Decision making **with ultrasound** in rheumatology

Myrthe van der Ven

Decision Making with Ultrasound in Rheumatology

Besluitvorming met echografie in de reumatologie

Myrthe van der Ven

Colofon

ISBN 978-94-6332-275-1

Cover design: Gregor Hoelen
Lay-out: Ferdinand van Nispen, CitroenVlinder DTP & Vormgeving, *my*-thesis.nl
Printed by: GVO drukkers & vormgevers B.V., Ede, the Netherlands

Financial support for the publication of this thesis was kindly provided by the Erasmus University Medical Center Rotterdam, Pfizer B.V. and Esaote B.V.

Decision Making with Ultrasound in Rheumatology

Besluitvorming met echografie in de reumatologie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 14 februari 2018 om 13.30 uur

door

Myrthe van der Ven
geboren te Roosendaal en Nispen

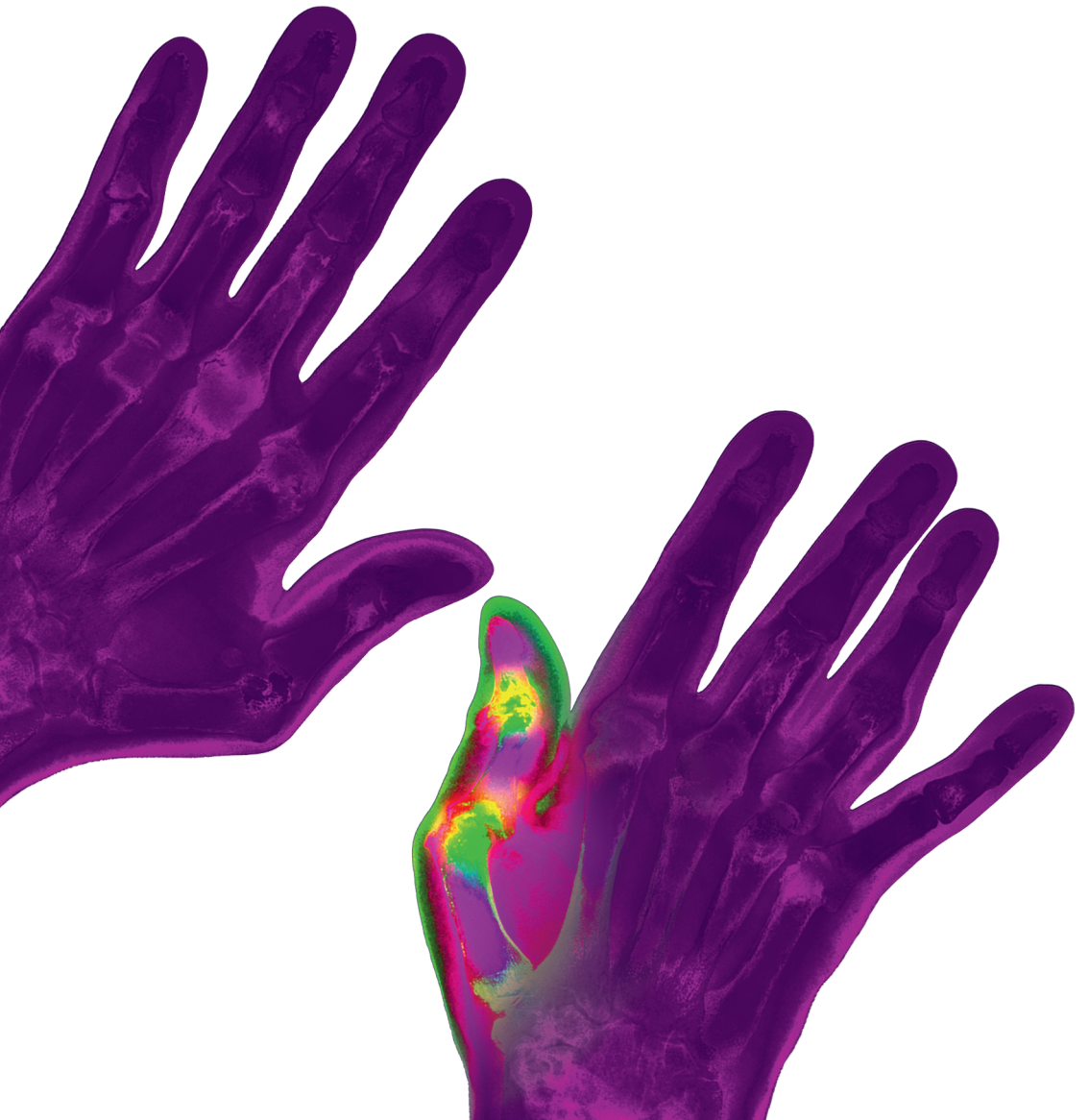
Erasmus University Rotterdam

Erasmus

Promotiecommissie:

Promotor:	Prof.dr. J.M.W. Hazes
Overige leden:	Prof.dr. W.J. Niessen Prof.dr. A.H.M. van der Helm – van Mil Dr. J.W.G. Jacobs
Copromotor:	Dr. J.J. Luime

Table of contents



CHAPTER 1

Introduction, aims and outline

Over the last years ultrasound has become an important tool in the assessment of rheumatic diseases, as it accurately detects many essential lesions including joint effusion, synovial hypertrophy, enthesopathy, bursitis and bone erosions. This introduction will start with a short background in ultrasound physics. This is followed by current perspectives of ultrasound in early recognition, diagnosis and monitoring in rheumatology and the challenges that are faced. The introduction will end with the aims and outline of this thesis.

Basic ultrasound physics

Ultrasound B-mode [1,2]

Sounds with a frequency above 20,000Hz are called ultrasonic, since these frequencies are above the range of the human hearing (20-20,000Hz) [Figure 1]. The frequencies used for ultrasound imaging vary significantly dependent on the application, for diagnostic ultrasound frequency ranges from 5MHz to 20MHz.

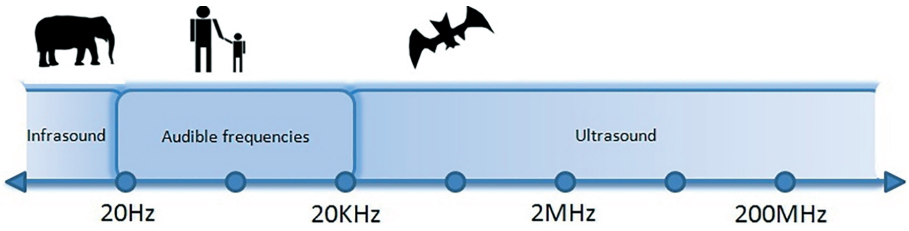


Figure 1. Range of sound frequencies with the audible range (20Hz-20kHz) and the ultrasonic range (>20kHz).

When sound is emitted at short bursts, ultrasound waves are generated and machines receive the reflected echoes. Soundwaves are emitted from piezoelectric crystals from the ultrasound transducer. These crystals are fabricated from material that changes electrical signals to mechanical vibrations and vice versa. This property is called the piezoelectric effect. Ultrasound pulses are formed by applying electrical waveforms to the piezoelectric element, causing it to vibrate and emit mechanical ultrasound waves. Mechanical waves must travel through physical medium like air, water or tissue. As ultrasound waves pass through various body tissues, they are reflected back to the transducer where the vibrations are converted by the piezoelectric material into electrical signals, creating an image on the screen as a brightness-mode (B-mode; grayscale) image [Figure 2]. Ultrasound transducers consist of arrays of many narrow

piezoelectric elements. In linear-array transducers, the ultrasound beam is created by electrically exciting only a subset of these elements. Successive beams are obtained by shifting the subset of excited elements across the array, shifting the beam laterally. Ultrasound images result from the interaction of the incident ultrasound pulse with structures in the tissue. When an incident ultrasound pulse encounters an interface between two types of tissue with different acoustic impedance a partially reflected echo will travel back to the transducer and a partially transmitted pulse will travel deeper into the patient. Acoustic impedance is defined as the resistance for propagation of ultrasound waves. The acoustic impedance varies according to the density of the tissue. The intensity of the reflected echo increases with increasing impedance difference between two tissues. If two tissues have identical impedance, no echo results. As ultrasound pulses and echoes travel through tissue, their intensity is reduced. This is called attenuation. Attenuation is due to reflection and scattering, which remove intensity from the pulse. These losses result from the induced oscillatory tissue motion produced by the pulse, which causes conversion of energy from the original mechanical wave into heat. This is referred to as absorption and is the most important component of ultrasound attenuation. Longer path lengths (depths) and higher frequencies result in greater attenuation. The frequency dependence of attenuation suggests that to image structures deep in the body, lower ultrasound frequencies are needed to ensure that adequate echo intensity is detected by the transducer.

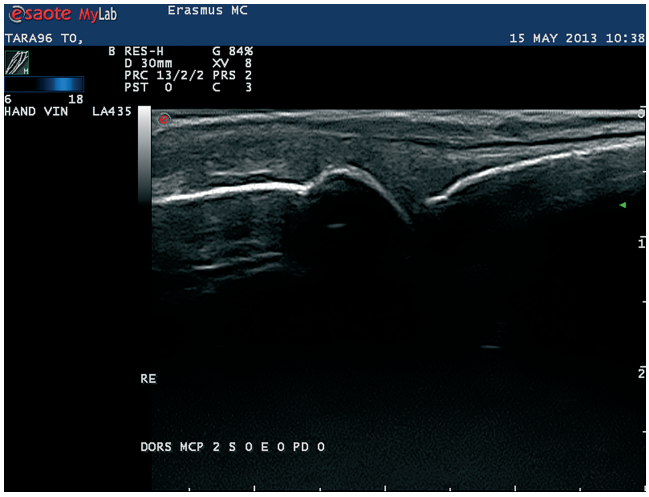


Figure 2. B-mode (grayscale) ultrasound image of an MCP2 joint. The white line on the right hand side of the image is the proximal phalanx; from the middle to the left is the caput of the metacarpal bone.

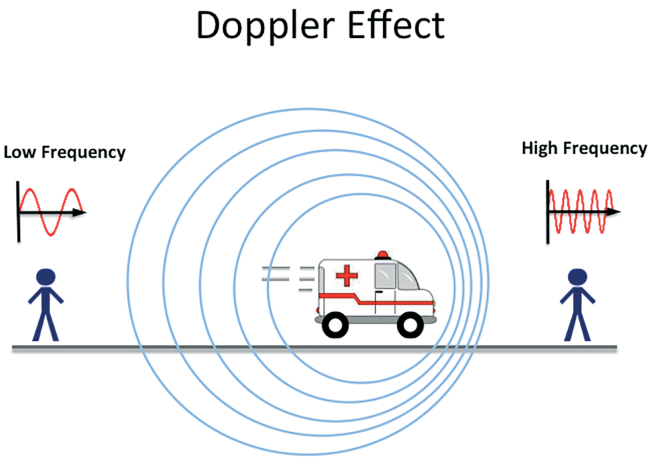


Figure 3. The Doppler effect is experienced when a vehicle approaches, passes and moves away from an observer. The received frequency is higher during approach and lower during the recession.

Ultrasound Doppler mode [3]

The Doppler effect has been used in medicine for over 50 years. Advances in equipment and data processing have made it possible to use the Doppler effect to visualise flow. The Doppler effect is commonly experienced when a vehicle sounding a siren or horn approaches, passes and moves away from an observer [Figure 3]. Compared to the emitted frequency, the received frequency is higher during the approach, identical at the instant of passing by, and lower during the recession. The shift in frequency is related to the contraction or expansion of wavelengths ahead of or behind the sound-emitting moving vehicle. In ultrasound there is a Doppler effect with the sound arriving at the moving object (red blood cells) and a Doppler effect as the sound is reflected from that object back toward the ultrasound transducer. From the frequency shift estimates of blood flow velocity can be produced by ultrasound machines, which is valuable clinical information. However, there are a number of complicating aspects of which some are related to the geometry of the blood vessel and the ultrasound beam; others are related to varying blood flow velocities across the vessel lumen and variation of velocity with the cardiac cycle. There are various manners to process Doppler ultrasound, like continuous-wave Doppler ultrasound, pulsed-wave Doppler ultrasound, colour Doppler ultrasound and power Doppler ultrasound. Power Doppler ultrasound is most commonly used in rheumatological clinical practice to detect blood flow, which would indicate ongoing inflammation. Power Doppler imaging adds all of the Doppler shift frequencies and presents on the display a pixel intensity based on that summed value. In power Doppler mode only the intensity of the Doppler shift is shown, the velocity information and directional information are not preserved.

The advantages of power Doppler ultrasound in comparison with other Doppler imaging modes is that slow flows and small vessels are more readily depicted due to the fact that all phase shifts are summed up.

Current perspectives on ultrasound in rheumatology

The importance of early diagnosis and accurate monitoring of inflammation in rheumatic diseases has contributed to the increasing interest in ultrasound.[4] Minimising disease activity through strict monitoring and aggressive treatment (tight-control) improves long-term outcomes for patients with rheumatoid arthritis (RA), including radiographic progression and increased remission rates.[5] Since ultrasound is more sensitive than physical examination in the detection of synovitis, it is increasingly used in daily clinical practice.[6, 7] Yet, its added value to the already existing diagnostic and monitoring tools needs to be established. Ultrasound synovitis is based on grayscale (GS; B-mode) ultrasound images combined with the power Doppler mode.[8]

Inflammatory arthralgia

Up till now it has been fairly difficult to identify those arthralgia patients who would benefit from early initiation of treatment. Although ACPA positivity is a good predictor for those patients who will develop inflammatory arthritis (IA) within a year, it is still difficult to distinguish at patient level. Recent developments in ultrasound suggest that earlier detection of inflammation should be possible before clinical manifestation. Therefore, the prognostic value of ultrasound in patients with inflammatory arthralgia has been investigated. In auto-antibody positive arthralgia patients, patients with ultrasound synovitis had an increased risk for developing IA.[9, 10] In the seronegative patients the prediction of IA is even more difficult and the added value of ultrasound needs to be addressed more extensively.

Rheumatoid arthritis

A European League Against Rheumatism (EULAR) task force developed recommendations for the use of imaging of joints in the clinical management of RA.[11] One of their recommendations was, when there is diagnostic doubt, ultrasound can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.[12, 13] The value of ultrasound in classifying patients as having RA, has also been recognised in the 2010 ACR/EULAR classification criteria for RA, which includes imaging evidence of synovitis in joint involvement.[14] In addition, in RA patients who were clinically in remission ongoing active ultrasound synovitis has been found in 48-73% of the

patients.[6, 15-18] In these RA patients, ultrasound synovitis (power Doppler positive) predicts short-term relapse and radiographic progression.[16, 19-22] This means ultrasound could be used as a tool to monitor RA patients to identify patients who can taper their medication or to recognise those patients who might need more intensive treatment.

Psoriatic arthritis

Psoriatic arthritis (PsA) is a progressive inflammatory disease, that can lead to serious joint damage over time.[23] It can manifest with peripheral arthritis, mostly in an asymmetrical distribution, but also with entheseal or spinal involvement. Since the introduction of the CASPAR classification criteria for PsA in 2006, psoriasis patients can classify as PsA with only enthesitis as inflammatory articular involvement.[24] However, there are difficulties regarding clinical assessment of the entheses such as overuse and anatomical location, which could lead to clinically false-positive patients.[25-27] Assessment of the entheses could be improved by using ultrasound, especially the power Doppler mode.[28, 29] In addition, it is possible to differentiate patients with PsA from healthy controls with ultrasound.[30, 31] Since it is important to diagnose PsA at an early stage, the prevalence of PsA in primary care psoriasis patients was studied by Karreman et al.[32] The frequency of PsA in psoriasis patients was estimated to be 3.1% for arthritis and axial disease, increasing to 4.6% when enthesitis would be included. To differentiate between active inflammation and other manifestations of enthesopathy ultrasound could be a tool to diagnose enthesitis.

Challenges regarding ultrasound in rheumatology

At this moment several clinical questions regarding ultrasound in rheumatic diseases are addressed. However, there is still a large amount of research required to determine the added value of ultrasound and to optimise the use of ultrasound in current clinical practice. Technological developments in ultrasound machines could also improve early detection of inflammation. Developments in 3D ultrasound, plane wave imaging and contrast imaging are very promising.[33-36]

Plane wave ultrasound imaging

Clinical application of ultrasonic plane wave imaging was made possible by advances in the electronic hardware of ultrasound machines. With the use of plane wave imaging ultrafast frame rates can be achieved, since the entire field of view is imaged with a single transmission [Figure 4B].[37] Backscattered echoes are simultaneously recorded form the entire scan plane,

and all imaging lines are simultaneously computed using parallel beamforming processes. The increase in frame rate comes at the expense of image contrast and spatial resolution. To improve image quality, a set of plane waves can be sent at different angles at an ultrafast frame rate, which is called compounding [Figure 4C, 4D].

High-frame rate ensures high temporal correlation between frames, which facilitates good separation between relatively slow tissuemotion, and blood flow. Therefore, this technique allows detection of slow flow in very small vessels.[34, 37, 38] The high temporal correlation between frames also allows for using spatial correlation to further discriminate blood flow in small localised vessels from global motion of soft tissue and bone.[39, 40] Since high-frame rate Doppler ultrasound imaging is more sensitive to low flow than conventional ultrasound, it might provide accurate detection of active inflammation in joints of RA patients. This could enable earlier diagnosis of RA and better treatment monitoring.

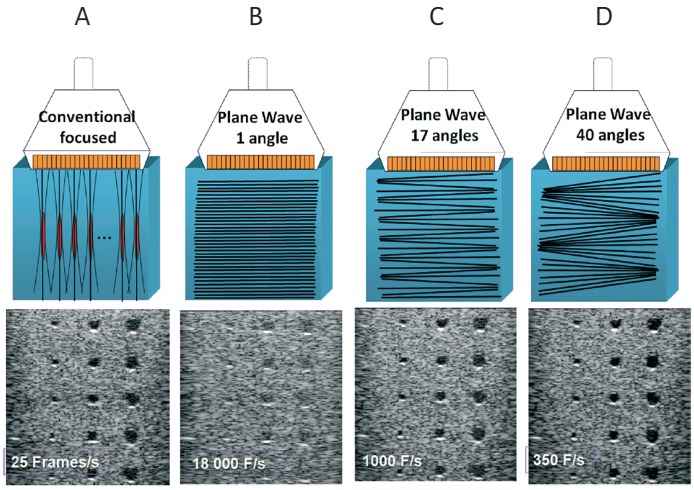


Figure 4. Conventional focused and ultrafast ultrasound imaging sequences (4-cm deep region of interest): (a) conventional focused imaging, (b) plane-wave imaging, (c) plane-wave compounding with 17 angles, and (d) plane-wave compounding with 40 angles. [Adapted from Tanter et al.[34]]

Aims and outline of this thesis

The aims of this thesis were:

1. to evaluate the added value of ultrasound in clinical decision making in:
   a. Patients with arthralgia
   b. Patients with psoriasis
   c. Monitoring RA patients
2. to increase sensitivity of power Doppler ultrasound for MCP joints.

Early diagnosis of RA and thereby facilitating early initiation of effective disease-modifying drugs can slow down disease progression and diminish joint damage.[41] With the introduction of the 2010 ACR/EULAR classification criteria for RA we are able to classify patients as having RA at an earlier stage.[14] **Chapter 2** will describe which cut point of the 2010 criteria would enable us to earlier identify RA patients among recent onset inflammatory arthritis patients.

Part one – Ultrasound in clinical practice

Since physical examination reached its maximum to identify synovitis, the first chapters of this thesis focus on the added value of ultrasound in daily clinical practice. The association of ultrasound inflammation and the development of inflammatory arthritis in an early arthralgia cohort is described in **chapter 3**. In **chapter 4** the frequency of ultrasound enthesitis in primary care psoriasis patients with musculoskeletal complaints is explored. The course of ultrasound inflammation and clinical findings in the feet in newly diagnosed RA patients is investigated in **chapter 5**. The association of the presence of ultrasound synovitis and health status in RA patients who are in clinical remission is studied in **chapter 6**. The focus of **chapter 7** is to evaluate if ultrasound synovitis is a biomarker for clinical flare in RA patients who are tapering their medication.

