**74**(5):867-75.
109. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases 2014;**73**(3):492-509.
110. Schmidt WA, Schmidt H, Schicke B, et al. Standard reference values for musculoskeletal ultrasonography. Annals of the rheumatic diseases 2004;**63**(8):988-94.
111. Witt M, Mueller F, Nigg A, et al. Relevance of grade 1 gray-scale ultrasound findings in wrists and small joints to the assessment of subclinical synovitis in rheumatoid arthritis. Arthritis and rheumatism 2013;**65**(7):1694-701.
112. Cunnington J, Marshall N, Hide G, et al. A randomized, double-blind, controlled study of ultrasound-guided corticosteroid injection into the joint of patients with inflammatory arthritis. Arthritis and rheumatism 2010;**62**(7):1862-9.
113. Sibbitt WL, Jr., Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? The Journal of rheumatology 2009;**36**(9):1892-902.
114. Hetland ML, Ostergaard M, Ejbjerg B, et al. Short- and long-term efficacy of intra-articular injections with betamethasone as part of a treat-to-target strategy in early rheumatoid arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. Annals of the rheumatic diseases 2012;**71**(6):851-6.