Part two – Experimental technical research

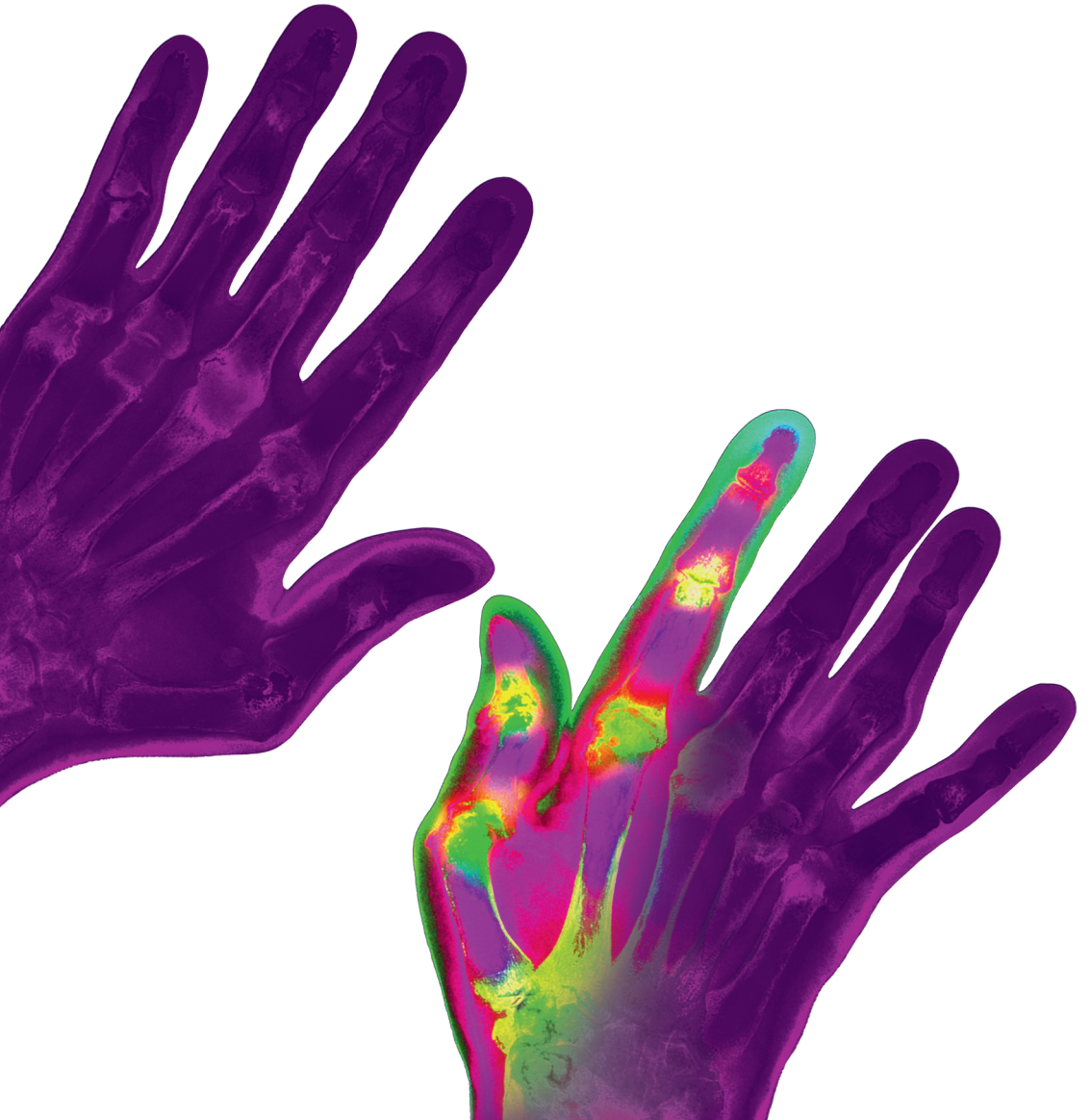
The performance of the power Doppler modality of several ultrasound machines is compared by a flow phantom and this study is described in **chapter 8**. The same flow phantom was used to compare conventional ultrasound with high-frame rate Doppler ultrasound, which is explored in **chapter 9**. This chapter also gives the results of high-frame rate Doppler ultrasound imaging in RA patients to evaluate whether it is possible to detect higher levels of vascularisation than with conventional ultrasound.

In **chapter 10** the conclusions of this thesis are discussed in light of current practice and implications for future research. Finally, in the **addendum** a summary of the complete thesis is given.

References

1. Abu-Zidan FM, Hefny AF, Corr P. Clinical ultrasound physics. J Emerg Trauma Shock. 2011;4(4):501-3.
2. Hangiandreou NJ. AAPM/RSNA physics tutorial for residents. Topics in US: B-mode US: basic concepts and new technology. Radiographics. 2003;23(4):1019-33.
3. Boote EJ. AAPM/RSNA physics tutorial for residents: topics in US: Doppler US techniques: concepts of blood flow detection and flow dynamics. Radiographics. 2003;23(5):1315-27.
4. Brown AK. Using ultrasonography to facilitate best practice in diagnosis and management of RA. Nat Rev Rheumatol. 2009;5(12):698-706.
5. Wells AF, Haddad RH. Emerging role of ultrasonography in rheumatoid arthritis: optimizing diagnosis, measuring disease activity and identifying prognostic factors. Ultrasound Med Biol. 2011;37(8):1173-84.
6. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54(12):3761-73.
7. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis. 2005;64(3):375-81.
8. Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM, et al. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis - a systematic review of the literature. Arthritis Res Ther. 2013;15(1):R4.
9. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis. 2015;74(9):1659-66.
10. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther. 2010;12(3):R98.
11. Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804-14.
12. Rezaei H, Torp-Pedersen S, af Klint E, Backheden M, Kisten Y, Gyori N, et al. Diagnostic utility of musculoskeletal ultrasound in patients with suspected arthritis--a probabilistic approach. Arthritis Res Ther. 2014;16(5):448.
13. Tamas MM, Rednic N, Felea I, Rednic S. Ultrasound assessment for the rapid classification of early arthritis patients. J Investig Med. 2013;61(8):1184-91.
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
15. Ozgocmen S, Ozdemir H, Kiris A, Bozgeyik Z, Ardicoglu O. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. South Med J. 2008;101(3):240-5.
16. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis. 2011;70(1):172-5.
17. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum. 2009;60(7):1915-22.
18. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456-65.
19. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis. 2012;71(8):1316-21.
20. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford). 2009;48(9):1092-7.

21. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
22. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum. 2012;64(1):67-76.
23. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64 Suppl 2:ii14-7.
24. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73.
25. Mandl P, Niedermayer DS, Balint PV. Ultrasound for enthesitis: handle with care! Ann Rheum Dis. 2012;71(4):477-9.
26. McGonagle DG, Helliwell P, Veale D. Enthesitis in psoriatic disease. Dermatology. 2012;225(2):100-9.
27. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. J Rheumatol. 2006;33(7):1435-8.
28. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. Arthritis Rheum. 2003;48(2):523-33.
29. Kiris A, Kaya A, Ozgocmen S, Kocakoc E. Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. Skeletal Radiol. 2006;35(7):522-8.
30. Eder L, Jayakar J, Thavaneswaran A, Haddad A, Chandran V, Salonen D, et al. Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? J Rheumatol. 2014;41(3):466-72.
31. Munoz-Fernandez S, de Miguel E, Cobo-Ibanez T, Madero R, Ferreira A, Hidalgo MV, et al. Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis. Arthritis Rheum. 2009;60(7):1985-90.
32. Karreman MC, Weel AE, van der Ven M, Vis M, Tchetverikov I, Nijsten TE, et al. Prevalence of Psoriatic Arthritis in Primary Care Patients with Psoriasis. Arthritis Rheumatol. 2015.
33. Maresca D, Tanter M, Pernot M, editors. Ultrasound microangiography of the metacarophalangeal joint using ultrafast Doppler. IEEE International Ultrasonics Symposium, IUS; 2014.
34. Tanter M, Fink M. Ultrafast imaging in biomedical ultrasound. IEEE Trans Ultrason Ferroelectr Freq Control. 2014;61(1):102-19.
35. Filippucci E, Meenagh G, Delle Sedie A, Salaffi F, Riente L, Iagnocco 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. Clin Exp Rheumatol. 2009;27(2):197-200.
36. Ohrndorf S, Hensch A, Naumann L, Hermann KG, Scheurig-Munkler C, Meier S, et al. Contrast-enhanced ultrasonography is more sensitive than grayscale and power Doppler ultrasonography compared to MRI in therapy monitoring of rheumatoid arthritis patients. Ultraschall Med. 2011;32 Suppl 2:E38-44.
37. Bercoff J, Montaldo G, Loupas T, Savery D, Meziere F, Fink M, et al. Ultrafast compound Doppler imaging: providing full blood flow characterization. IEEE Trans Ultrason Ferroelectr Freq Control. 2011;58(1):134-47.
38. Maresca D, Skachkov I, Renaud G, Jansen K, van Soest G, de Jong N, et al. Imaging microvasculature with contrast-enhanced ultraharmonic ultrasound. Ultrasound Med Biol. 2014;40(6):1318-28.
39. Song P, Manduca A, Trzasko JD, Chen S. Ultrasound Small Vessel Imaging With Block-Wise Adaptive Local Clutter Filtering. IEEE Trans Med Imaging. 2017;36(1):251-62.
40. Demene C, Deffieux T, Pernot M, Osmanski BF, Biran V, Gennisson JL, et al. Spatiotemporal Clutter Filtering of Ultrafast Ultrasound Data Highly Increases Doppler and fUltrasound Sensitivity. IEEE Trans Med Imaging. 2015;34(11):2271-85.
41. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum. 2006;55(6):864-72.



CHAPTER 2

Do we need to lower the cut point of the 2010 ACR/EULAR classification criteria for diagnosing rheumatoid arthritis?

Myrthe van der Ven
Celina Alves
Jolanda J. Luime
Andreas H. Gerards
Pieternella J. Barendregt
Derkjen van Zeben
Barbara van Schaeybroeck
Peter B.J. de Sonnaville
Bernard A. Grillet
Johanna M.W. Hazes

Rheumatology (Oxford). 2016 Apr;55(4):636-9

Abstract

Objectives: In part of the patients who do not fulfil the 2010 ACR/EULAR classification criteria at first consultation (<6 points) arthritis persists. To be able to identify more patients with rheumatoid arthritis, we evaluated the effect of lowering the cut point of the 2010 criteria.

Methods: We included early arthritis patients from the Rotterdam Early Arthritis Cohort (REACH) with at least one joint with clinical synovitis and symptoms less than 1 year with no other explanation for their symptoms. Demographic and clinical characteristics of each patient were recorded at baseline. Patients were classified as case or non-case at 1 year follow-up by the definition used in the development of the 2010 criteria (methotrexate initiation). To assess diagnostic performance of the 2010 criteria sensitivity and specificity at each cut point was determined.

Results: We included 557 patients in our analysis. After 1 year follow-up 253 patients (45%) were classified as case (methotrexate use). In the group of patients who scored 0-5 points (n=328) 98 patients (30%) were classified as case (methotrexate use). Sensitivity and specificity of the 2010 criteria using the cut point of 6 were 61% and 76% respectively. With the cut point of 5, sensitivity would increase to 76% and specificity would decrease to 68%.

Conclusions: By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify 15% more rheumatoid arthritis patients at the cost of 8% more false-positive patients.

Introduction

Recently, the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis (RA) were developed to facilitate research in earlier stages of the disease. The 2010 criteria also facilitate optimal use of the window of opportunity by starting disease modifying drugs at an earlier time point.[1] The 2010 criteria assign the risk or probability of developing RA on a continuous score (from 0 to 10). A score of ≥6/10 is needed to classify a patient as having definite RA.

Some of the patients in whom arthritis persists over time do not fulfil the 2010 criteria (<6/10 points) at first consultation.[2] In unselected early arthritis cohorts, the proportion of missed persistent arthritis patients can increase to almost 40%, which is likely to reflect the case-load of daily practice.[3] As Krabben et al. showed neither ACPA nor the Leiden prediction rule are able to identify which individual patients will be missed by the 2010 criteria.[4] Therefore, we need another way to identify patients whose arthritis will persist.

The developers of the 2010 criteria suggest that there is scope for using other cut points for different purposes.[1] In this study we evaluated which cut point of the 2010 criteria would enable us to identify more early rheumatoid arthritis patients among early inflammatory arthritis patients at first consultation.

Methods

Patients

For the present study we used clinical data from early arthritis patients from the Rotterdam Early Arthritis Cohort (REACH). These patients had at least one joint with clinical synovitis and had symptoms for less than 1 year with no other explanation for their symptoms. Patients were recruited via their general practitioner, or via the outpatient rheumatology clinic. Patients were included in REACH in case of one or more swollen joints. Patients were excluded if their symptoms resulted from trauma or overuse, if their symptoms were present for over 12 months, or if they were younger than 16 years. For a detailed description of REACH, see Alves et al.[5]

Each patient was assigned a score from 0 to 10 points using the four domains of the 2010 criteria: i) joint involvement; ii) serology; iii) acute-phase reactants; iv) symptom duration.[1] If results were not available for a domain, results were regarded as normal or

negative following the guidelines of the developers of the 2010 criteria.[6] Demographic and clinical characteristics of each patient were recorded at baseline, 6 months and 12 months. Data collection included a detailed medical examination (swollen joint count, tender joint count), laboratory variables (ACPA, RF, ESR), diagnosis and medication used.

Written informed consent was obtained from the participants according to the declaration of Helsinki. The REACH study was approved by the local medical ethic committee of Erasmus MC, University Medical Center Rotterdam, the Netherlands. This secondary analysis was covered by this ethical approval.

Case definition

Patients were classified as case (true-positive patients) or non-case after 1 year follow-up by the definition used in the development of the 2010 criteria.[1] This definition includes the use of methotrexate (MTX) after one year. If a patient had to stop MTX due to side-effects, and was assigned another DMARD, it was also considered a case. If no MTX was used and no other classifiable disease was present after one year follow-up the patient was regarded a non-case.

Statistical analysis

Discriminative performance of the 2010 criteria in relation to the case definition was determined by calculating the receiver operating characteristic (ROC) curve. Sensitivity and specificity were calculated for each cut point (0-10 points). To obtain information on potential other clinical characteristics that could help improve the diagnostic performance we tested differences between cases and non-cases among the patients with <6/10 points using the independent T-test or Wilcoxon-Mann-Whitney test depending on the distribution of the data. Frequencies were compared using a Chi-square test. Analyses were done using STATA 12.0.

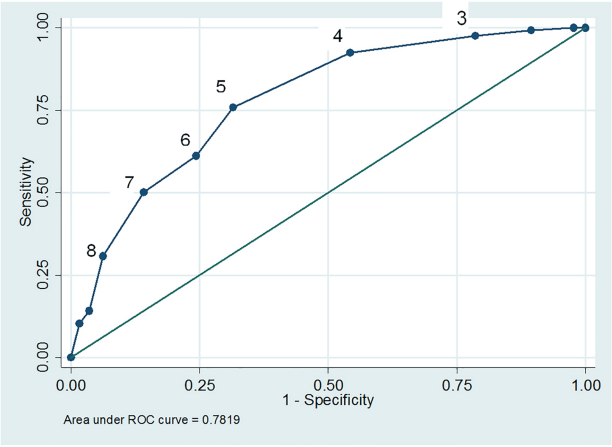
Results

In REACH we identified 726 early arthritis patients. At baseline we excluded 169 patients with another classifiable disease, such as gout, psoriatic arthritis and systemic diseases. Consequently, in 557 patients the 2010 criteria could be applied of which 328 patients (69%) obtained a score from 0 to 5.

Sensitivity and specificity 2010 criteria

The ROC curve was calculated for the 2010 criteria in relation to MTX use in the total study population (0-10 points; n=557) [Figure 1]. The area under the ROC curve (AUC) was 0.79 (SE 0.02). From this curve sensitivity and specificity for each score were determined.

Sensitivity and specificity of the 2010 criteria using the cut point of 6 were 61% and 76% respectively. With the cut point of 5, sensitivity increased to 76% and specificity decreased to 68%. Among patients with 5 points (n=59) 22 patients (37%) would be false-positively classified as RA. After one year follow-up the diagnosis of these false-positive patients was osteoarthritis (n=2) or remitting oligoarthritis/polyarthritis (n=20) .



Cut point	Sens (%)	Spec (%)
0	100	0
1	100	2
2	99	11
3	98	21
4	92	46
5	76	68
6	61	76
7	50	86
8	31	94
9	14	96
10	10	98

Figure 1. The receiver operator characteristic curve, and sensitivity (Sens) and specificity (Spec) for the 2010 criteria and MTX use (n = 557)

Patients with 0-5 points

In the patients with 0-5 points (n=328) 98 patients (30%) used MTX (case) after 1 year follow-up. The distribution of cases and non-cases over the 2010 score can be described that patients with a higher score on the 2010 criteria showed a higher frequency of MTX use after one year.

Characteristics of patients with MTX (case; n=98) were compared with patients who did not use MTX (non-case; n=230) [Table 1]. Patients who used MTX tended to have more tender and swollen joints and higher ESR values, but showed no differences on the other characteristics such as rheumatoid factor and ACPA positivity.

Table 1 Baseline characteristics of patients with 0-5 points who used MTX after 1 year follow-up (case) and of those patients who did not use MTX (non-case)

	Case (MTX use) (n=98)	Non-case (n=230)	p-value*
Women, %	69	67	0.667
Age, mean (s.d.), years	54 (16)	50 (16)	0.051
SJC, median (IQR)	5 (3-7)	2 (1-4)	<0.001
TJC, median (IQR)	9 (4-12)	5 (2-10)	<0.001
RF positive, %	7	5	0.494
ACCP positive, %	2	5	0.370
ESR, median (IQR)	24 (12-39)	13 (6-25)	<0.001
CRP, median (IQR)	6 (3-35)	5 (2-16) mv=50	0.032
Morning stiffness, median (IQR), min	60 (30-140) mv=20	45 (30-90) mv=78	0.034
DAS44 score, mean (s.d.)	4.6 (1.0)	3.8 (1.1)	<0.001
Symptom duration, median (IQR), months	3 (2-6)	3 (1-5)	0.029
MCP symmetry, %	62	40	<0.001
PIP symmetry, %	46	36	0.077
Wrist symmetry, %	39	19	<0.001
MTP symmetry, %	12	7	0.164

s.d. = standard deviation, IQR = interquartile range, mv = missing values, *depending on distribution of the data we used independent T-test or Wilcoxon-Mann-Whitney test, frequencies were compared using a Chi-square test

Discussion

By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify 15% more rheumatoid arthritis patients at a cost of 8% more false-positive patients. If these reclassified patients had started DMARD therapy after first consultation, 2/3 of the patients would have received optimal treatment earlier, while the other 1/3 of the patients might not have needed this treatment, as their symptoms were not related to the presence of RA. Each rheumatologist has to weigh the benefit of early treatment in true-positive rheumatoid arthritis patients against the harm of treatment in oligoarthritis/polyarthritis and osteoarthritis patients, i.e. the false-positive patients. Balancing the benefit and harm of treatment depends on the safety profile of the DMARDs and the quality of life lost if true-positive patients are left untreated.[7] In general, the safety profile of the different DMARDs is regarded as acceptable in the treatment of RA[8], but it is not clear whether this also holds for arthritis patients who score 5 points. Treatment in arthritis patients with 5 points seems beneficial[9], but none of these studies have evaluated the potentially negative effect of treatment in the false-positive patients. In terms of quality of life, Geuskens et al found no difference in health-related quality of life between RA patients and non-RA patients[10], which might

imply that treatment in arthritis patients with 5 points will improve their quality of life. Data is lacking on the presence of off-days mentioned by patients, which affects worker productivity due to the side-effects of medication.

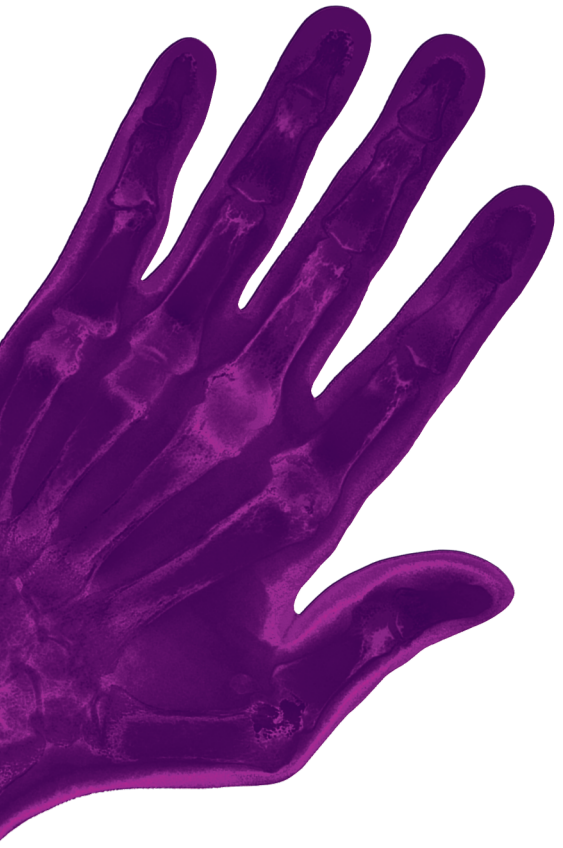
The characteristics of the patients with 0-5 points (n=328) differed little between those with and those without MTX. Although swollen and tender joint counts differed, the differences were not strong enough to be used as an additional diagnostic criterion [data not shown]. This is in accordance with findings of Krabben et al.[4] To reduce over-treatment in false-positive patients and to be more certain which patients could start early DMARD treatment, it might be beneficial to add other (imaging) biomarkers that distinguish true positive patients from false-positive patients at an earlier stage.[11-13] Nevertheless, lowering the cut point from 6 to 5 points would be a more feasible way to identify more persistent arthritis patients. This study showed that 2/3 of the patients with 5 points were already treated with MTX after one year follow-up, which could indicate that our results reflected daily clinical practice.

Our study has certain strengths and limitations. The REACH dataset was one of the early arthritis cohorts included in the pooled analysis to develop the new criteria for RA.[1, 14] The cut point of 6 was chosen using the AUC of three cohorts, including REACH. When we removed those patients (n=184) from our analysis, the results were similar [data not shown]. However, external validation of our results in another early arthritis cohort is recommended. Especially larger cohorts could advance our work and could give more insight in other variables. The strength of our study includes the selection of patients, which was not biased towards RA. In REACH, no limits were set regarding the minimal number of swollen joints required, and the sample represents patients in an early phase of their disease (median duration of symptoms of 3 months).

In conclusion, by lowering the cut point of the 2010 criteria, we identified more rheumatoid arthritis patients in whom early treatment could have been initiated. This could have led to better patient outcomes.

References

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569-81.
2. Krabben A, Huizinga TW, van der Helm-van Mil AH. Undifferentiated arthritis characteristics and outcomes when applying the 2010 and 1987 criteria for rheumatoid arthritis. Ann Rheum Dis 2012;71(2):238-41.
3. Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2013.
4. Krabben A, Abhishek A, Britsemmer K, Filer A, Huizinga TWJ, Raza K, et al. Risk of rheumatoid arthritis development in patients with unclassified arthritis according to the 2010 ACR/EULAR criteria for rheumatoid arthritis. Rheumatology 2013;52(7):1265-70.
5. Alves C, Luime JJ, van Zeben D, Huisman AM, Weel AE, Barendregt PJ, et al. Diagnostic performance of the ACR/EULAR 2010 criteria for rheumatoid arthritis and two diagnostic algorithms in an early arthritis clinic (REACH). Ann Rheum Dis 2011;70(9):1645-7.
6. Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum 2010;62(9):2582-91.
7. Verstappen SMM, McCoy MJ, Roberts C, Dale NE, Hassell AB, Symmons DPM, et al. Disease Activity, Smoking, and Reproductive-related Predictors of Poor Prognosis in Patients with Very Early Inflammatory Polyarthritis. Journal of Rheumatology 2011;38(3):429-33.
8. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014;73(3):529-35.
9. Wevers-de Boer KVC, Heimans L, Huizinga TWJ, Allaart CF. Drug therapy in undifferentiated arthritis: a systematic literature review. Annals of the Rheumatic Diseases 2013;72(9):1436-44.
10. Geuskens GA, Burdorf A, Evers AW, Hazes JM. Clear associations between demographic and psychosocial factors and health-related quality of life in patients with early inflammatory joint complaints. J Rheumatol 2008;35(9):1754-61.
11. Bakker MF, Cavet G, Jacobs JW, Bijlsma JW, Haney DJ, Shen Y, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis 2012;71(10):1692-7.
12. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis 2011;70(3):500-7.
13. Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Ann Rheum Dis 2004;63(4):382-5.
14. Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Methodological Report Phase I. Annals of the Rheumatic Diseases 2010;69(9):1589-95.



PART ONE

Ultrasound in clinical practice

CHAPTER 3

Absence of ultrasound inflammation in patients presenting with arthralgia rules out the development of arthritis

Myrthe van der Ven
Marjolein van der Veer-Meerkerk
David F. ten Cate
Nigara Rasappu
Marc R.Kok
Dora Csakvari
Johanna M.W. Hazes
Andreas H. Gerards
Jolanda J. Luime

Arthritis Res Ther. 2017 Sep 15;19(1):202. [Epub ahead of print]

Abstract

Background: To decrease burden of disease of rheumatoid arthritis (RA) we need to identify patients at risk for RA as early as possible, preferably as no clinical apparent synovitis could be detected yet. Up to now it has been fairly difficult to identify those arthralgia patients who develop inflammatory arthritis (IA), but recent studies in ultrasound suggest that earlier detection is possible. We aim to identify arthralgia patients developing IA within a year using ultrasound to detect subclinical synovitis at first consultation.

Methods: In a multi-centre cohort study we followed arthralgia patients with ≥2 painful joints of hands, feet or shoulders without clinical synovitis over one year. Symptom duration was <1 year and symptoms were not explained by other conditions. At baseline, 6 and 12 months data were collected on physical examination, laboratory values and diagnosis. At baseline we examined 26 joints ultrasonographically (bilateral MCP2-5,PIP2-5,wrist,MTP2-5). Images were scored semi-quantitatively on grayscale (GS;0-3) and power Doppler (PD;0-3). Ultrasound synovitis was defined as GS≥2 and/or PD≥1. IA was defined as clinical soft tissue swelling. Sensitivity and specificity were used to assess the diagnostic value of ultrasound for the development of IA. Univariate logistic regression was used to analyse the association between independent variables and the incidence of IA. For multivariate logistic regression strongest variables ($p<0.157$) were selected. Missing values in independent variables were imputed.

Results: 196 patients were included, 159 completed 12 months follow-up. Thirty-one (16%) patients developed IA of whom 59% showed ultrasound synovitis at baseline. Sensitivity and specificity of ultrasound synovitis were 59% and 68% respectively. If no joints were positive on ultrasound, negative predictive value was 89%. In the multivariate logistic regression age (OR1.1), the presence of morning stiffness >30 minutes (OR3.3) and PD signal (OR3.4) were associated with incident IA.

Conclusions: The presence of PD signal, morning stiffness >30 minutes and age at baseline were independently associated with the development of IA. Regarding the value of ultrasound in the diagnostic work up of early arthralgia patients at risk for IA, ultrasound did perform well in ruling out IA in patients who did not have ultrasound synovitis.

Background

Rheumatoid arthritis is a debilitating chronic auto-immune disease. Early initiation of effective disease-modifying drugs can slow down disease progression and diminish joint damage.[1, 2] It could be that starting DMARD therapy already in the arthralgia phase or even before that could provide better patient outcome.[3, 4] Up till now it has been fairly difficult to identify those arthralgia patients who would benefit from such early initiation of DMARD therapy. Because only those that would have subsequently developed inflammatory arthritis (IA) related to a chronic inflammatory joint disease would benefit from such an early intervention. Recent technical developments in magnetic resonance imaging (MRI) and ultrasound suggest that earlier detection of inflammation should be possible before clinical manifestation.[5]

We know from previous research that 15% of arthralgia patients who present themselves without clinical signs of inflammation at baseline, will be diagnosed with IA one year later of whom half were ACPA positive.[6] Although ACPA positivity is a very good predictor for those patients who will develop IA within a year, it is still difficult to identify the exact individual who will develop IA as any ACPA positive individual has a priori chance of 50%. In the seronegative patients the prediction of IA is even more difficult as only 5% develops IA in the subsequent year. Imaging techniques have shown to be able to detect synovitis before clinical appearance and could be of help to identify those that are at risk of IA.[5, 7] MRI and ultrasound are both available in the daily rheumatological clinic. MRI has the disadvantage of being time consuming and thereby constraining the number of joints which could be assessed. In addition, MRI is expensive and not accessible for everyone (e.g. joint replacement, pacemaker). When we focus on ultrasound, this modality is more operator dependable, due to probe position multiple examiners can have different observations. However, ultrasound is more flexible and easily applied in the clinic.

In this study we aim to identify which arthralgia patients will develop clinically apparent IA within one year using ultrasound to detect subclinical synovitis at first consultation added to demographic and clinical variables.

Methods

This study was a multi-centre prospective cohort study in which we followed patients with inflammatory joint complaints for one year.

Patients

Patients with inflammatory joint complaints of hands, feet or shoulders without clinical apparent synovitis at any joint were recruited from the outpatient clinic. Patients had a symptom duration of less than one year which could not be explained by other conditions, such as IA, fibromyalgia, overuse or trauma. To distinguish inflammatory arthralgia from other forms of arthralgia, patients had to have at least two painful joints in hands, feet or shoulders and 2 of the following criteria adapted from REACH[8]: morning stiffness for more than 1h; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings or shoes; family history of RA; unexplained fatigue for less than 1 year. Patients had to be able to understand, speak and write in Dutch. Patients received treatment as the rheumatologists saw fit, but no disease modifying anti-rheumatic drugs were prescribed at first consultation. Written informed consent was obtained from the participants according to the declaration of Helsinki. The study was approved by the medical ethic committee of Erasmus MC, University Medical Centre Rotterdam, the Netherlands (MEC-2010-353) and was assessed for feasibility by the local ethical bodies of Maasstad Hospital and Vlietland Hospital.

Clinical examination

A trained research nurse collected data about articular symptoms, extra-articular symptoms, family history and previous medical history. Data collection at baseline, six months and twelve months follow-up included a detailed medical examination (swollen joint count in 44 joints, tender joint count in 44 joints), laboratory variables (ACPA, RF, ESR), diagnosis and medication used. Observed soft tissue swelling needed to be confirmed as an arthritis by the treating rheumatologist. As substantial lost to follow-up was expected at the start of the study due to the nature of recovering arthralgia for the majority of patients, a telephone interview was scheduled if patients did not want to return to the clinic for their 6 and 12 months evaluation. Patients were asked about their clinical symptoms. If the interviewer doubted about potential presence of clinical synovitis, patients were asked to return to the outpatient clinic for clinical evaluation.

Ultrasound examination

At baseline, trained ultrasound examiners blinded for the clinical details applied ultrasound, following the 'European League Against Rheumatism' (EULAR) guidelines, concerning patient position and scanning planes.[9] To minimise inter-variability ultrasound examiners followed a standardised scanning protocol regarding acquisition and scoring. The ultrasound machine used was the Esaote MyLab60 with a high-frequency linear array probe (LA435, 10-18MHz). Twenty-six joints were evaluated using grayscale (GS) and power Doppler (PD) imaging. We scanned MTP2-5 (dorsal aspect), MCP2-5 and PIP2-5 (dorsal and palmar aspects), and wrist (radiocarpal and intercarpal joints). A single midline (longitudinal 12 o'clock position) scan perpendicularly to the bone surface was used as advised by the OMERACT ultrasound working group.[10] The following PD settings were used: colour gain was set at the disappearance of colour noise. The Pulse Repetition Frequency (PRF) was set as low as possible to have maximum sensitivity, but minimising noise, which resulted in a frequency of 750 Hz. We adjusted the size and position of the colour box to include the subcutaneous tissue to recognize artefacts caused by vessels above the joint.[11] PD signals were measured only in joints with GS≥1. The total scanning time was ½ hour per patient per session. The treating rheumatologist and the research nurse were blinded for the results of the ultrasound examination at baseline.

Ultrasound evaluation

Image evaluation followed the recommendations of the Spanish society for Rheumatology, which is a modified version of the previously developed OMERACT definitions of sonographic pathology.[12] Joints were graded according to a semi-quantitative scoring system (0-3) for both GS and PD. For GS, all joints were graded as: 0 = no capsular distension, 1 = hypoechoic material only at the level of the joint margins; 2 = partial distension of the whole capsule which appears mostly concave or flat; 3 = complete distension of the whole capsule which appears mostly convex. Synovial vascularisation was measured using PD and graded as: 0 = absent; 1 = mild single vessel signal or isolated signal; 2 = moderate confluent vessels; 3 = marked vessel signals in more than half of the intra-articular area.[13]

Ultrasound synovitis was defined as GS grade 2 or 3 and/or presence of PD (grade 1, 2 or 3).

Outcome

One-year incident IA was defined as clinical soft tissue swelling. Observed soft tissue swelling needed to be confirmed as an arthritis by the treating rheumatologist whom was unaware of the ultrasound findings.

Statistical analysis

If patients had no clinical evaluation for both their 6 and 12 months visits they were classified as lost to follow-up and not included in the analysis.

Simple descriptives were used to describe baseline characteristics and the ultrasound findings. Depending on the distribution of the data we used the independent T-test or Wilcoxon-Mann-Whitney test to examine differences between cases and non-cases. Frequencies were compared using a Chi-square test. Sensitivity and specificity were used to assess the diagnostic value of ultrasound for the development of IA.

After consideration of the available literature[14, 15] we identified the following variables as relevant in the association with emerging IA: demographic characteristics (age, gender), clinical characteristics (tender joint count, high positive auto-antibodies (ACPA, RF), morning stiffness lasting ≥30 minutes), and ultrasound findings (presence of ultrasound synovitis, positive PD signal in at least one joint).[14-16] These variables were tested for their association with IA using univariate logistic regression. For multivariate logistic regression, we used a backward stepwise model procedure to select the strongest predictors (p=0.157).[17] The p-value of 0.157 is equal to Akaike's Information Criterion for predictors with one regression coefficient and is recommended to use in stepwise selection of predictors.[18] Missing values of independent variables were handled by multiple imputation using the STATA MICE routine (multiple imputation by chained equations; M=20).[19] Analyses were done using STATA 14.

Results

In total, 297 patients were recruited to participate. The flowchart [Figure 1] shows the distribution of patients during follow-up. At baseline, 196 patients met the inclusion criteria. One-hundred seventy-eight patients (91%) returned for their clinical evaluation at six months and 159 patients (81%) had their twelve months assessment. We could determine our primary outcome for 174 patients (89%). In total, 31 (16%) patients had developed IA within one year follow-up, of whom 15 had started DMARD therapy. Twenty-two patients had no definite diagnosis; 12 patients had mono-

arthritis, 10 patients had poly-arthritis. Definite diagnosis after 12 months was given for nine patients (rheumatoid arthritis: n=4; psoriatic arthritis: n=4; spondyloarthritis: n=1). Baseline characteristics of IA patients and non-IA patients are shown in table 1. We found statistically significant difference in baseline characteristics between IA and non-IA for age (mean 50 vs 44 years; p=0.005). In addition, ULTRASOUND synovitis was found more often in IA than in non-IA (59% vs 32%; p=0.007) and PD signal was present in 31% of the IA patients vs 12% of the non-IA patients (p=0.012).

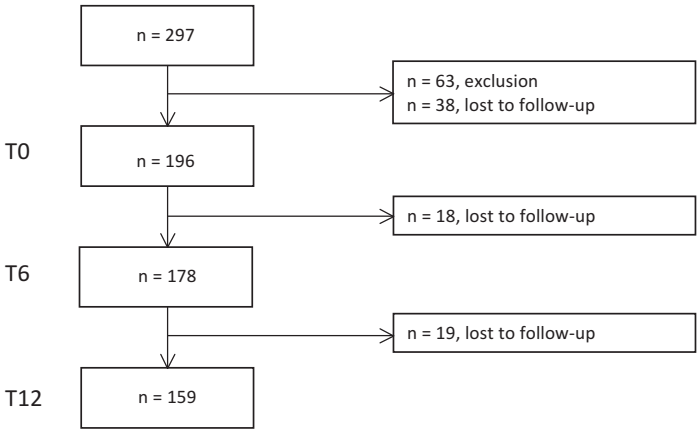


Figure 1. Flowchart of SONAR study showing the distribution of patients during follow-up.

Ultrasound findings

Ultrasound findings are described in more detail in table 2. In total, 72 arthralgia patients (37%) had ultrasound synovitis of whom 29 had a positive PD signal. Wrists (26%) and MTP joints (11%) were most commonly involved which was also observed if only PD was taken into consideration. Distribution of ultrasound synovitis over the different joint groups between patients who developed IA and who did not develop IA was comparable, except for the MTP joints which were more involved in the IA group.

Diagnostic value of ultrasound

Sensitivity and specificity of ultrasound synovitis in relation to the incidence of IA if one joint was positive on ultrasound were 59% and 68% respectively. Positive predictive value (PPV) was 26% and negative predictive value (NPV) was 74%. When we required two joints to be ultrasound positive to identify a IA case sensitivity decreased to 28% and specificity increased to 86% (PPV 27%; NPV 73%). For the presence of PD signal, sensitivity was 31% and specificity was 88% for one positive PD joint (PPV 33%; NPV

67%). When two joints were required, sensitivity decreased to 14% and specificity increased to 95% (PPV 38%; NPV 63%). If no joints were positive on ultrasound, the NPV was 89%.

Table 1 Baseline characteristics (n=174)

	IA patients (n=31)	Non-IA patients (n=143)	p-value*
Women, n (%)	25 (81)	119 (83)	0.731
Age, years, mean (sd)	50 (8)	44 (12)	0.005
BMI, mean (sd)	26.8 (4.4)	27.5 (5.2)	0.534
SJC44, median (IQR)	0 (0-0)	0 (0-0)	-
TJC44, median (IQR)	4 (2-9)	5 (3-8)	0.828
RF positive, n (%)	9 (31)	37 (27)	0.628
ACPA positive, n (%)	7 (24)	19 (14)	0.161
ESR, median (IQR)	10.5 (5-22)	10.5 (5-21)	0.824
Morning stiffness, minutes, median (IQR)	30 (30-60)	30 (15-60)	0.515
DAS28, mean (sd)	3.4 (1.1)	3.3 (1.0)	0.710
US synovitis†, n (%)	17 (59)	44 (32)	0.007
PD score >0, n (%)	9 (31)	17 (12)	0.012

IA: inflammatory arthritis; BMI: body mass index; SJC44: swollen joint count in 44 joints; TJC44: tender joint count in 44 joints; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28: disease activity score in 28 joints; US: ultrasound; PD: power Doppler; IQR: interquartile range; sd: standard deviation; *Depending on the distribution of the data, we used the independent ***t*** test or the Wilcoxon-Mann-Whitney test, frequencies were compared using a Chi2 test, p-value≤0.05; †US synovitis: grayscale grade 2 or 3 and/or presence of PD (≥1)

Table 2 Distribution of ultrasound findings

	US synovitis*, n (%)		PD positive, n (%)	
	IA (n=31)	Non-IA (n=143)	IA (n=31)	Non-IA (n=143)
US positive	17 (55)	45 (31)	9 (29)	17 (12)
MCP	3 (10)	9 (6)	1 (3)	3 (2)
PIP	3 (10)	1 (1)	2 (6)	0 (0)
wrists	8 (26)	35 (24)	4 (13)	15 (10)
MTP	9 (29)	11 (8)	4 (13)	2 (1)

US: ultrasound; PD: power Doppler; MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; MTP: metatarsophalangeal joint; *US synovitis: grayscale grade 2 or 3 and/or presence of PD (≥1)

Association of independent variables with development of IA

To quantify the associations between baseline characteristics and incident IA at follow-up we performed univariate and multivariate logistic regression after multiple imputation (M=20). Results are presented in table 3. Age (OR 1.06: 95% CI 1.03-1.09), morning stiffness >30 minutes (OR 2.39: 95% CI 1.20-4.73) and positive ACPA (OR 2.08:

95% CI 1.07-4.07) were univariately associated with IA. Other clinical and demographic characteristics did not differentiate IA patients from non-IA patients. For the presence of ultrasound synovitis in at least one joint the OR was 3.03 (95% CI 1.69-5.41) and for the presence of PD signal in at least one joint the OR was 3.12 (95% CI 1.61-6.03). In the multivariate logistic regression analysis, age (OR 1.06: 95% CI 1.03-1.10), morning stiffness >30 minutes (OR 2.80: 95% CI 1.33-5.90), positive ACPA (OR 2.35: 95% CI 1.13-4.87) and ultrasound synovitis (OR 2.65: 95% CI 1.44-4.88) remained associated with the development of arthritis during one year follow-up. If we replaced ultrasound synovitis by the presence of PD signal (OR 3.44: 95% CI 1.71-6.95), the OR for age and morning stiffness were similar, but positive ACPA was not associated with the development of arthritis.

Discussion

Sixteen percent of early arthralgia patients developed IA after one year follow-up of whom 59% showed ultrasound synovitis at baseline. Age, morning stiffness >30 minutes and positive PD signal were all significantly associated with the development of IA after one year in a multivariate model. Regarding the value of ultrasound in the diagnostic work up of early arthralgia patients at risk for IA, ultrasound did not perform well in ruling in IA (PPV 26%), but did perform well in ruling out IA in patients who did not have ultrasound synovitis (NPV 89%).

Up to now only few studies investigated subclinical synovitis in arthralgia patients by making use of imaging modalities. In an auto-antibody positive arthralgia cohort, patients with positive ultrasound had an increased risk for IA.[14, 15] This was confirmed in our study although only 15% of the patients was ACPA positive and 24% was RF positive. In another study evaluating patients with very early hand symptoms, the presence of PD signal was associated with IA in addition to clinical features (e.g. swollen joints) and laboratory tests (e.g. serology, RF, ACPA).[20] For MRI, results are not conclusive. Among a seropositive arthralgia population, changes on MRI indicative for inflammation of MCP and PIP joints were not associated with the development of arthritis at three year follow-up.[21] In opposite, MRI findings in the most affected hand in patients with clinically suspect arthralgia showed that subclinical MRI inflammation preceded clinical arthritis with a few months. This was also found in a sub analysis in a seronegative arthralgia population.[22, 23]

Table 3 Association between baseline characteristics and development of IA using univariate logistic regression analyses and multivariate logistic regression analysis after multiple imputation (n=174)

	Univariate model		Multivariate model including US synovitis		Multivariate model including presence of PD	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Demographics						
Age, years	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.10)	<0.001	1.07 (1.04-1.10)	<0.001
Sex	0.84 (0.42-1.70)	0.627				
BMI	0.98 (0.92-1.04)	0.438				
Clinical variables						
Tender joints	1.01 (0.96-1.07)	0.676				
DAS28	1.21 (0.92-1.58)	0.175				
Morning stiffness*	2.39 (1.20-4.73)	0.013	2.80 (1.33-5.90)	0.007	3.34 (1.60-6.96)	0.001
RF positive	1.21 (0.65-2.23)	0.545				
ACPA positive	2.08 (1.07-4.07)	0.032	2.35 (1.13-4.87)	0.021		
ESR	1.00 (0.98-1.02)	0.850				
Ultrasound						
US positive	3.03 (1.69-5.41)	<0.001	2.65 (1.44-4.88)	0.007		
PD positive	3.12 (1.61-6.03)	0.001			3.44 (1.71-6.95)	0.001

IA: inflammatory arthritis defined as clinical soft tissue swelling; BMI: body mass index; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; US: ultrasound; PD: power Doppler; OR: odds ratio; US synovitis: grayscale grade 2 or 3 and/or presence of PD (≥1); * morning stiffness >30 minutes

Our results should be interpreted in the light of the choices we made. As explained in the introduction we aimed for very early identification of IA. For this study we restricted the population to patients with at least two painful joints and in addition two criteria related to inflammation to be more sure of the inflammatory component. These inclusion criteria may have driven the selection to a population at increased risk for poly-arthritis. We missed those patients who might be at risk for IA, but only had one painful (large) joint. However, our inclusion criteria are in line with other arthralgia cohorts and with the new EULAR guidelines regarding clinically suspect arthralgia.[22, 24] Other forms of selection may have occurred due to rheumatologists who recruited clinically suspected patients with possibly more severe symptoms.[25] In addition, 38 patients decided not to participate without giving specific reasons which could have introduced a bias to patients with more severe complaints. These patients did not differ in age and sex compared to the responders, but we do not know whether their clinical symptoms differed. Information bias could have occurred as patients were lost to follow-up (14%). This was anticipated at the start of the study so we included a telephone service if patients did not respond to their initial invitation for follow-up. If those patients did not wish to return they were asked a small set of questions to establish whether they were at risk to be a case of IA. We saw no differences in their

baseline characteristics compared to those returning to the clinic. We did not include these patients in the analysis. Other bias could have been introduced by not blinding the clinical examination and ultrasound examination as we only included arthralgia patients. This could have led unconsciously to less sensitive assessment of clinical and ultrasound synovitis. However, at baseline several patients were excluded because of clinical apparent arthritis confirmed by a trained research nurse. Another item to take into account is that ultrasound is still considered operator-dependent, therefore the ultrasound examiners scanned patients following the ultrasound study protocol as training prior to the start of the study. In addition, ultrasound examiners followed protocol regarding acquisition and scoring. Previous research regarding inter-reliability confirmed that a consensus scoring system combined with a standardised acquisition protocol provided good inter-reliability.[26, 27] In our definition of ultrasound synovitis we combined GS abnormalities with PD signal. Studies showed that GS abnormalities also occur in non-arthritic individuals, and especially the discriminative value of GS score 1 is debatable.[14, 28] Therefore, we used a threshold of 2 for grayscale ultrasound abnormalities.

Conclusions

Sixteen percent of the arthralgia patients developed IA after one year follow-up of whom 59% showed ultrasound synovitis at baseline. Positive PD signal, morning stiffness and age were independently associated with the development of IA after one year. Given the high negative predictive value, ultrasound has added value to identify which patients will not develop into IA. Further research is recommended to determine confirm our results regarding the diagnostic value of the presence of PD ultrasound synovitis to predict the progression to IA in early arthralgia patients.

References

1. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum. 2006;55(6):864-72.
2. Verstappen SM, McCoy MJ, Roberts C, Dale NE, Hassell AB, Symmons DP, et al. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: results of the STIVEA trial. Ann Rheum Dis. 2010;69(3):503-9.
3. Hazes JM, Luime JJ. The epidemiology of early inflammatory arthritis. Nat Rev Rheumatol. 2011;7(7):381-90.
4. van Steenbergen HW, Huizinga TW, van der Helm-van Mil AH. The preclinical phase of rheumatoid arthritis: what is acknowledged and what needs to be assessed? Arthritis Rheum. 2013;65(9):2219-32.
5. Wakefield RJ, Freeston JE, O'Connor P, Reay N, Budgen A, Hensor EM, et al. The optimal assessment of the rheumatoid arthritis hindfoot: a comparative study of clinical examination, ultrasound and high field MRI. Ann Rheum Dis. 2008;67(12):1678-82.
6. Alves C. Early detection of patients at risk for rheumatoid arthritis - A challenge for primary and secondary care. Erasmus University Rotterdam; 2015, February 6. p. Retrieved from http://hdl.handle.net/1765/78432.
7. Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804-14.
8. Geuskens GA, Burdorf A, Evers AW, Hazes JM. Clear associations between demographic and psychosocial factors and health-related quality of life in patients with early inflammatory joint complaints. J Rheumatol. 2008;35(9):1754-61.
9. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60(7):641-9.
10. Naredo E, Moller I, Moragues C, de Agustin JJ, Scheel AK, Grassi W, et al. Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course. Ann Rheum Dis. 2006;65(1):14-9.
11. Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann Rheum Dis. 2008;67(2):143-9.
12. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485-7.
13. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
14. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther. 2010;12(3):R98.
15. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis. 2015;74(9):1659-66.
16. Bos WH, Wolbink GJ, Boers M, Tijhuis GJ, de Vries N, van der Horst-Bruinsma IE, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis. 2010;69(3):490-4.
17. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-87.
18. Ambler G, Brady AR, Royston P. Simplifying a prognostic model: a simulation study based on clinical data. Stat Med. 2002;21(24):3803-22.
19. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999;18(6):681-94.
20. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis. 2010;69(2):417-9.

21. Gent YY, Ter Wee MM, Ahmadi N, van Kuijk C, Voskuyl AE, van der Laken CJ, et al. Three-year clinical outcome following baseline magnetic resonance imaging in anti-citrullinated protein antibody-positive arthralgia patients: an exploratory study. Arthritis Rheumatol. 2014;66(10):2909-10.
22. van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis. 2015.
23. van Steenbergen HW, van Nies JA, Huizinga TW, Reijnierse M, van der Helm-van Mil AH. Subclinical inflammation on MRI of hand and foot of anticitrullinated peptide antibody-negative arthralgia patients at risk for rheumatoid arthritis. Arthritis Res Ther. 2014;16(2):R92.
24. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJJ, Brouwer E, Codreanu C, Combe B, et al. Development of draft criteria for arthralgia that is clinically suspect for progression to rheumatoid arthritis; results of phase 1. Ann Rheum Dis. 2015;74:240.
25. van Steenbergen HW, van der Helm-van Mil AH. Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms. Rheumatology (Oxford). 2016;55(6):1140-1.
26. Wakefield RJ, D'Agostino MA, Iagnocco A, Filippucci E, Backhaus M, Scheel AK, et al. The OMERACT Ultrasound Group: status of current activities and research directions. J Rheumatol. 2007;34(4):848-51.
27. D'Agostino MA, Conaghan PG, Naredo E, Aegerter P, Iagnocco A, Freeston JE, et al. The OMERACT ultrasound task force -- Advances and priorities. J Rheumatol. 2009;36(8):1829-32.
28. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford). 2010;49(4):683-90.

CHAPTER 4

Adding ultrasound to clinical examination reduced frequency of enthesitis in primary care psoriasis patients with musculoskeletal complaints

Myrthe van der Ven
Maren C. Karreman
Angelique E.A.M. Weel
Ilja Tchetverikov
Marijn Vis
Tamar E.C. Nijsten
Johanna M.W. Hazes
Jolanda J. Luime

Clin Exp Rheumatol. 2016 Nov-Dec;34(6):1020-1025

Abstract

Objective: Part of the psoriasis patients with musculoskeletal complaints will have inflammation of the entheses. Entheseal inflammation is difficult to assess by clinical examination only. Therefore, we aimed to determine the frequency of clinically relevant ultrasound inflammation at the most commonly assessed entheses (MASEI; Madrid Sonographic Enthesis Index) in primary care psoriasis patients with one or more tender entheses.

Methods: Adult primary care psoriasis patients with musculoskeletal complaints (tender enthesis or arthritis at physical examination) had an ultrasound examination of seven entheses according to the MASEI. Clinically relevant ultrasound inflammation was defined as active inflammation on ultrasound in combination with at least one clinical feature at the same enthesis. Active ultrasound inflammation contained positive power Doppler signal or in case of the plantar aponeurosis increased thickness. Structural changes entailed calcifications, enthesophytes, increased thickness, hypoechogeneicity indicating irregular fiber structure and erosions. Clinically, an enthesis was scored positive by a tender enthesis at clinical examination, reported pain in the history or self-reported pain in the questionnaires.

Results: Of 542 primary care psoriasis patient, 111 patients had tender entheses and/or arthritis. These patients were both clinically and ultrasonographically evaluated. Active ultrasound inflammation accompanied with pain or tenderness at the enthesis was found in 36% of the patients (n=40). Most common were inflammation at the knee (n=11) and at the plantar aponeurosis (n=10). Structural changes were observed in 95% of the psoriasis patients independent of their clinical manifestation.

Conclusion: We found concurrent presence of ultrasound inflammatory changes and clinical symptoms in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites.

Introduction

Enthesitis is an important domain in psoriatic arthritis (PsA). Since the introduction of the CASPAR classification criteria for PsA in 2006, psoriasis patients can classify as PsA with only enthesitis as inflammatory articular involvement.[1] Increasing attention is paid to its assessment[2, 3], but up to now no consensus has been achieved on its measurements in the diagnostic setting. In both the classification criteria for PsA and spondyloarthritis (SpA), enthesitis is included. The CASPAR criteria suggest that the doctor diagnoses enthesitis as he sees fit. The ASAS criteria for peripheral SpA include only the Achilles tendon and the plantar aponeurosis without being specific which clinical characteristics need to present.[4]

Enthesitis is defined as inflammation at tendon, ligament, joint capsules or aponeurosis insertion sites to bone. Entheseal pain can be severe, disabling and continuous, and can last for several years.[5, 6] The ethiopathogenesis is poorly understood and may relate to mechanical stress on top of the immune response.[7] Clinical assessment of the entheses is difficult as inflammation is often not visible or palpable. In addition, it may be difficult to anatomically locate the enthesis if it lies deep within the surrounding tissue.[8] The location of several entheseal sites overlaps with those of the tender points of fibromyalgia.[9] Furthermore, the presence of a tender enthesis is not necessarily indicative for underlying inflammatory disease as it could be related to overuse, metabolic disease or ageing.[10] These challenges could lead to clinically false-positive patients.

To resolve the difficulties regarding clinical assessment of the entheses, inflammatory characteristics at the enthesis can be visualized by ultrasound.[11] Especially the use of the power Doppler mode improves the assessment of inflammation at the entheses.[12, 13] New data about ultrasound enthesitis emerged in patients with psoriasis, PsA and healthy controls.[14-16] So far, studies evaluated enthesitis in patients with psoriasis who were referred from the dermatologist.[16-20] A significant higher prevalence of both grayscale (GS) and power Doppler (PD) ultrasound enthesopathy was found in patients with psoriasis than in controls (patients with dermatological diseases other than psoriasis).[16-18] In patients with PsA the severity of ultrasound abnormalities was even higher than in patients with psoriasis.[20] Ultrasound abnormalities at the entheses were present in both symptomatic (true-positive) and asymptomatic (false-positive or subclinical disease) psoriasis patients which suggests single application of ultrasound is not sufficient to detect clinically relevant entheseal inflammation.[19, 21]

Little data is available on the presence of PsA in primary care psoriasis patients.[22, 23] In several countries psoriasis patients are treated by their general practitioner and this might mean that cases of PsA are missed. In addition, these studies did not include ultrasound to assess inflammation at the entheses. In a large primary care based study the frequency of PsA in psoriasis patients was estimated to be 3.1% for arthritis and axial disease, increasing to 4.6% when enthesitis would be included.[24]
In this study we describe the frequency of ultrasound abnormalities at the entheses and its clinical information in primary care psoriasis patients who had at least one tender enthesis at clinical examination. We combined PD ultrasound and clinical information at the same enthesis to differentiate between active inflammation and other manifestations of enthesopathy.

Materials and methods

Patients

Adult patients with psoriasis (ICPC S91) were identified from 97 general practitioners (GPs) in the Rotterdam area. These patients were invited to participate in the SENSOR study. Details of this cross-sectional study can be found in Karreman et al.[24] In brief, patients who reported regular episodes of pain in joints, entheses or the lower back were eligible and invited for clinical evaluation by a trained nurse. Patients were not recruited consecutively. Data collection included a detailed clinical examination (amongst others, swollen joint count, tender joint count, entheses evaluation), demographic characteristics and symptom history.
Written informed consent was obtained from the participants. The study was approved by the medical ethic committee of Catharina Hospital, Eindhoven, the Netherlands.

Entheses evaluation

Clinical examination

Physical examination included the 66/68 joint count for PsA and entheseal assessment following the Leeds Enthesitis Index (LEI) and the Maastricht Ankylosing Spondylitis Enthesis Score (MASES).[2, 3] Other assessments included measurement of psoriasis severity by the PASI and body mass index. If clinical examination indicated a painful enthesis on the LEI/MASES or indicated an arthritis, ultrasound examination of the entheses was performed.

Ultrasound examination

An independent ultrasound examiner blinded for the clinical details performed the ultrasound using Esoate MyLab60 (probe LA 435). The six entheses of the Madrid Sonographic Enthesis Index (MASEI)[25] and the lateral epicondyle tendon insertion (elbow) were examined. Each tendon was examined in the longitudinal plane. Knee entheses were examined with the patient in supine position and the knee flexed at 20°. The Achilles tendon and the plantar aponeurosis were examined with the patient in prone position and the feet hanging over the edge of the examination table in neutral position. To examine the lateral aspect of the elbow, the patient was positioned with the elbow flexed, forearm extended and palm down. To examine the olecranon, the patient was asked to raise the elbow and to keep the elbow flexed (90°) with the hand palm resting on the table. According to the MASEI scoring system the following elemental lesions of enthesitis were evaluated at each site: calcifications, bursitis, erosions, PD signal in bursa or enthesis full tendon (cortical bone profile, intratendon and paratendon on the enthesis insertion) and thickness and structure.[25] Ultrasound abnormalities were divided into 'active inflammation' and 'structural change' parameters. Active inflammatory components on ultrasound included the presence of PD signal (<2mm of the bony cortex)[15] or in case of the plantar aponeurosis an increased thickness (≥4.4mm).[26] Structural changes included calcifications, erosions, structure, and increased thickness.

Self-reported pain at the entheses

Patients completed online self-reported questionnaires including the EARP[27] and PEST[28]. From the EARP questionnaire we used the question regarding the Achilles tendon. From the PEST questionnaire we used those questions regarding pain of the heel, elbows, and knees. Patient history included questions about symptom history regarding previous episodes of entheseal inflammatory complaints, which were diagnosed by a GP.

Enthesitis definition

In this study we combined data from ultrasound and clinical examination, and patient-reported questionnaires to define active inflammation at the enthesis. We defined enthesitis as active inflammation on ultrasound (presence of PD signal and/or increased thickness of the plantar aponeurosis) in combination with at least one clinical feature at the same enthesis: i) tender point LEI/MASES, ii) self-reported pain at the elbow, knee, Achilles tendon and heel from the EARP or PEST questionnaire,

iii) self-reported entheseal complaints (defined as previous episodes of entheseal inflammatory complaints, diagnosed by a GP).

Statistical analysis

To determine differences in baseline characteristics and ultrasound findings between patients suspected for enthesitis and patients suspected for arthritis we used descriptive statistics. Depending on the distribution of the data we used the independent T-test or Wilcoxon-Mann-Whitney test. Frequencies were compared using a Chi-square test. Analyses were done using STATA 12.0.

Results

In total, 111 patients of the total study population with psoriasis (n=524) who reported regularly musculoskeletal complaints were evaluated by ultrasound. Of these patients, 88 patients were referred for ultrasound because they had at least one tender enthesis on the LEI/MASES. The other 23 patients were referred for suspected arthritis and also underwent an evaluation of the entheses by ultrasound. Nine (8%) patients had a confirmed diagnosis of PsA by a rheumatologist. Patient characteristics are presented in Table 1.

Table 1 Baseline characteristics of primary care psoriasis patients (n=111)

	Suspected for enthesitis (n=88)	Suspected for arthritis (n=23)	p-value
Women (%)	57	39	0.130
Age, years (mean, sd)	54 (13)	54 (14)	0.936
LEI (median, IQR)	2 (1-4)	0 (0-1)	<0.001
MASES (median, IQR)	2 (0-4)	0 (0-1)	<0.001
MASEI (median, IQR)	7 (5-12)	10 (5-13)	0.302
Power Doppler positive, n (%)			0.626
- 1 enthesis	14 (16)	2 (9)	
- 2 entheses	12 (14)	3 (13)	
- 3 entheses	3 (3)	1 (4)	

LEI = Leeds Enthesitis Index (range: 0-6); MASES = Maastricht Ankylosing Spondylitis Enthesis Score (range: 0-13); MASEI = Madrid Sonographic Enthesis Index (range: 0-136); sd = standard deviation; IQR = interquartile range

Entheses evaluation

Clinical examination

The median number of tender entheses on the LEI was 2 (IQR: 0-3). The median number of tender entheses on the MASES was 1 (IQR: 0-3). Patients suspected for enthesitis had more tender entheses on both the LEI and the MASES (median (IQR): 4 (1-7)) than patients suspected for arthritis (median (IQR): 2 (0-4); p<0.0001). The most common tender entheses were found at the lateral epicondyle of the humerus (52%) and at the medial epicondyle of the femur (50%) [Table 3].

Ultrasound examination

In 106 (95%) patients (n=111) we detected one or more ultrasound abnormalities at the enthesis [Table 2]. There was no difference in ultrasound findings between patients suspected for enthesitis and patients suspected for arthritis.

Table 2 Ultrasound abnormalities at the enthesis using the MASEI score (n=111) , n (%)

Insertion	PD signal	Structure	Thickness	Bursitis	Erosion	Calcification
Lateral epicondyle tendon (elbow)	21 (19)	19 (17)	51 (46)		35 (32)	47 (42)
Triceps tendon	0	25 (23)	18 (16)		9 (8)	26 (23)
Quadriceps tendon	13 (12)	12 (11)	53 (48)		3 (3)	66 (59)
Proximal patella tendon	2 (2)	4 (4)	29 (26)		2 (1)	15 (14)
Distal patella tendon	9 (8)	3 (3)	77 (69)	1 (1)	3 (3)	23 (21)
Achilles tendon	4 (4)	1 (1)	12 (11)	0	1 (1)	70 (63)
Plantar aponeurosis	†	1 (1)	20 (18)		0	20 (18)

MASEI = Madrid Sonographic Enthesis Index (range: 0-136); PD = power Doppler; † = not detectable

In 50 (45%) patients we found ultrasound abnormalities indicating inflammatory disease at the enthesis [Table 3]. Thirty-five (32%) patients were PD positive on ultrasound of whom 5 (5%) also had a thickened plantar aponeurosis. Fifteen (14%) patients only had a thickened plantar aponeurosis.

Positive PD signal was found most often at the lateral epicondyle of the humerus (21 patients, 19%) and at the insertion of the quadriceps tendon at the superior pole of the patella (13 patients, 12%). In 19 (17%) patients we found positive PD signal at more than one enthesis. Of note, we did not find any indication of inflammatory disease at the triceps enthesis at the olecranon.

Structural changes of the enthesis on ultrasound [Table 3] were very common. Increased thickness of the distal patella tendon at the tuberositas tibiae (69%), and calcifications at the enthesis of the quadriceps tendon (superior pole patella: 59%) and

at the enthesis of the Achilles tendon (63%) were found most often. Structural changes without indication of inflammatory disease were found in 56 (50%) patients.

Self-reported pain at the entheses

In total, 105 patients (95%) reported pain at a location relevant to the enthesis: the elbow, knee, Achilles tendon, or heel. Pain in the knee was most frequently reported (71%), followed by the heel (55%) and elbow (49%). Nineteen (17%) patients reported pain at the Achilles tendon insertion.

Patients fulfilling enthesitis definition

Patients who had clinical symptoms and PD at one of their enthesis or a thickened plantar aponeurosis were classified as having ultrasound confirmed inflammatory enthesitis. Of the 50 patients with ultrasound abnormalities indicating inflammatory disease, the ultrasound findings were confirmed by clinical information in 40 patients (36%). These patients were classified as having active (ultrasound confirmed inflammatory) enthesitis. Twenty-eight patients had active enthesitis at one enthesis. These were found at the knee (n=11), at the insertion of the plantar aponeurosis (n=10), at the lateral epicondyle of the humerus (n=6) and at the Achilles tendon (n=1). Ten patients had active enthesitis at two entheses, and two patients had active enthesitis at three entheses. Thirty-two cases were referred because they had at least one tender enthesis on the LEI/MASES. The other eight cases were referred for suspected arthritis.

Table 3 Ultrasound and clinical findings per entheseal site (n=111), n (%)

Insertion	*US inflammatory*	*US structural*	*Tender point*	*Self-reported*
Lateral epicondyle tendon (elbow)	21 (19)	62 (56)	58 (52)	54 (49)
Triceps tendon	0	49 (44)	†	54 (49)
Quadriceps tendon	13 (12)	68 (61)	55 (50)*	79 (71)
Proximal patella tendon	2 (2)	37 (33)		
Distal patella tendon	9 (8)	74 (67)		
Achilles tendon	4 (4)	68 (61)	32 (29)	19 (17)
Plantar aponeurosis	20 (18)	16 (14)	†	61 (55)

US = ultrasound; † = not included in LEI/MASES; * = medial epicondyle femur

Ten patients had inflammatory ultrasound abnormalities while they did not report clinical problems. We found a positive PD signal in five patients. The PD signal was found at the enthesis of the lateral epicondyle of the humerus (n=3), at the entheses of the knee (n=1), and in one patient both at the lateral epicondyle (humerus) and

the Achilles enthesis. The plantar aponeurosis was thickened in five patients without clinical symptoms.

Figure 1 shows the distribution of the ultrasound findings, both structural changes and active inflammation combined with the clinical findings at each entheseal site.

Five patients had a painful enthesis clinically without having any ultrasound abnormalities. These patients all had a painful knee, combined with a painful enthesis at the lateral epicondyle of the humerus (n=4), with a painful heel (n=2), or a tender Achilles enthesis (n=1).

The other 56 patients had a painful enthesis with structural changes on ultrasound.

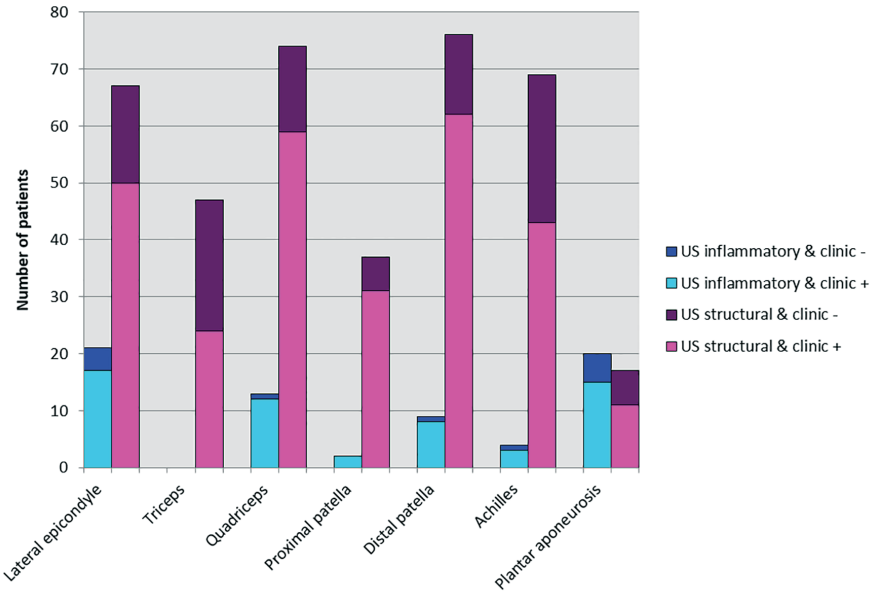


Figure 1. Distribution of the ultrasound findings, both structural changes (US structural) and active inflammation (US inflammatory), in combination with the clinical findings (- = negative; + = positive) at each entheseal site (US = ultrasound).

Discussion

In 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites (n=111) enthesitis was present, defined as concurrent presence of ultrasound inflammatory changes and clinical symptoms. Ultrasound assessment included five elemental lesions: the presence of calcifications, erosions, increased thickness, changes in fiber structure, and positive PD signal. We indicated the first 4 lesions as 'structural changes' of the enthesis which were present in 95% of the patients, while we named positive PD signal the 'inflammatory component', present in 32% of the patients. One exception was made for the plantar aponeurosis as ultrasound was not able to elicit any PD signal in this area. Therefore, increased thickness was chosen to assess inflammatory changes at the enthesis of the plantar aponeurosis, which was present in 18% of the patients. In total, 45% of the patients (n=50) had ultrasound inflammatory changes. Combined with clinical information at the same enthesis this led to 36% of the patients (n=40) having enthesitis. In part of our study population (9%; n=10) we found ultrasound inflammatory components, but these were not confirmed by clinical information. This could be related to subclinical disease, which could be predictive for the development of PsA in patients with psoriasis.[21, 29-31]

Considerable advances have been made in the use of ultrasound to evaluate entheses. Nevertheless, context of clinical information remains needed to differentiate between active inflammation and other manifestations of enthesopathy.[10] By adding ultrasound to the clinical evaluation of entheses we were able to visualize the presence of active inflammatory involvement of the enthesis. This could help to differentiate patients with non-inflammatory entheseal pain from patients with entheseal involvement related to inflammation, helping physicians to make informed decisions about whom to treat with anti-inflammatory drugs. First-line treatment recommendations for enthesitis in PsA patients are NSAIDs. After insufficient response to NSAIDs, treatment can be switched to biological agents.[32, 33] Since rheumatologists are quite reserved to prescribe biologic agents to treat enthesitis, ultrasound might give more certainty for detecting inflammatory disease at tender entheses. However, further research regarding the treatment of ultrasound confirmed enthesitis is needed.

One of the difficulties we came across was the absence of general accepted definitions for both the clinical presentation as well as the ultrasound presentation of enthesitis. The OMERACT Ultrasound Task Force recently debated the latter, but they did not come to a definite conclusion what would be inflammatory.[15] The main reason for this was the discussion on entheseal thickness. Part of the ultrasound examiners felt this to belong to inflammatory changes while other examiners attributed this to structural changes.

Both could be true. In the acute phase, increased thickness might be present due to inflammation as shown by McGonagle et al with soft tissue and bone edema at the plantar aponeurosis insertion on MRI appearances.[34] However, thickening could also be the result of a disorganized repair process (scar tissue) in which no inflammation is present anymore.
There are several strengths and weaknesses to discuss when interpreting the results of our study. At first, for practical reasons we choose to apply ultrasound, rather than MRI. Ultrasound was easy accessible, we could apply it to different locations at once and there were no safety issues. It has the disadvantage that it is reader dependable, which was solved by one examiner for all patients. However, ultrasound cannot depict bone edema which is also indicative for inflammatory changes like MRI does. MRI is capable of detecting soft tissue changes associated with surrounding soft tissue edema in the region adjacent to the enthesis.[10] However, application of MRI would require long acquisition time to evaluate six entheses bilaterally. There have been recent advances in whole body MRI but issues need to be solved such as field of view, image resolution for small structures and body position.[35] Secondly, patient position during the ultrasound examination of the knee entheses was not ideal. In our study maximum flexion of the knee was 20°, which could have influenced our PD signal at the entheseal level of the knee entheses. Previous studies found an severe decrease of PD signal when the knee was flexed at 30°.[36] Flexion of the knee could increase intratendinous tension, which facilitates collapse of the microvessels. Thirdly, due to the aim of our initial study, which was to estimate the prevalence of PsA in primary care psoriasis patients, we did not include control patients. However, there is a substantial body of evidence that shows the usefulness of the MASEI score in differentiating patients with PsA/SpA from healthy controls[20, 37], especially if using inflammatory changes (PD signal) rather than structural changes.[21] This stresses our choice to use a positive PD signal at the enthesis as an indication for active ultrasound enthesitis. A strength of our study is that we included primary care patients with psoriasis with musculoskeletal complaints. Most studies evaluating enthesitis with ultrasound have included psoriasis patients in secondary care referred by the dermatologist.[16] Our study population is a different population in which it would be beneficial to screen for PsA and to improve early diagnosis of PsA.
In conclusion, enthesitis defined as concurrent presence of ultrasound inflammatory changes and clinical symptoms was present in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites. Combining clinical data and ultrasound at the same enthesis reduced the frequency of entheseal lesions that should be evaluated by the rheumatologist compared to clinical exam only. Consensus needs to be reached to find a generally accepted definition for enthesitis which would be feasible in daily clinical work.

References

1. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73.
2. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum. 2008;59(5):686-91.
3. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003;62(2):127-32.
4. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.
5. D'Agostino MA, Olivieri I. Enthesitis. Best Pract Res Clin Rheumatol. 2006;20(3):473-86.
6. Bandinelli F, Cerinic MM. The role of ultrasound of entheses in spondyloarthritis - New perspectives in diagnosis and the importance of 'occult enthesitis'. European Musculoskeletal Review. 2012;7(2):116-20.
7. Jacques P, Lambrecht S, Verheugen E, Pauwels E, Kollias G, Armaka M, et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis. 2014;73(2):437-45.
8. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. J Rheumatol. 2006;33(7):1435-8.
9. McGonagle DG, Helliwell P, Veale D. Enthesitis in psoriatic disease. Dermatology. 2012;225(2):100-9.
10. Mandl P, Niedermayer DS, Balint PV. Ultrasound for enthesitis: handle with care! Ann Rheum Dis. 2012;71(4):477-9.
11. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis. 2002;61(10):905-10.
12. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. Arthritis Rheum. 2003;48(2):523-33.
13. Kiris A, Kaya A, Ozgocmen S, Kocakoc E. Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. Skeletal Radiol. 2006;35(7):522-8.
14. Gandjbakhch F, Terslev L, Joshua F, Wakefield RJ, Naredo E, D'Agostino MA, et al. Ultrasound in the evaluation of enthesitis: status and perspectives. Arthritis Res Ther. 2011;13(6):R188.
15. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al. Defining enthesitis in spondyloarthritis by ultrasound: results of a delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken). 2014;66(5):741-8.
16. Gutierrez M, Filippucci E, De Angelis R, Salaffi F, Filosa G, Ruta S, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. Semin Arthritis Rheum. 2011;40(5):407-12.
17. Naredo E, Moller I, de Miguel E, Batlle-Gualda E, Acebes C, Brito E, et al. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study. Rheumatology (Oxford). 2011;50(10):1838-48.
18. De Filippis LG, Caliri A, Lo Gullo R, Bartolone S, Miceli G, Cannavo SP, et al. Ultrasonography in the early diagnosis of psoriasis-associated enthesopathy. Int J Tissue React. 2005;27(4):159-62.
19. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. Ann Rheum Dis. 2008;67(1):26-30.
20. Eder L, Jayakar J, Thavaneswaran A, Haddad A, Chandran V, Salonen D, et al. Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? J Rheumatol. 2014;41(3):466-72.
21. Freeston JE, Coates LC, Helliwell PS, Hensor EM, Wakefield RJ, Emery P, et al. Is there subclinical enthesitis in early psoriatic arthritis? A clinical comparison with power doppler ultrasound. Arthritis Care Res (Hoboken). 2012;64(10):1617-21.
22. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis. 2015;74(9):1659-66.

23. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther. 2010;12(3):R98.
24. Karreman MC, Weel AE, van der Ven M, Vis M, Tchetverikov I, Nijsten TE, et al. Prevalence of Psoriatic Arthritis in Primary Care Patients With Psoriasis. Arthritis Rheumatol. 2016;68(4):924-31.
25. de Miguel E, Cobo T, Munoz-Fernandez S, Naredo E, Uson J, Acebes JC, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis. 2009;68(2):169-74.
26. Gibbon WW, Long G. Ultrasound of the plantar aponeurosis (fascia). Skeletal Radiol. 1999;28(1):21-6.
27. Tinazzi I, Adami S, Zanolin EM, Caimmi C, Confente S, Girolomoni G, et al. The early psoriatic arthritis screening questionnaire: a simple and fast method for the identification of arthritis in patients with psoriasis. Rheumatology (Oxford). 2012;51(11):2058-63.
28. Helliwell PS. Psoriasis Epidemiology Screening Tool (PEST): a report from the GRAPPA 2009 annual meeting. J Rheumatol. 2011;38(3):551-2.
29. Bandinelli F, Prignano F, Bonciani D, Bartoli F, Collaku L, Candelieri A, et al. Ultrasound detects occult entheseal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity. Clin Exp Rheumatol. 2013;31(2):219-24.
30. Tinazzi I, McGonagle D, Biasi D, Confente S, Caimmi C, Girolomoni G, et al. Preliminary evidence that subclinical enthesopathy may predict psoriatic arthritis in patients with psoriasis. J Rheumatol. 2011;38(12):2691-2.
31. Delle Sedie A, Riente L. Psoriatic arthritis: what ultrasound can provide us. Clin Exp Rheumatol. 2015;33(5 Suppl 93):S60-5.
32. Richard MA, Barnetche T, Rouzaud M, Sevrain M, Villani AP, Aractingi S, et al. Evidence-based recommendations on the role of dermatologists in the diagnosis and management of psoriatic arthritis: systematic review and expert opinion. J Eur Acad Dermatol Venereol. 2014;28 Suppl 5:3-12.
33. Kocijan R, Muschitz C, Rech J. Biological agents in psoriatic arthritis Biologikatherapie bei Psoriasisarthritis. Wien Med Wochenschr. 2014.
34. McGonagle D, Marzo-Ortega H, O'Connor P, Gibbon W, Pease C, Reece R, et al. The role of biomechanical factors and HLA-B27 in magnetic resonance imaging-determined bone changes in plantar fascia enthesopathy. Arthritis Rheum. 2002;46(2):489-93.
35. Poggenborg RP, Eshed I, Ostergaard M, Sorensen IJ, Moller JM, Madsen OR, et al. Enthesitis in patients with psoriatic arthritis, axial spondyloarthritis and healthy subjects assessed by 'head-to-toe' whole-body MRI and clinical examination. Ann Rheum Dis. 2014.
36. Gutierrez M, Filippucci E, Grassi W, Rosemffet M. Intratendinous power Doppler changes related to patient position in seronegative spondyloarthritis. J Rheumatol. 2010;37(5):1057-9.
37. Munoz-Fernandez S, de Miguel E, Cobo-Ibanez T, Madero R, Ferreira A, Hidalgo MV, et al. Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis. Arthritis Rheum. 2009;60(7):1985-90.

CHAPTER 5

Can ultrasound of the feet help us to monitor disease activity in RA?

Myrthe van der Ven
David F. Ten Cate
Johannes W.G. Jacobs
Andreas H. Gerards
Wijnand A.A. Swen
Mike H. de Jager
Natalja Basoski
Cees J. Haagsma
Johanna M.W. Hazes
Jolanda J. Luime

Submitted

Abstract

Objective: Investigating the agreement of ultrasonographical findings at the MTP joints with physical examination in newly diagnosed RA patients who were treated to target.

Methods: In a multicenter cohort study, newly diagnosed RA patients were followed for one year. Symptom duration was <1 year and patients were treatment naïve. Patients underwent physical (SJC, TJC, squeeze test), laboratory and ultrasound examination (MTP2-5) at baseline, three months and one year follow-up. Ultrasound images were scored semi-quantitatively for grayscale (GS;0-3) and power Doppler (PD;0-3). Ultrasound synovitis was defined as GS≥2 and/or PD≥1. Kappa-statistic (κ), positive and negative percent agreement were calculated.

Results: In total, 174 patients were included of whom 62% achieved DAS28 remission (DAS28≤2.6) at one year follow-up. At baseline, 63% of patients had ≥1 ultrasound positive MTP joint, which decreased to 25% at one year follow-up, irrespective of achieving remission or not. Positive percent agreement between physically swollen MTP joints and ultrasound was 16% at baseline (κ=0.02); 5% at one year follow-up (κ=0.01). The percentage negative agreement between physically non-swollen MTP joints and negative ultrasound was 86% at baseline. Agreement of the squeeze test and ultrasound at MTP joints ranged from 64% (κ=0.08) at baseline to 29% (κ=0.09) after one year follow-up.

Conclusion: In newly diagnosed RA patients, we saw a decrease in mean DAS score and number of ultrasound positive MTP joints. However, 25% of ultrasound synovitis remained irrespective of DAS. Agreement between ultrasound and physical examination at joint level was poor.

Introduction

In patients with rheumatoid arthritis (RA), metatarsophalangeal (MTP) joints are frequently affected early in the course of the disease.[1] Up to 36% of RA patients has involvement of the foot joints prior to involvement of the hands.[2] In diagnosing and monitoring RA, physical examination of the joints is important, but is characterised by poor reproducibility and accuracy.[3] Especially physical examination of the feet is more difficult than that of other joints. For instance, other causes of pain and swelling of the feet such as osteoarthritis, polyneuropathy and oedema could confound accurate assessment of RA disease activity.[4,5]

Nowadays, intensive treatment of early RA results in improved outcomes and treat-to-target management strategies are recommended by international guidelines.[6,7] The goal of the treat-to-target strategies is to achieve clinical remission, of which the assessment includes physical examination of the joints. In 2011, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) together with an Outcome Measures in Rheumatology (OMERACT) task force have redefined the definition of remission in RA.[8] Both the Boolean-based definition and the SDAI-based definition are based on 28-joint counts. Theoretically, a patient could be classified as being in remission according to 28-joint counts, while having considerable disease activity in ankles and feet joints. Previous research regarding this issue shows conflicting results. Several studies agreed that remission assessing 28-joint counts is inferior to remission using the original DAS, which counts 44 joints including the assessment of the feet, and showed that up to 40% of patients in DAS28 remission had disease activity in the feet.[9-12] On the other hand, it has been shown that DAS28 and SDAI may overrate disease activity and classify patients into higher disease activity states, compared with the DAS.[13] However, other studies concluded that reduced joint counts are appropriate and valid to assess disease activity at group level in observational studies or in clinical trials.[4,14,15]

Previous research showed that ultrasonography could be a useful tool in clinical decision making since ultrasound detects synovitis more sensitively than physical examination.[16,17] Many RA patients with physically no swollen joints have synovitis at ultrasound, which appears to be predictive of worse outcomes.[18-20]

In this study we investigated the agreement of inflammation of the MTP joints as assessed by ultrasound and as assessed with physical examination in newly diagnosed RA patients who are treated to target. This way we can answer the question whether ultrasound may be added to physical examination in daily clinical practice for monitoring the feet.

Patients and methods

Patients

This was a multicentre (7 centres in the Netherlands) study in which a cohort of consecutively recruited newly diagnosed RA patients (1987 ACR criteria)[21] was prospectively followed for one year. At study entry, symptom duration was less than 1 year and all patients were naïve for treatment with conventional synthetic DMARDs, biologicals and glucocorticoids. All patients were treated to target (low disease activity or remission) with regular visits. Patients had to be able to understand, speak and write in Dutch. Patients underwent physical (44 swollen joint count (SJC), 44 tender joint count (TJC)), laboratory (CRP, BSE, serology) and ultrasound examination at enrolment in the study (T0), at three months (T3) and at one year follow up (T12). Patients were categorised into three groups depending on their disease activity state: i) remission: DAS28≤2.6, ii) low disease activity (LDA): 2.6<DAS28≤3.2, and iii) high disease activity (HDA): DAS28>3.2. In addition, in four centres the squeeze test was performed, assessing pain at tangential compression of the metatarsophalangeal (MTP) joints[22], scored as absent or present.

Written informed consent was obtained from the participants according to the declaration of Helsinki. The study was approved by the local medical ethic committee of Erasmus MC, University Medical Centre Rotterdam, the Netherlands.

Ultrasound assessment

The ultrasonographers had nine trainings sessions prior to and during the study to optimise interpretation and acquisition reliability between them. For the ultrasound examination each centre used the same machine and transducer (Esaote MyLab60 with linear array LA-435 probe 6-18MHz). MTP 2 to 5 joints were scanned bilaterally at the dorsal orientation. Patient and probe positioning were according to EULAR guidelines.[23] Joints were graded according to a semi-quantitative scoring system (0-3) for both grayscale (GS) and power Doppler (PD). For GS, all joints were graded according to Szkudlarek et al., 0 = no synovial thickening, 1 = minimal synovial thickening, filling the angle between the periarticular bones, without bulging over the line linking the bone diaphyses of the periarticular bone regions; 2 = synovial thickening without extension over the bone diaphyses; 3 = synovial thickening over at least one of the bone diaphysis.[24] Synovial vascularisation was measured using power Doppler. Power Doppler was graded according to Naredo et al., 0 = absent; 1 = mild, single vessel signal or isolated signal; 2 = moderate, confluent vessel signals in the intra-articular area; 3 =

marked, vessel signals in more than half of the intra-articular area.[17] For power Doppler (PD) we used a colour gain setting at the disappearance of colour noise, frequency of 10 MHz, a pulse repetition frequency of 750 Hz and wall filter at level 3 out of 5 (=max). We adjusted the size and position of the colour box to include the subcutaneous tissue to recognize artefacts caused by vessels above the joint. Based on data in the literature, we considered a joint to have ultrasound synovitis if it was scored with at least grade 2 in the GS ultrasound domain or at least grade 1 in the PD ultrasound domain.[25, 26]

Primary outcome

Ultrasound synovitis in MTP joints defined as GS≥2 and/or PD≥1.

Analysis

We used descriptive statistics to present physical examination and ultrasound findings in the MTP joints. No statistical inferences were conducted in the study. At joint level we calculated the kappa statistic[27], and positive and negative percent agreements (PPA/NPA)[28] between physical examination (SJC, TJC and squeeze test) and ultrasound findings. All analyses were done using STATA14.

Results

In total, 174 patients were included in the study. Baseline characteristics are shown in table 1. After three months 9 patients were lost to follow-up. At one year follow-up we had complete data for 157 patients. At one year follow-up, 62% of the patients achieved DAS28 remission and 18% had LDA.

Ultrasound assessment

At baseline, 63% of the patients had at least one MTP joint with ultrasound synovitis (GS≥2 and/or PD≥1). The median number of MTP joints with ultrasound synovitis was 1 (IQR: 0-4). At one year follow-up the median was 0 (IQR: 0-0). At one year follow-up 25% of the patients showed ultrasound synovitis in at least one MTP joint. Figure 1 shows the course of ultrasound positive and ultrasound negative MTP joints during follow-up. Twenty-three (13%) patients had at least one MTP joint ultrasound positive at all three visits, 42 (24%) patients had no ultrasound positive MTP joint at one year in the study.

Table 1 Patient characteristics and ultrasound findings at baseline and during the study

	Baseline (n = 174)	at 3 months (n=165)	at 12 months (n = 157)
Age, mean (sd), years	55 (14)		
Women, n (%)	111 (64)		
RF positive, n (%)	115 (66)		
ACCP positive, n (%)	103 (60)		
DAS28, mean (sd)	4.9 (1.3)	2.9 (1.3)	2.3 (1.2)
SJC28, median (IQR)	6 (3-11)	1 (0-4)	0 (0-1)
TJC28, median (IQR)	6 (2-10)	1 (0-4)	0 (0-2)
BSE, median (IQR)	27 (12-47)	10 (5-22)	8 (3-17)
DAS28 remission, n (%)	8 (5)	71 (43)	98 (62)
DAS28 LDA, n (%)	13 (7)	26 (16)	29 (18)
DAS28 HDA, n (%)	153 (88)	68 (41)	32 (20)
US MTP, median (IQR)	1 (0-4)	0 (0-2)	0 (0-0)
US MTP >0, n (%)	109 (63)	71 (43)	39 (25)

ACCP = anti-cyclic citrullinated peptide; SJC = swollen joint count in 28 joints; TJC = tender joint count in 28 joints; LDA = low disease activity (2.6<DAS28≤3.2); US = ultrasound; sd = standard deviation; IQR = interquartile range; US MTP = GS≥2 and/or PD≥1; GS = grayscale; PD = power Doppler

Clinical disease activity and ultrasound

At baseline, the majority (88%) of the early RA patients had HDA. During follow-up disease activity decreased. After 12 months, 20% of the patients had HDA and 62% of the patients achieved DAS28 remission. Figure 2 shows the distribution of ultrasound synovitis over the different disease activity categories (HDA; LDA and remission). The number of patients with at least one ultrasound positive MTP joint decreased over time from 63% on average overall to 25% in all three categories of disease activity at 12 months.

Physical assessment and ultrasound

At joint level, we had complete data of 1032 MTP joints of which 302 (29%) were swollen at physical examination and 149 (14%) had ultrasound synovitis at baseline. Table 2 shows the kappa statistic, PPA and NPA during follow-up. Overall, agreement was poor. PPA of SJC with ultrasound was 16% (n=47). Focussing on physically non-swollen joints (n=730; 71%), NPA with ultrasound findings was 86% (n=628). During follow-up PPA between physically swollen joints and ultrasound decreased to 5%. NPA between physically non-swollen joints and ultrasound increased to 96%.

In addition, we evaluated the agreement between physically tender joints and ultrasound findings at joint level for MTP joints. These results were comparable to those of physically swollen joints [data not shown].

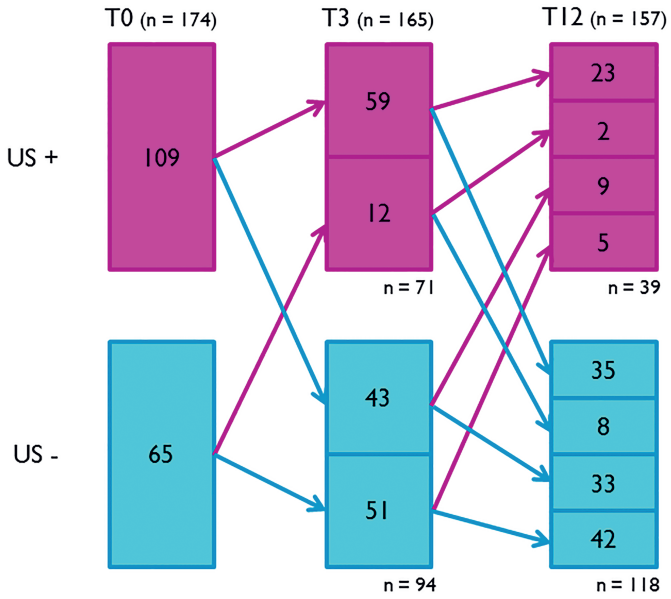


Figure 1. Course of ultrasound (US) findings in time in patients**.** Ultrasound synovitis positive and ultrasound negative patients (MTP joints) at baseline (T0), three months (T3), and twelve months (T12). At 12 months, 39 patients showed US synovitis (US+: GS≥2 and/or PD≥1) in the MTP joints and 118 patients showed no US synovitis.

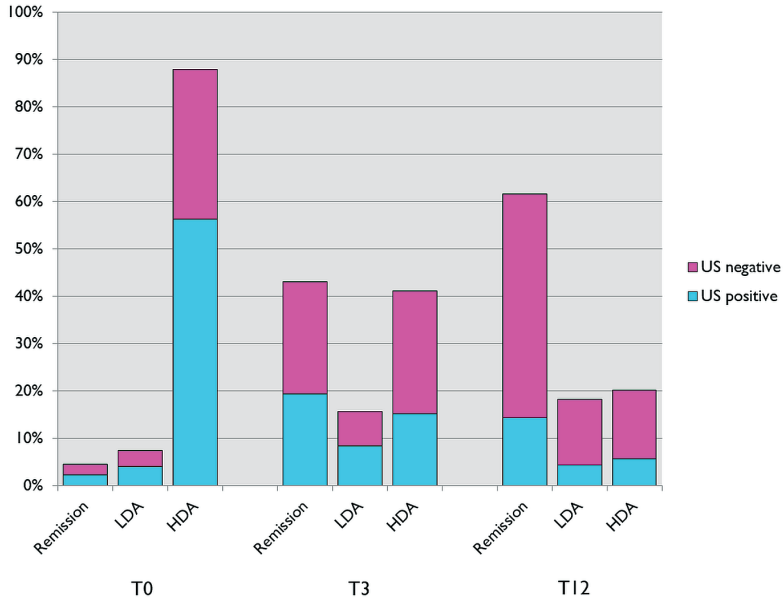


Figure 2. Distribution of early RA patients according to disease activity (DAS28) at baseline (T0), three months (T3), and twelve months (T12). The green bar depicts the percentage of patients who have at least one US positive MTP joint. (HDA = high disease activity; LDA = low disease activity; US = ultrasound)

Squeeze test and ultrasound

We had data on bilateral compression pain of MTP joints of 71 patients at baseline. We found positive test results in 44 patients of the MTP joints. During the study, the number of patients with positive squeeze test decreased to 7 (12%) after 12 months. Focusing on the PPA between the squeeze test and the ultrasound findings, 64% of the patients with a positive squeeze test of the MTP joints had a positive ultrasound of the MTP joints at baseline. After 12 months follow-up, the PPA decreased to 29%. NPA increased from 70% at baseline to 89% after 12 months.

Table 2 Agreement at joint level between US and physical examination of MTP joints

		SJC +	SJC -
T0 (n=1032)	US +	47	102
	US -	255	628
	K: 0.02	PPA: 15.6%	NPA: 86.0%
		SJC +	SJC -
T3 (n=944)	US +	5	57
	US -	81	801
	K: -0.01	PPA: 5.8%	NPA: 93.4%
		SJC +	SJC -
T12 (n=856)	US +	1	33
	US -	18	804
	K: 0.01	PPA: 5.3%	NPA: 96.1%

US: ultrasound; + = positive; - = negative; MTP: metatarsophalangeal joint; SJC: swollen joint count; PPA: positive percent agreement (agreement on positive cases); NPA: negative percent agreement (agreement on negative cases)

Discussion

In this study we investigated the course of ultrasound inflammation and its agreement with physical examination of the MTP joints in newly diagnosed RA patients who were treated to target. At one year of follow-up, we saw a decrease both in mean DAS score and number of ultrasound positive MTP joints. Eighty percent of the patients achieved DAS28 remission (DAS28≤2.6) or LDA (2.6<DAS28≤3.2), while irrespective of patients' clinical disease activity status, in 25% of the patients at least one MTP joint remained positive on ultrasound. Ultrasound and physical examination agreed poorly for individual joints. At baseline, positive ultrasound findings agreed in 14-16%

with joints that were both physically swollen or tender. This decreased to 1-5% at one year. Conversely, we found high agreement between physically non-swollen or non-tender MTP joints and a negative ultrasound. In 33 joints (4%) ultrasound synovitis was found in a physically non-swollen MTP joint at 12 months, which could indicate ongoing subclinical disease activity. This could lead to structural damage in the feet joints.[29, 30] In addition, we evaluated the agreement between the squeeze test of the feet and ultrasound findings in a subpopulation. The agreement on positive cases ranged from 64% at baseline to 29% after one year follow-up. In a previous study it was shown that adding the squeeze test of MTP joints to the DAS28 improved disease state categorisation in patients with RA.[22]

The discordance between physical examination and ultrasound results raises discussion to what extent adding ultrasound findings of the MTPs to physical exam results would lead to better patient care. Assessing MTP joints physically may be difficult in patients with high BMI, osteoarthritis and/or oedema.[4, 5] Our results show that scanning patients' feet at baseline is not effective as the number of ultrasound affected joints decreased over time comparable to the DAS. However, scanning the feet at turning points in the treatment may very well be effective. Persistent activity of the feet joints might justify intensification of treatment, or in a situation of DAS28 remission when treatment de-escalation would be an option, one could scan the feet to assess whether the feet are really in remission.

Previous studies concluded that subclinical joint inflammation detected by ultrasound could account for joint destruction in RA patients in clinical remission.[19, 20] Therefore, it would be recommended for future research to follow-up this study population to investigate whether we will find radiological progression, especially in the feet, in patients who have positive ultrasound findings of the MTP joints but do not show swelling at physical examination and vice versa (physically swollen, but negative ultrasound).

Heterogeneity in treatment strategies between centres could be considered as a limitation. However, all patients were treated according to a treat-to-target protocol, which reflects daily clinical practice. Another issue is that ultrasound is operator-dependent, therefore the ultrasound examiners attended training sessions to increase interobserver-reliability regarding acquisition and scoring. On joint level, interobserver reliability between the 7 ultrasonographers was 0.58 (ICC(A,1)) after four trainings sessions prior to the start of our study. Previous research regarding ultrasound interobserver-reliability confirmed that a consensus scoring system combined with a standardised acquisition protocol performed well.[31-33]

In summary, we evaluated inflammation of the MTP joints, both physically and by ultrasound, to answer the question whether ultrasound may be added routinely to physical examination in daily clinical practice for monitoring the feet. From our results we conclude that ultrasound synovitis is still present in one or more MTP joints in a quarter of the patients regardless of the status (remission or not) of their disease activity. This might imply that ultrasound of the feet could help us at turning points in the treatment of RA patients. At joint level, ultrasound synovitis in the MTP joints correlated poorly with physical examination findings. The clinical implications at patient level in an era aiming for remission may be vast and need to be further investigated.

References

1. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum. 2000;43(9):1927-40.
2. Dixey J, Solymossy C, Young A, Early RAS. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol Suppl. 2004;69:48-54.
3. Szkudlarek M, Narvestad E, Klarlund M, Court-Payen M, Thomsen HS, Ostergaard M. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. Arthritis Rheum. 2004;50(7):2103-12.
4. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38(1):38-43.
5. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum. 1989;32(5):531-7.
6. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69(6):964-75.
7. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69(4):631-7.
8. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404-13.
9. Landewe R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006;65(5):637-41.
10. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis. 2005;64(10):1410-3.
11. van der Leeden M, Steultjens MP, van Schaardenburg D, Dekker J. Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. Arthritis Res Ther. 2010;12(1):R3.
12. Jacobs JW, Ten Cate DF, van Laar JM. Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice. Rheumatology (Oxford). 2015;54(6):959-61.
13. de Jong PH, Hazes JM, van Zeben D, van der Lubbe PA, de Jager MH, de Sonnaville PB, et al. Treatment decisions and related costs differ significantly depending on the choice of a disease activity index in RA, according to 1987 and 2010 classification criteria. Rheumatology (Oxford). 2012;51(7):1269-77.
14. Kapral T, Dernoschnig F, Machold KP, Stamm T, Schoels M, Smolen JS, et al. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? Arthritis Res Ther. 2007;9(4):R72.
15. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum. 1994;37(4):470-5.
16. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54(12):3761-73.
17. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis. 2005;64(3):375-81.
18. Funck-Brentano T, Gandjbakhch F, Etchepare F, Jousse-Joulin S, Miquel A, Cyteval C, et al. Prediction of radiographic damage in early arthritis by sonographic erosions and power doppler signal: A longitudinal observational study. Arthritis Care and Research. 2013;65(6):896-902.
19. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
20. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456-65.

21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
22. de Jong PH, Weel AE, de Man YA, Huisman AM, Gerards AH, van Krugten MV, et al. Brief Report: to squeeze or not to squeeze, that is the question! Optimizing the disease activity score in 28 joints by adding the squeeze test of metatarsophalangeal joints in early rheumatoid arthritis. Arthritis Rheum. 2012;64(10):3095-101.
23. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60(7):641-9.
24. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
25. Witt M, Mueller F, Nigg A, Reindl C, Leipe J, Proft F, 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 Rheum. 2013;65(7):1694-701.
26. Ten Cate DF, Luime JJ, Hazes JM, Kleinrensink GJ, Jacobs JW. Is the frequent sonographic anechoic area distally in metacarpophalangeal joints a sign of arthritis? Ultrasound Med Biol. 2014;40(10):2537-41.
27. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
28. Kundel HL, Polansky M. Measurement of observer agreement. Radiology. 2003;228(2):303-8.
29. Bakker MF, Jacobs JW, Kruize AA, van der Veen MJ, van Booma-Frankfort C, Vreugdenhil SA, et al. Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices that do not include joints of feet. Ann Rheum Dis. 2012;71(6):830-5.
30. Sheane BJ, Beddy P, O'Connor M, Miller S, Cunnane G. Targeted ultrasound of the fifth metatarsophalangeal joint in an early inflammatory arthritis cohort. Arthritis Rheum. 2009;61(7):1004-8.
31. Wakefield RJ, D'Agostino MA, Iagnocco A, Filippucci E, Backhaus M, Scheel AK, et al. The OMERACT Ultrasound Group: status of current activities and research directions. J Rheumatol. 2007;34(4):848-51.
32. D'Agostino MA, Conaghan PG, Naredo E, Aegerter P, Iagnocco A, Freeston JE, et al. The OMERACT ultrasound task force -- Advances and priorities. J Rheumatol. 2009;36(8):1829-32.
33. Thiele RG. Ultrasonography applications in diagnosis and management of early rheumatoid arthritis. Rheum Dis Clin North Am. 2012;38(2):259-75.

CHAPTER 6

No clear association between ultrasound remission and health status in RA patients in clinical remission

Myrthe van der Ven
T. Martijn Kuijper
Andreas H. Gerards
Ilja Tchetverikov
Angelique E.A.M. Weel
Derkjen van Zeben
Johanna M.W. Hazes
Jolanda J. Luime

Rheumatology (Oxford). 2017 Aug 1;56(8):1276-1281

Abstract

Objectives: Although rheumatoid arthritis (RA) patients achieve clinical remission, risk of flare still exists. Given the association between ultrasound synovitis and increased risk of flare, it is of clinical interest whether these patients report a different health status. Therefore, we evaluated the frequency of ultrasound remission in RA patients in clinical remission. In addition, we compared health status of RA patients in clinical remission with them who were also in ultrasound remission.

Methods: In a prospective study we included 89 RA patients (aged>17 years) treated with a synthetic DMARD and a TNF-inhibitor who were in remission (DAS44≤2.4&SJC≤1). Demographic characteristics, swollen and tender joints, laboratory variables, ultrasound (MCP2-5;PIP2-5;wrists;MTP2-5) and patient reported outcomes (general health, functional ability, fatigue, depression and anxiety, pain, morning stiffness) were recorded at two consecutive visits (three months in-between). Ultrasound remission was defined as grayscale grade≤1 and power Doppler=0.

Results: At visit 1, 39% of patients were in ultrasound remission. At visit 2, 32% of patients were in ultrasound remission. At visit 1, functional ability (Health Assessment Questionnaire (HAQ)) was scored lower by patients in ultrasound remission (p=0.029). At visit 2, HAQ scores were similar (p=0.928). At visit 2, Hospital Anxiety and Depression Scale (HADS) anxiety score and VAS pain were significantly higher in patients in ultrasound remission. Similar levels were found for the other patient reported outcomes.

Conclusions: One-third of RA patients in clinical remission were in ultrasound remission. In our study population we could not find a clear association between health status of RA patients and being in ultrasound remission.

Introduction

Due to the effectiveness of synthetic and biological disease modifying anti-rheumatic drugs (DMARDs), and tight-controlled treatment, many rheumatoid arthritis (RA) patients are able to reach a state of clinical remission.[1] Although patients achieve clinical remission, studies reported that risk of flare still exists in these patients while DMARD treatment is continued.[2, 3] This might indicate that underlying inflammation is still present. Such subclinical inflammation could be detected with ultrasound. Previous studies found ongoing active ultrasound synovitis in 48-73% of RA patients who were clinically in remission.[3-7] Furthermore, previous research indicated that ultrasound synovitis (power Doppler (PD) positive) predicts short-term relapse in RA patients in clinical remission.[3, 8, 9]

Given the association between ultrasound synovitis and increased risk of flare, it is of clinical interest whether these patients with ultrasound synovitis report a different health status regarding pain, fatigue and general health. Subtle changes in health status may precede clinical flare.[9, 10] This could be used by physicians to adapt their treatment different in these patients compared to patients who are both in clinical and ultrasound remission. However, the association between health status and clinical remission or ultrasound remission has not been investigated thoroughly. If a better health status is associated with ultrasound remission, regularly measuring the self-reported health of RA patients would help to monitor patients at risk of flare. This relates to the aim of the Outcome Measures in Rheumatology (OMERACT) RA Flare Group, working on a validated outcome measure to identify flare including both the patient and the physician perspective.[11, 12]

In this study, we evaluated the frequency of ultrasound remission in RA patients who were in clinical sustained remission while they were continuing their synthetic and biological DMARD treatment. Our second objective was to compare the health status of RA patients in clinical remission with RA patients who were also in ultrasound remission.

Patients and methods

Patients

We used consecutive RA patients (aged >17 years) who were included in the ongoing TARA (TApering strategies in Rheumatoid Arthritis) study. Patients were treated with

the combination of a synthetic DMARD (sDMARD) and a TNF-inhibitor (TNFi) and were in remission defined as DAS44≤2.4 and SJC ≤1 (TARA remission). According to the Boolean remission definition we permitted one swollen joint.[13] This study focusses on the first two visits (baseline and three months follow-up) of the TARA study. During these three months follow-up, patients continued their medication. The use of concomitant NSAIDs was allowed. Patients were asked to refrain from corticosteroids, but there were no restrictions on the use of intra-articular injections with glucocorticosteroids. At baseline (visit 1) demographic characteristics, medication use, swollen and tender joint count (44 joint count), laboratory variables (ESR, serology), ultrasound and patient reported outcomes were recorded for each patient. After three months (visit 2), if the patient was still in TARA remission, laboratory variables, swollen and tender joint count, ultrasound and patient reported outcomes were recorded again.

Patients had to be able to understand, speak and write in Dutch. Written informed consent was obtained from the participants according to the declaration of Helsinki. The study was approved by the local medical ethic committee of Erasmus MC, University Medical Centre Rotterdam, the Netherlands.

Ultrasound examination

A trained ultrasound examiner blinded for the clinical details performed ultrasound following the 'European League Against Rheumatism' (EULAR) guidelines, concerning patient position and scanning planes.[14] Twenty-six joints were evaluated with the Esaote Mylab60 (probe LA435) using grayscale (GS) and power Doppler (PD) imaging. We scanned MTP2-5 (dorsal aspect), MCP2-5 and PIP2-5 (dorsal and palmar aspects), and wrist (radiocarpal and intercarpal joints) bilaterally. A single midline (longitudinal 12 o'clock position) scan perpendicularly to the bone surface was used as advised by the OMERACT ultrasound working group.[15] The following PD settings were used: colour gain was set at the disappearance of colour noise. The Pulse Repetition Frequency (PRF) was set as low as possible to yield maximum sensitivity which resulted in a frequency of 750 Hz. We adjusted the size and position of the colour box to include the subcutaneous tissue to recognize artefacts caused by superficial vessels.[16] PD signals were measured only in joints with GS≥1. The total scanning time was ½ hour per patient per session. The treating rheumatologist was unaware of the results from the ultrasound examination.

Ultrasound evaluation

Image evaluation followed the recommendations of the Spanish society for Rheumatology. This is a modified version of the previously developed OMERACT

definitions of sonographic pathology.[17] Joints were graded according to a semi-quantitative scoring system (0-3) for both GS and PD. For GS, all joints were graded according to Szkudlarek et al., 0 = no synovial thickening, 1 = minimal synovial thickening, filling the angle between the periarticular bones, without bulging over the line linking the bone diaphyses of the periarticular bone regions; 2 = synovial thickening without extension over the bone diaphyses; 3 = synovial thickening over at least one of the bone diaphysis.[18]

Synovial vascularisation was measured using power Doppler. Power Doppler was graded according to Naredo et al., 0 = absent; 1 = mild, single vessel signal or isolated signal; 2 = moderate, confluent vessel signals in the intra-articular area; 3 = marked, vessel signals in more than half of the intra-articular area.[19]

Ultrasound remission was defined as GS grade 0 or 1 and absence of PD.

Health status

Patients completed questionnaires regarding their health status before each visit. General health and functional ability were assessed at baseline and after three months. Fatigue, morning stiffness, pain, depression and anxiety were evaluated after three months.

General health. Physical and mental health was assessed by the Medical Outcomes Study Short Form 36 (SF-36) health survey. The SF-36 includes eight scales that assess pain, physical functioning, general health, fatigue/vitality, mental health, social functioning, and role limitations due to either physical or emotional problems. Two summary scores, the physical component summary (PCS) and mental component summary (MCS) were computed.[20, 21] The scores range from 0–100, where a higher score indicates a better physical or mental health.

Functional ability. Functional ability was assessed by the Health Assessment Questionnaire (HAQ).[22] The HAQ comprises 20 questions on eight dimensions of functional ability (e.g. dressing, arising, eating). The score ranges from 0–3, where higher scores indicate more disability.

Fatigue. Fatigue was measured by two questionnaires: the Fatigue Assessment Scale (FAS) and the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ). The FAS asks about fatigue on an average day and has two dimensions (physical and mental). Scores range from 10–50, with scores above 21 being regarded as fatigued and scores above 34 as severely fatigued.[23] The BRAF-MDQ asks about how fatigue has affected the patient in the past seven days and has four dimensions (i.e. physical, living, cognition and emotion). Scores range from 0-70.[24] For both the FAS and the BRAF, higher scores indicate higher levels of fatigue.

Depression and anxiety. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression status. A HADS score ≥8 (range: 0-21) is indicative of the presence of symptoms of mild, moderate or severe depression or anxiety.[25]
Pain. Pain was measured by tender joint count and by the Visual Analogue Scale (VAS) for pain. Tender joint count was measured during physical examination and included 44 joints. For the VAS pain patients were asked to self-assess the joint pain they have due to their arthritis. VAS pain ranges from 0-10 cm. The level of pain increases with higher scores.
Morning stiffness. Patients were asked if they encountered morning stiffness, for how long the morning stiffness was present (in minutes) and they were asked to self-assess the severity of the morning stiffness by a score ranging from 0 to 10. The severity of morning stiffness increases with higher scores.

Statistical analysis

Our primary outcome was ultrasound remission. Ultrasound remission was defined as GS grade ≤1 and absence of power Doppler signal. Simple descriptive techniques were used to describe the study sample. We analysed differences in health status between patients who were and who were not in ultrasound remission cross-sectionally for both baseline (visit 1) and after three months (visit 2). Since the data were not normally distributed we used the Wilcoxon-Mann-Whitney test. Frequencies were compared using a Chi-square test. Analyses were done using STATA 13.0, using a p-value ≤ 0.05 as the level of statistical significance.

Results

For this analysis we included 89 patients. Table 1 shows the baseline characteristics of all patients. According to the DAS44, 82% of the patients were in clinical remission (DAS44<1.6). Eighteen percent of the patients had low disease activity (LDA; 1.6<DAS44≤2.4). After three months (visit 2) we had data of 71 patients. Seven patients had a flare (DAS44≥2.4 or ≥1 swollen joint) while continuing their combination treatment of synthetic and biological DMARDs. Of these seven patients, four patients had ultrasound synovitis at visit 1. At joint level, there was no concordance between the clinical findings (SJC) and ultrasound synovitis. Eleven patients were lost to follow-up at visit 2.

Ultrasound examination

In total, 39% of the patients in TARA remission were in ultrasound remission at visit 1. At visit 2 after three months 32% of the patients were in ultrasound remission. Eighteen percent of the patients were in ultrasound remission at both visits. In the patients who were not in ultrasound remission, ultrasound synovitis was found most often in the wrists (visit 1: 39%; visit 2: 45%) and in the MTP joints (visit 1: 27%; visit 2: 30%). Ultrasound synovitis was found in 3% (visit 1) to 6% (visit 2) of the patients in the PIP joints. When we focussed on the absence of PD signal, the number of patients in ultrasound remission increased to 54% (visit 1) and 42% (visit 2). Table 2 shows the ultrasound findings for visit 1 and visit 2.

Table 1: Baseline characteristics of patients in TARA remission - DAS44≤2.4 & SJC ≤1 (n=89)

Characteristic	
Age, mean ±sd years	55 (12)
Women, n (%)	59 (66)
Time since diagnosis, mean ±sd years	5 (3.4)
DAS44, mean ±sd	1.1 (0.5)
DAS44 remission (DAS44<1.6) , n (%)	73 (82)
SJC = 1, n (%)	12 (14)
BSE, median (IQR)	8 (3-16)
RF positive, n (%)	45 (55)
ACCP positive, n (%)	56 (69)

DAS44 = disease activity score in 44 joints; SJC = swollen joint count; ACCP = anti-cyclic citrullinated peptide antibody; sd = standard deviation; IQR = interquartile range

Table 2: Ultrasound findings at baseline and at three months

	Visit 1 (n=89)	Visit 2 (n=71)
GS, # positive joints, median (IQR)	0 (0-2)	0 (0-1)
PD, # positive joints, median (IQR)	0 (0-1)	1 (0-1)
US synovitis, %		
MCP	12	10
PIP	6	3
Wrists	39	45
MTP	30	27
US remission, %	39	32
PD remission, %	54	42

GS = grayscale (GS≥2); PD = power Doppler; # = number; US = ultrasound; IQR = interquartile range; US synovitis = GS≥2 and/or presence of PD; US remission = GS≤1 and absence of PD; PD remission = absence of PD

Health status and ultrasound remission

Table 3 shows the health status at baseline and at three months. No clear pattern emerged on health status between patients who were in ultrasound remission and who were not in ultrasound remission. At visit 1 functional ability (HAQ) was scored lower by patients who were in ultrasound remission than by patients who were not in remission (p=0.029), while general health (SF36) and TJC were similar. At visit 2 similar levels in both ultrasound groups were observed for functional ability, general health, TJC, depressive symptoms and fatigue. In general we found low scores for HADS anxiety, HADS depression and for VAS pain. But the HADS anxiety score and VAS pain were significantly higher in patients who were in ultrasound remission than in patients who were not ultrasound remission at visit 2 (HADS anxiety: p<0.001; VAS pain: p=0.014).

We conducted the same analysis on health status and the presence or absence PD signal. The results were not analogous with the results we found with ultrasound remission. At visit 1 SF36 physical scale was significantly lower in patients with the presence of PD signal (no PD ultrasound remission; p=0.015). At visit 2 we could not find any association between health status and the presence or absence of PD signal.

Discussion

Thirty-nine percent of the RA patients in TARA remission were in ultrasound remission (GS grade ≤1 and absence of PD signal) at baseline. This indicates that the remaining two-third of the patients had ultrasound synovitis (GS grade 2 or 3 and/or PD grade 1, 2 or 3) while they were in TARA remission and continued their synthetic and biological DMARDs. This is comparable with previous studies who found active ultrasound synovitis in 48-73% of RA patients who were clinically in remission.[3-7, 26] After three months follow-up patients returned to the outpatient clinic, at this visit 32% of the RA patients were in ultrasound remission. Comparing the ultrasound results at both visits, 18% of the patients were in ultrasound remission at visit 1 and at visit 2. If we focussed on the absence of PD signal, 31% of the patients had no PD signal at both visits. According to the Boolean remission criteria for RA we allowed one clinically swollen joint. At joint level however, the ultrasound findings were not consistent with the clinically swollen joints.

In our study population we could not find a clear association between health status and being in ultrasound remission. Overall patients reported good health with low

Table 3 Patient reported outcomes at baseline and at three months (all patients were in TARA remission†)

	Visit 1			Visit 2		
	US remission (n=35)	non-US remission (n=54)	p-value*	US remission (n=23)	non-US remission (n=48)	p-value*
HAQ (range 0-3), median (IQR)	0.3 (0-0.9)	0.6 (0.1-1.4)	0.029	0.3 (0-0.6)	0.3 (0-0.6)	0.928
SF36 (range 0-100), median (IQR)						
PCS	49 (44-52)	44 (38-50)	0.084	48 (44-52)	46 (40-52)	0.780
MCS	54 (49-59)	57 (54-59)	0.134	55 (41-59)	58 (54-61)	0.054
TJC (range 0-44), median (IQR)	0 (0-2)	0 (0-1)	0.528	0 (0-2)	0 (0-1)	0.478
VAS pain (range 0-10), median (IQR)				3 (2-4)	1 (1-3)	0.014
Morning stiffness severity (range 0-10), median (IQR)				3 (0-4)	1 (0-2)	0.084
HADS anxiety (range 0-21), median (IQR)				5 (3-7)	3 (1-5)	<0.001
HADS depression (range 0-21), median (IQR)				2 (1-3)	1 (0-3)	0.250
BRAF (range 0-70), median (IQR)				21 (13-26)	14 (6-23)	0.070
Fatigue (FAS; range 10-50), median (IQR)				21 (18-23)	18 (14-23)	0.160

US = Ultrasound; HAQ = Health Assessment Questionnaire; SF-36 = Short Form 36; HADS = Hospital Anxiety and Depression Scale; BRAF = Bristol RA Fatigue Multi-Dimensional Questionnaire; FAS = Fatigue Assessment Scale; PCCL = Pain Coping and Cognition Scale; IQR = interquartile range; † TARA remission definition: DAS44≤2.4 & SJC≤1; *Wilcoxon-Mann-Whitney test for continuous scales, Chi-square test for binary scales, p-value≤0.05

scores for pain, functional disability, anxiety, depression and fatigue and higher scores for general health. These self-reported patient outcomes were expected, because all patients were in clinical remission or had LDA. A study of Sakellariou et al. showed that being in clinical remission was associated with low disability (low HAQ-score) and absence of PD signal.[27] We found low HAQ-scores overall, but we did find positive PD signals in half of our population, while they were in clinical remission.

In our definition of ultrasound synovitis we combined GS abnormalities with PD signal. GS abnormalities in RA patients could also be explained as hypertrophy of the synovium after inflammation.[28] Other studies showed that GS abnormalities also occur in non-arthritic individuals, and especially the discriminative value of GS score 1 is debatable.[29, 30] In addition, it has been shown that the presence of PD signal increases the risk of flare.[3, 8, 9] We found a positive PD signal in 46% (visit 1) to 58% (visit 2). These percentages are comparable with other studies evaluating the presence of PD signal in RA patients in clinical remission.[3-7, 26] After analysis of health status and the presence or absence of PD signal the results were not analogous with the results we found with ultrasound remission. This indicates that using a different definition for ultrasound remission is not helpful to distinguish between patients by their health status. We choose to include 26 joints (MCP2-5, PIP2-5, wrists, MTP2-5), because these joints are most frequently involved in RA.[31] Based on a review of Ten Cate et al. it also seemed that it is not necessary to include large joints in the ultrasound assessment.[28]

We found significant higher scores on the HADS anxiety score and VAS pain in patients who were in ultrasound remission than in patients who were not in ultrasound remission. Although the median score on both outcomes was low, these were still unexpected findings since one might expect an association in the opposite direction. It might be explained by the fact that patients who were not in ultrasound remission were less sensitive to pain or could cope better, or these results might be spurious findings. Another explanation could be related to a drop-out bias, since seven patients had a flare and 11 patients were lost to follow-up at visit 2. The majority (n=13) of these patients were not in ultrasound remission at visit 1, which might imply that they had worse health status. However, we do not have data for HADS anxiety and VAS pain at visit 1 which made it not possible to say whether this explanation holds.

There are limitations to monitor patients only with self-reported health status. Previous studies showed that changes in self-reported health status were of limited value to predict disease activity in individual patients.[32, 33] We know from previous research in RA patients in clinical remission that clinically swollen or tender joints and ultrasound synovitis can predict disease relapse. Our results indicate that ultrasound remission

does not distinguish between patients with different health status. Therefore, it might be desirable to combine physical examination, self-reported health status and ultrasound examination to optimise patient care.

Our study has some limitations. At three months follow-up (visit 2) only 8% (n=7) of the patients in TARA remission had a flare, which was capture by DAS44≥2.4 or ≥1 swollen joint. This low flare rate might be explained by selection bias by the rheumatologists who included the patients. Rheumatologists could be tempted to only refer RA patients who achieved remission easily and who had less severe disease.

In this study we included patients with a mean disease duration of five years. These patients were treated following a tight treatment protocol and with the availability of biologicals. Our study population possibly consisted of patients with less severe disease, because they had no longstanding disease and were in clinical remission on combination therapy of a synthetic and a biological DMARD.

In conclusion, one-third of the RA patients in clinical remission were also in ultrasound remission. In our study population we could not find a clear association between health status of RA patients and being in ultrasound remission. We did find that patients in ultrasound remission experienced more pain and anxiety, however this in the opposite direction than expected. This might indicate that health status is not be a suitable tool to distinguish patients who have or have not underlying ultrasound synovitis while they are continuing their synthetic and biological DMARDs. We recommend that our results need to be confirmed in other cohorts with RA patients who are in clinical remission.

References

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.
2. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum. 2004;50(1):36-42.
3. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis. 2011;70(1):172-5.
4. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54(12):3761-73.
5. Ozgocmen S, Ozdemir H, Kiris A, Bozgeyik Z, Ardicoglu O. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. South Med J. 2008;101(3):240-5.
6. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum. 2009;60(7):1915-22.
7. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456-65.
8. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford). 2009;48(9):1092-7.
9. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis. 2012;71(8):1316-21.
10. Bingham CO, 3rd, Alten R, de Wit MP. The importance of patient participation in measuring rheumatoid arthritis flares. Ann Rheum Dis. 2012;71(7):1107-9.
11. Bingham CO, 3rd, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, et al. Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. J Rheumatol. 2011;38(8):1751-8.
12. Bykerk VP, Lie E, Bartlett SJ, Alten R, Boonen A, Christensen R, et al. Establishing a core domain set to measure rheumatoid arthritis flares: report of the OMERACT 11 RA flare Workshop. J Rheumatol. 2014;41(4):799-809.
13. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404-13.
14. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60(7):641-9.
15. Naredo E, Moller I, Moragues C, de Agustin JJ, Scheel AK, Grassi W, et al. Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course. Ann Rheum Dis. 2006;65(1):14-9.
16. Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann Rheum Dis. 2008;67(2):143-9.
17. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485-7.
18. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
19. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis. 2005;64(3):375-81.
20. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

21. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247-63.
22. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45.
23. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res. 2003;54(4):345-52.
24. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res (Hoboken). 2010;62(11):1559-68.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
26. Naredo E, Valor L, De la Torre I, Martinez-Barrio J, Hinojosa M, Aramburu F, et al. Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? Arthritis Care Res (Hoboken). 2013;65(4):512-7.
27. Sakellariou G, Scire CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis. 2013;72(2):245-9.
28. Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM, et al. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis - a systematic review of the literature. Arthritis Res Ther. 2013;15(1):R4.
29. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford). 2010;49(4):683-90.
30. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther. 2010;12(3):R98.
31. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903-11.
32. Walter MJ, Mohd Din SH, Hazes JM, Lesaffre E, Barendregt PJ, Luime JJ. Is tightly controlled disease activity possible with online patient-reported outcomes? J Rheumatol. 2014;41(4):640-7.
33. Blanchais A, Berthelot JM, Fontenoy AM, le Goff B, Maugars Y. Weekly home self-assessment of RAPID-4/3 scores in rheumatoid arthritis: a 6-month study in 26 patients. Joint Bone Spine. 2010;77(6):582-7.

CHAPTER 7

Three-monthly ultrasound monitoring of rheumatoid arthritis patients tapering their medication has limited value in predicting disease relapse

Myrthe van der Ven
T. Martijn Kuijper
Andreas H. Gerards
Ilja Tchetverikov
Angelique E.A.M. Weel
Derkjen van Zeben
Cees Bijkerk
Yaël A. de Man
Johanna M.W. Hazes
Jolanda J. Luime

Submitted

Abstract

Objectives: Prognostic factors that may guide tapering decisions for DMARDs and TNFi on individual patient level are not available. Studies using ultrasound suggest that the presence of subclinical synovitis may elicit early disease relapse in remission. Our aim is to determine if ultrasound synovitis precedes disease relapse while tapering synthetic DMARD (sDMARD) or TNFi in patients with RA who achieved clinical remission on sDMARD and TNFi.

Methods: We included 125 RA patients (aged>17 years) treated with an sDMARD and a TNF-inhibitor who were in remission (DAS44≤2.4&SJC≤1). Demographic characteristics, swollen and tender joints, laboratory variables and ultrasound synovitis (MCP2-5;PIP2-5;wrists;MTP2-5) were recorded at each visit (every three months) during one year follow-up. Patients were randomised to two tapering strategies: i) tapering sDMARD; ii) tapering TNFi. Disease relapse was defined as DAS44>2.4 or SJC>1. Ultrasound synovitis was defined as GS≤1 and/or PD≤0.

Results: Ultrasound synovitis was found in 58% of RA patients in clinical remission. After one year follow-up 36% of RA patients had a disease relapse. In the multivariate Cox model increasing number of joints with ultrasound synovitis was not significantly associated with disease relapse (HR 1.21; 95%CI:0.97-1.51). Positive predictive value of ultrasound for having a disease relapse was 14%, negative predictive value was 92%.

Conclusions: Monitoring RA patients who started tapering their medication every three months showed limited value for ultrasound to identify patients who will have a disease relapse.

Introduction

Effective tapering of medication in rheumatoid arthritis (RA) patients in early remission might help to reduce the costs of expensive TNF inhibitors (TNFi) without compromising on the health of our patients. One of the possible ways is to taper the TNFi early in the remission state. For the majority of patients, tapering is in line with the patient's willingness to reduce their medication for their rheumatoid arthritis when signs and symptoms of joint inflammation disappeared. They would like to live without medication but are also worried about disease relapse when tapering medication.

Prognostic factors that may guide tapering decisions for classical disease modifying anti-rheumatic drugs (DMARDs) and TNFi on individual patient level are not available. Previous research suggested that failure of tapering of classical DMARDs is associated with anti-CCP positivity and a high mean DAS preceding the period of remission. None of the characteristics in the remission state itself were associated with tapering failure.[1]

To improve successful tapering subclinical synovitis may play a role in maintaining the remission state. Studies using ultrasound suggest that the presence of subclinical synovitis may elicit early disease relapse in remission.[2-5] This may be because the true underlying inflammation process is insufficiently suppressed, and a clinical detectable disease relapse easily provoked.[2, 3, 6-9]

To improve individual tapering decisions in remission we need to know which risk factors for disease relapse play a role. One important factor is insufficient suppression of disease activity. Therefore, we monitored RA patients in clinical remission tapering their TNFi or synthetic DMARD (sDMARD) every three months during one year follow-up with ultrasound. This information will help to optimise tapering strategies in future patients in remission. Our main aim is to determine if ultrasound synovitis precedes disease relapse while tapering sDMARD or TNFi in patients with RA who achieved clinical remission on sDMARD and TNFi.

Methods

Patients

We used consecutive RA patients (aged >17 years) who were included in the TARA (TApering strategies in Rheumatoid Arthritis) study. The TARA study is a multicentre randomised single-blind controlled trial. Patients were treated with the combination of a sDMARD and a TNFi and were in remission defined as DAS44≤2.4 and SJC ≤1 (TARA

remission) for two consecutive visits (three months). In line with the Boolean remission definition we permitted one swollen joint.[10] Patients were excluded if they needed to taper or stop their medication due to other reasons such as the wish to get pregnant or a scheduled surgery. The use of concomitant NSAIDs was allowed. Patients were asked to refrain from corticosteroids, but there were no restrictions on the use of intra-articular injections with glucocorticosteroids. If patients were in TARA remission at the second visit, they were randomised to two tapering strategies: i) Tapering sDMARD and ii) Tapering TNFi, and followed for one year. Tapering was terminated if the DAS>2.4 or SJC>1 at one of the 3-month follow-ups. Depending on the DAS and the number of swollen joints at physical examination, patients were either switched to the last effective dosage in case of a flare (DAS>2.4 or SJC>1) or tapered down further when they were still in TARA remission (DAS44≤2.4 and SJC ≤1). In case of a flare, one intramuscular injection with glucocorticosteroids was allowed to be given as bridging therapy in addition to switching to the last effective dosage. Every three months patients returned to the outpatients clinic and demographic characteristics, medication use, swollen and tender joint count (44 joint count), laboratory variables (ESR, CRP, serology) and ultrasound examination were recorded.

Patients had to be able to understand, speak and write in Dutch. Written informed consent was obtained from the participants according to the declaration of Helsinki. The study was approved by the local medical ethic committee of Erasmus MC, University Medical Centre Rotterdam, the Netherlands.

Ultrasound examination

A trained ultrasound examiner blinded for the clinical details performed ultrasound following the 'European League Against Rheumatism' (EULAR) guidelines, concerning patient position and scanning planes.[11] Twenty-six joints were evaluated with the Esaote Mylab60 (probe LA435) using grayscale (GS) and power Doppler (PD) imaging. We scanned MTP2-5 (dorsal aspect), MCP2-5 and PIP2-5 (dorsal and palmar aspects), and wrist (radiocarpal and intercarpal joints) bilaterally. A single midline (longitudinal 12 o'clock position) scan perpendicularly to the bone surface was used as advised by the OMERACT ultrasound working group.[12] The following PD settings were used: colour gain was set at the disappearance of colour noise. The Pulse Repetition Frequency (PRF) was set as low as possible to yield maximum sensitivity which resulted in a frequency of 750 Hz. We adjusted the size and position of the colour box to include the subcutaneous tissue to recognise artefacts caused by superficial vessels.[13] PD signals were measured only in joints with GS≥1. The total scanning time was ½ hour per patient per session. The treating rheumatologist was unaware of the results from the ultrasound examination.

Ultrasound evaluation

Image evaluation followed the recommendations of the Spanish society for Rheumatology. This is a modified version of the previously developed OMERACT definitions of sonographic pathology.[14] Joints were graded according to a semi-quantitative scoring system (0-3) for both GS and PD. For GS, all joints were graded according to Szkudlarek et al., 0 = no synovial thickening, 1 = minimal synovial thickening, filling the angle between the periarticular bones, without bulging over the line linking the tops bone diaphyses of the periarticular bone regions; 2 = synovial thickening without extension over the bone diaphyses; 3 = synovial thickening over at least one of the bone diaphysis.[15]

Synovial vascularisation was measured using PD. PD was graded according to Naredo et al., 0 = absent; 1 = mild, single vessel signal or isolated signal; 2 = moderate, confluent vessel signals in less than half of the intra-articular area; 3 = marked, vessel signals in more than half of the intra-articular area.[16]

Outcomes

The primary and secondary outcomes were defined as follows:

Primary outcome: Disease relapse defined as DAS44>2.4 or SJC>1 during one year follow-up.

Secondary outcome: Presence of ultrasound synovitis defined as GS>1 and/or PD>0.

Analysis

Simple descriptive techniques were used to describe the study sample.

Sensitivity and specificity were used to assess the prognostic value of ultrasound for having a disease relapse.

To estimate whether ultrasound is able to identify patients who will have a disease relapse while tapering their medication a Cox proportional regression model for time to event data was used. Estimates were corrected for potential confounding variables (age, gender, ACCP, time since diagnosis and DAS at time of ultrasound). For each event, DAS and number of joints with ultrasound synovitis recorded at the previous visit were included as time-varying covariates. The validity of the proportional hazard assumption of the variables in each model was determined using Schoenfeld's residuals. The analysis was stratified for tapering strategy. Since this study is still ongoing, randomisation is still concealed. We performed a second analysis with the number of joints with power Doppler signal.

All analyses were performed using intention-to-treat analysis and per-protocol analysis. Analyses were done using STATA 14.0.

Results

We included 125 patients in this analysis who were in TARA remission at baseline and started tapering their medication. Baseline characteristics are shown in Table 1. Disease relapse was defined as DAS44>2.4 or SJC>1. After one-year follow-up 45 patients (36%) had a disease relapse. The mean time to flare was 8 months (sd: 3 months). Patients had a relapse because they had two or more swollen joints (23/45; 51%), because they had both a DAS44>2.4 and SJC>1 (14/45; 31%) or because they had a DAS44>2.4 (8/45; 18%). Table 2 shows the number of patients who had a disease relapse and the number of patients who had ultrasound synovitis at each visit. At baseline 72 patients (58%) had ultrasound synovitis.

Table 1: Baseline characteristics of patients in TARA remission - DAS44≤2.4 & SJC ≤1 (n=125)

Characteristic	
Age, mean (sd) years	56 (13)
Women, n (%)	78 (62)
Time since diagnosis, mean (sd) years	5.4 (3.3)
SJC44, median (IQR)	0 (0-0)
TJC44, median (IQR)	0 (0-1)
DAS44, mean (sd)	1.0 (0.5)
ESR, median (IQR)	9 (3-15)
CRP, median (IQR)	2 (1-6)
RF positive, n (%)	65 (52)
ACCP positive, n (%)	80 (64)
US synovitis, n (%)	72 (58)

DAS44 = disease activity score in 44 joints; SJC = swollen joint count; TJC = tender joint count; ACCP = anti-cyclic citrullinated peptide antibody; US = ultrasound; sd = standard deviation; IQR = interquartile range

Table 2: Distribution of disease relapse and US synovitis during follow-up, n (%)

	T0	T3	T6	T9	T12
US synovitis	72/125 (58)	60/124 (48)	62/112 (55)	40/96 (42)	-
Disease relapse	0	6/124 (5)	8/112 (7)	23/96 (24)	8/67 (12)
US synovitis at previous visit	-	*4/6 (67)*	*5/8 (63)*	*14/23 (61)*	*6/8 (75)*
No disease relapse	0	118/124 (95)	104/112 (93)	73/93 (78)	59/67 (88)
No US synovitis at previous visit	-	*46/118 (39)*	*47/104 (45)*	*23/73 (32)*	*29/59 (49)*

US = ultrasound

Ultrasound findings

At baseline, ultrasound synovitis was found in 27 patients (60%) who had a disease relapse during the subsequent year. PD signal was present at baseline in 25 patients (56%) who had a disease relapse. Table 3 shows the distribution of joints with GS synovitis and PD synovitis at baseline in the RA patients who had a disease relapse.

Table 3. Ultrasound findings at baseline in RA patients who had a disease relapse (n = 45), n (%)

Joint group	GS >1	PD >0
MCP	8 (18)	5 (11)
PIP	1 (2)	0 (0)
wrist	18 (40)	17 (38)
MTP	14 (31)	6 (13)

GS: grayscale; PD: power Doppler

Agreement ultrasound and disease relapse

At patient level, 29 (64%) patients showed ultrasound synovitis at the previous visit before they had a disease relapse [Table 2].

In 13 patients (29%) who had a disease relapse, at least one joint which was found clinically swollen, showed ultrasound synovitis at the previous visit. Most frequently, agreement was found in the wrist joints (7/13; 54%). Eight patients had a disease relapse occurring in their large joints (elbow or knee), which were not included in the ultrasound assessment. In 13 patients who had a disease relapse no ultrasound synovitis was detected in any joint at the previous visit. In 15 patients ultrasound synovitis was detected, but the ultrasound positive joints did not match the clinically swollen joints during disease relapse.

Prognostic value of ultrasound

Given that patients returned to the outpatient clinic every three months, we had 368 observations during follow-up at which we could determine the prognostic value of ultrasound. Sensitivity and specificity of ultrasound synovitis in relation to the incidence of disease relapse were 69% and 44% respectively. Positive predictive value (PPV) was 14% and negative predictive value (NPV) was 92%. For the presence of PD signal, sensitivity was 45% and specificity was 65% (PPV 14%; NPV 90%).

Predictors for disease relapse

Increasing number of joints with ultrasound synovitis was not significantly associated with disease relapse within three months (HR 1.21; 95%CI: 0.97-1.51) in the multivariate

Cox model. In the model with PD signal, increasing number of positive joints with PD was significantly associated with disease relapse within three months (HR1.35; 95%CI: 1.02-1.80). In both models DAS at time of ultrasound was significantly associated with disease relapse within three months.

Table 4. Multivariate Cox model with US synovitis or PD synovitis for disease relapse, HR (95% CI)

	Model US synovitis	Model PD synovitis
Age	0.99 (0.97-1.02)	0.99 (0.97-1.02)
Gender	1.08 (0.53-2.17)	1.05 (0.53-2.11)
Time since diagnosis	1.02 (0.92-1.13)	1.03 (0.93-1.14)
ACCP	0.47 (0.24-0.91)	0.51 (0.27-0.97)
DAS (at time of US)	2.25 (1.21-4.19)	2.34 (1.25-4.41)
US synovitis	1.21 (0.97-1.51)	
PD synovitis		1.35 (1.02-1.80)

US = ultrasound; PD = power Doppler; HR = hazard ratio; ACCP = anti-cyclic citrullinated peptide antibody; DAS = disease activity score

Discussion

Data from several ultrasound studies indicate that subclinical disease lingers in RA patients in clinical remission.[17-19] We found ultrasound synovitis in 58% of RA patients in clinical remission, which is comparable with previous research.[3, 20] During one year, an ultrasound assessment was done every three months in RA patients in clinical remission who tapered their medication. Increasing number of joints with a positive PD signal increased the risk for having a disease relapse within three months. However, at individual patient level ultrasound did not perform well in predicting disease relapse (post-test probability positive test 14%), but did perform well in ruling out disease relapse in patients who did not have ultrasound synovitis (post-test probability negative test 92%). These results were likely to occur due to the high number of patients who were ultrasound positive (about 50% at each time point) and the initial low level of disease flare (5%) at three months follow-up. In general, ultrasound identified two thirds of patients who had a disease relapse at a subsequent time point.

Recent work by Lamers-Karnebeek et al. showed that baseline ultrasound was informative at group level (HR: 1.7; 95% CI: 1.1-2.5) for predicting disease relapse within one year in RA patients discontinuing TNFi, but was the first to show that at patient level ultrasound had little added value over easy available clinical variables.[20]

Although we tapered rather than stopped medication, our results indicate the same as Lamers-Karnebeek that there seems no direct value in scanning every patient in clinical remission to decide if tapering could be safely initiated. However, this is conflicting with results from previous studies. There are two observational studies and one clinical trial showing more positive results for ultrasound as predictor of disease relapse. The observational studies found strong associations of the presence of PD at baseline with disease relapse (OR: 29.9; 95%CI: 6.81-131.40)[21] and high positive predictive value (89%) and negative predictive value (74%)[22], suggesting that PD ultrasound contributes to improve selection which RA patients in sustained clinical remission could taper or discontinue their biologic therapy. Both studies included a relatively small and very heterogeneous RA population with respect to disease characteristics and biological treatment. A randomised controlled trial included RA patients in sustained remission and evaluated disease relapse during continuation, tapering or stopping DMARDs or biologic treatment.[23] GS and PD scores at three months (GS OR: 4.51; PD OR: 4.62) were identified as predictors for disease relapse within 12 months in patients who tapered biologic treatment. In comparison with these studies, our study population visited the outpatient clinic every three months and if a patient had sustained remission (DAS44<2.4 & SJC<1) the next step in tapering was taken. At each treatment de-escalation step an ultrasound assessment was done, while three of four studies used baseline ultrasound data only.[20-22] In our study population, baseline ultrasound at the start of tapering did not contribute to identifying patients with a disease relapse at any time point during one year follow-up [data not shown]. With the notion that patients continued tapering at each visit when they had sustained clinical remission.

Agreement between swollen joints and ultrasound assessment was found in 13/45 patients who had a disease relapse during follow-up. Physical examination included 44 joints following the DAS and the ultrasound protocol used included only 26 joints (MCP2-5, PIP2-5, wrists, MTP2-5). Therefore, inflammation in large joints could have been missed. However, the presence of PD signal in any joint was associated with having a disease relapse. Other studies had a more extensive ultrasound protocol including 40 to 42 joints[21-23], but our results suggest that a reduced number of joints might be feasible as well. Since we found GS ultrasound synovitis in the PIP joint of one patient only, it could be considered to remove the PIP joints from the ultrasound protocol.

Several other studies provide results on disease relapse frequency when tapering or stopping drugs.[20-24] We found during one year follow-up that 36% of RA patients had a disease relapse. This flare rate is slightly lower compared with results from other

studies. In other RA populations in clinical remission, 40% to 50% of the patients failed tapering or discontinuation of biologic therapy.[20-24] This could be explained by the fact that definitions for clinical remission and for disease relapse were heterogeneous and different from the ones we used in the present study.

In our study patients were randomised to two tapering strategies, either tapering the sDMARD or tapering the TNFi. Since this study is still ongoing, randomisation is still concealed. It might be that tapering strategy does not influence disease relapse, but it could be that ultrasound has more added value in one strategy compared to the other strategy.

Our study results raises the debate whether we look at lingering disease or too many false positive findings. Previous histology data has shown that ultrasound findings show histological changes in the joint tissue, suggesting that our patients have lingering disease.[25] However, disease flare was only reported in 4 of the initial 72 ultrasound positive patients at 3 months. What does an ultrasound positive joint mean in the other 68 patients who stayed relapse free? Could we simply ignore ultrasound positive results and taper only those patients who are ultrasound negative? Given the high NPV, ultrasound might be useful to determine which patients could go to the next step in tapering their medication. This could help the rheumatologist in their decision making, especially in those patients in whom it was hard to reach remission and there is limited choice of other DMARDs to reintroduce remission after disease relapse.

We found ultrasound synovitis in 58% of RA patients in clinical remission. Subclinical inflammation can explain why some patients deteriorate in radiological damage.[17, 19] Follow-up of RA patients who had a disease relapse could be interesting to determine if radiological damage would occur.

In conclusion, monitoring RA patients who started tapering their medication every three months showed limited value for ultrasound to identify patients who will have a disease relapse.

References

1. Klarenbeek NB, van der Kooij SM, Guler-Yuksel M, van Groenendael JH, Han KH, Kerstens PJ, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis. 2011;70(2):315-9.
2. Ozgocmen S, Ozdemir H, Kiris A, Bozgeyik Z, Ardicoglu O. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. South Med J. 2008;101(3):240-5.
3. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis. 2011;70(1):172-5.
4. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum. 2009;60(7):1915-22.
5. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford). 2009;48(9):1092-7.
6. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003;48(1):64-71.
7. Lagana B, Picchianti Diamanti A, Ferlito C, Germano V, Migliore A, Cremona A, et al. Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption. Int J Immunopathol Pharmacol. 2009;22(2):447-54.
8. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis. 2011;70(5):792-8.
9. Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Ann Rheum Dis. 2004;63(4):382-5.
10. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404-13.
11. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60(7):641-9.
12. Naredo E, Moller I, Moragues C, de Agustin JJ, Scheel AK, Grassi W, et al. Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course. Ann Rheum Dis. 2006;65(1):14-9.
13. Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann Rheum Dis. 2008;67(2):143-9.
14. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485-7.
15. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
16. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis. 2005;64(3):375-81.
17. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
18. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis. 2011;70(3):500-7.

19. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456-65.

20. Lamers-Karnebeek FB, Luime JJ, Ten Cate DF, Teerenstra S, Swen N, Gerards AH, et al. Limited value for ultrasonography in predicting flare in rheumatoid arthritis patients with low disease activity stopping TNF inhibitors. Rheumatology (Oxford). 2017.

21. Naredo E, Valor L, De la Torre I, Montoro M, Bello N, Martinez-Barrio J, et al. Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. Rheumatology (Oxford). 2015;54(8):1408-14.

22. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka S, Norimoto A, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. Arthritis Care Res (Hoboken). 2014;66(10):1576-81.

23. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Bahlas S, Hegazi M, et al. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. Clin Rheumatol. 2016;35(12):2915-23.

24. Marks JL, Holroyd CR, Dimitrov BD, Armstrong RD, Calogeras A, Cooper C, et al. Does combined clinical and ultrasound assessment allow selection of individuals with rheumatoid arthritis for sustained reduction of anti-tumor necrosis factor therapy? Arthritis Care Res (Hoboken). 2015;67(6):746-53.

25. Andersen M, Ellegaard K, Hebsgaard JB, Christensen R, Torp-Pedersen S, Kvist PH, et al. Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. Ann Rheum Dis. 2014;73(4):678-83.

PART TWO

Experimental technical research

CHAPTER 8

Very different performance of the power Doppler modalities of several ultrasound machines ascertained by a microvessel flow phantom

David F. Ten Cate
Jolanda J. Luime
Myrthe van der Ven
Johanna M.W. Hazes
Klazina Kooiman
Nico de Jong
Johannes G. Bosch

Arthritis Res Ther. 2013 Oct 24;15(5):R162

Abstract

Introduction: In many patients with rheumatoid arthritis (RA) subclinical disease activity can be detected with ultrasound, especially using power Doppler ultrasound. However, power Doppler ultrasound may be highly dependent on type of machine. This could create problems both in clinical trials and in daily clinical practice. To clarify how the power Doppler ultrasound signal differs between machines we created a microvessel flow phantom.

Methods: The flow phantom contained three microvessels (150, 1000, 2000 micron). A syringe pump was used to generate flows. Five ultrasound machines were used. Settings were optimised to assess the lowest detectable flow for each ultrasound machine.

Results: The minimal detectable flow velocities showed very large differences between the machines. Only two of the machines may be able to detect the very low flows in capillaries in inflamed joints. There was no clear relation with price. One of the lower-end machines actually performed best in all three vessel sizes.

Conclusions: We created a flow phantom to test the sensitivity of ultrasound machines to very low flows in small vessels. The sensitivity of the power Doppler modalities of five different machines was very different. The differences found between the machines are probably caused by fundamental differences in processing of the power Doppler signal or internal settings inaccessible to users. Machines considered for power Doppler ultrasound assessment of RA patients should be tested using a flow phantom similar to ours. Within studies, only a single machine type should be used.

Introduction

Rheumatoid arthritis (RA) is a common disease with a prevalence of around 1% worldwide.[1] It is in potential an invalidating disease[2], but early diagnosis in the so called 'window of opportunity'[3, 4] and treating according to a 'treat to target'[5] protocol can optimize the outcome for RA patients. Adding ultrasound to the diagnostic workup and monitoring of treatment may provide even better results. In rheumatological ultrasound both grayscale and power Doppler is used of which power Doppler seems to have the largest value. It has the potential to reclassify patients to a higher joint group according to the 2010 classification criteria for RA increasing the risk for undifferentiated arthritis to be definite RA.[6] Furthermore, presence of power Doppler ultrasound inflammation in joints that are not swollen at clinical examination has shown to be clinically relevant in patients in remission of RA, since it predicts occurrence of flare and erosive progression.[7-10] Correct assessment of presence and absence of power Doppler signal indicating the presence of inflammation is therefore vital in rheumatological ultrasound.

However, it has been published that power Doppler ultrasound may be highly dependent of type of ultrasound machine used.[11, 12] We observed this in our centre also [Figure 1].

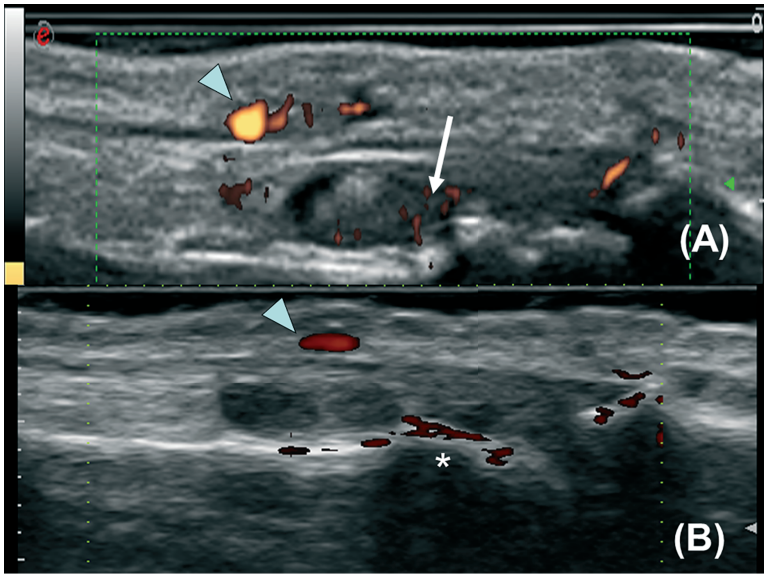


Figure 1. Interphalangeal joint of the first digit of the right hand with two different machines in the same patient. (A) Machine B: presence of positive power Doppler signal (arrow) within the region of synovial proliferation. (B) In the image made with machine A this signal is absent; vessel (arrowhead); Noise on cortical surface (*)

If there are indeed large differences in the performance of power Doppler ultrasound per machine, the choice of the machine might be essential for a valid detection of inflammation. Using different machines within a multimachine study or during patient treatment could then have a detrimental impact on treatment decisions or study outcome.

To quantify the suspected differences in power Doppler sensitivity of different machines in an objective way, we decided to perform an in-vitro experiment. To compare the power Doppler function of different ultrasound machines one could use a flow phantom. This flow phantom should mimic the tissue that is scanned by power Doppler ultrasound in rheumatology, i.e. very small vessels and very low flows. To our knowledge, no studies have been conducted investigating the size of capillaries and the blood flow velocity in an inflamed joint, but there is data on capillaries in healthy subjects' nail folds and capillaries in periulcerous regions. These capillaries have a diameter of around 30 micron and the blood flow velocity can be as low as 0.5 mm/s.[13,14] Flow phantoms previously presented did not compare ultrasound machines[15], used vessels that were considerably larger than capillaries, or assessed many capillaries close to each other at once, making it impossible to evaluate the flow velocity in the individual vessels.[11,12,16,17] For these reasons, we created a new flow phantom with a very small, single vessel to obtain the lowest detectable flow velocity of five ultrasound machines. Two additional larger vessels were included in the phantom for comparison with literature.[11,12]

Material and methods

Phantom

The flow phantom [Figure 2] consisted of an acrylic (PMMA) container filled with tissue mimicking material (TMM), according to a previously published recipe.[18] In this TMM we placed three microvessels (150 micron (inner diameter) made of Polyethylene Terephtalate Glycol-modified (PETG; Paradigm Optics, Vancouver, WA, USA) and 2000 and 1000 micron (inner diameter) made of silicone (Eriks bv, Alkmaar, NL). These two vessels were included to compare our phantom with already published studies.[11,12] Initially we used vessels with diameters of 50 micron and 100 micron made of PETG as well but these blocked almost instantly. The blood mimicking fluid (BMF) was based on the recipe by Ramnarine.[19]. Briefly, 91.07% (w/w) demineralised water, 1.18% (w/w) dextran (average 150 kDa; D4876, Sigma-Aldrich, Zwijndrecht, the Netherlands), 0.90% (w/w) ICI supersonic N surfactant, 5.03% (w/w) glycerol, and 1.82% w/w orgasol

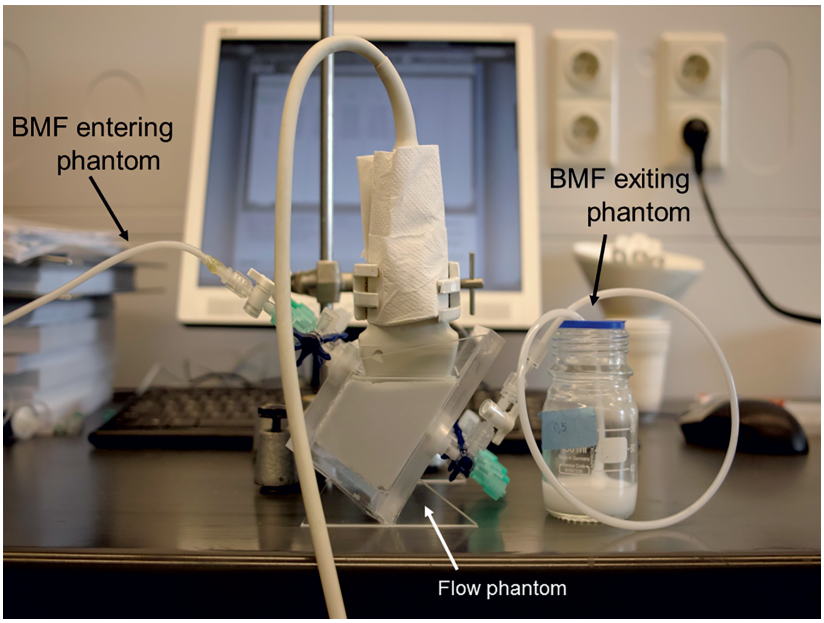


Figure 2. The flow phantom with a fixated probe.

particles (5 µm in diameter, Arkema) were mixed using a magnetic stirrer. The BMF was then filtered using a 40 micron sieve (352340, BD, Breda, the Netherlands) and degassed using a vacuum pump. Compared to the original recipe by Ramnarine, our BMF contained half the amount of dextran and glycerol, making our BMF less viscous which was necessary to prevent blockage of the vessels. A syringe pump (Harvard Apparatus Pump 11 Elite, Holliston, MA, USA) was used to generate flows. This pump can produce regular flows as low as 1.28 pl/min. For each vessel size, flow settings (ml/h) were calculated that corresponded to average flow velocities ranging from 40 to 0.005 mm/s, using the following equation, where Q is flow (m^3/second), V_{avg} is the average flow velocity (m/second) and R is the inner radius (m):

$$Q = V_{avg} \times \pi R^2 \qquad (1)$$

The actual volume flow through the vessels was tested by turning on the pump, completely filling the vessel until drops of BMF came out of the capillary. A complete number of drops were captured in a container while recording the time. This container was weighed before and after this experiment on a microbalance. With the relative density of the BMF we calculated the flow (transported volume per time).

Experiment

The lowest detectable flow for each machine/vessel diameter combination was defined as the flow that still resulted in a continuous power Doppler ultrasound signal [Figure 3]. First the pump was set to a high flow, then gradually decreasing it in steps until a continuous power Doppler signal could just still be detected. The value of the lowest flow was recorded. Between each change of pump flow we waited 5 minutes for the system to reach stable flow velocities. For each lowest detectable flow per vessel we stored an image and recorded the machine settings used to acquire this image.

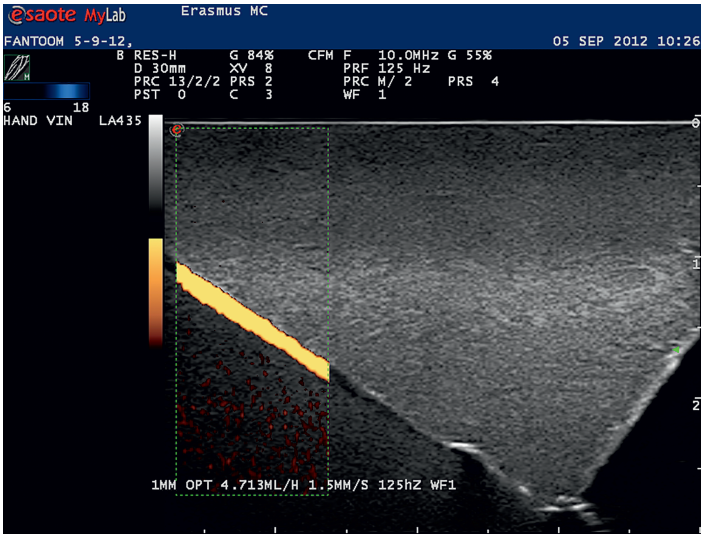


Figure 3. A continuous power Doppler ultrasound signal in a 1 mm vessel on Machine B.

Table 1. Machines tested in alphabetical order and probes used

Machine A	Aloka α7 (probe UST-5411)
Machine B	Esaote MyLab60 (probe LA 435)
Machine C	Philips iU22 (probe L9-3)
Machine D	Ultrasonix SonixTouch (probe L14-5/38)
Machine E	Visualsonics Vevo2100 (probe MS200)

Ultrasound machines and settings

Five available ultrasound machines were tested [Table 1]. Machines A and B are used in our department of Rheumatology in daily clinical practice. Machine C a high-end machine for general imaging. Machines D and E are specialised research machines, the latter is a highly specialised machine for high frequency small animal imaging. Four machines operated at or around the most common frequency of 10 MHz (Machine

A, B, D and E), one (Machine C) below at a frequency between 3 and 9 MHz (actual frequency not displayed on this machine). Settings on all machines were optimised to detect lowest flows by adjusting pulse repetition frequency (PRF)/velocity range, wall filters, Doppler frequency and Doppler gain. In general this meant using for all vessels the lowest wall filter, the lowest velocity range or PRF and the highest suitable Doppler gain with respect to noise level. One experienced musculoskeletal ultrasonographer (DTC) performed all ultrasound exams.

Results

We found that the pump was accurate enough for our purposes, especially when taking into account the very low flows used [Table 2]. The lowest detectable flow velocities in the different vessels are presented in table 3. These differed very much, by a factor of 100 between machines. This was the case for all vessel sizes. In the smallest vessel (150 micron), which most resembles the situation in an inflamed joint, two machines (D and E) could not detect a positive power Doppler signal at all at any flow velocity. For the others, the minimal detectable velocity ranged from 0.11 mm/s, (machine B), to 11.1 mm/s. (machine A). The settings were optimised for the detection of lowest flow. For settings of PRF/velocity range, wall filter and Doppler frequency per machine for the smallest vessel see table 4.

Table 2. Measuring the reliability of the pump.

Vessel size(micron) / Flow (ml/h)	2000	1000	150	150	150
Set flow	11.31	3.142	0.141	0.070	0.035
Measured flow	10.68	2.948	0.276	0.108	0.049

ml/h: millilitre per hour

Table 3. Lowest detected flow velocity (in mm/s) still resulting in a continuous positive power Doppler ultrasound signal

	Flow velocity (mm/s)		
Vessel size (micron) / Machine	2000	1000	150
A	4	2.22	11.1
B	0.005	0.06	0.11
C	1	0.56	1.68
D	1	0.56	N.D.
E	0.5	0.33	N.D.

mm/s: millimetre per second; N.D. = none detected

Table 4. Settings for detection of lowest flow velocity in the 150 micron vessel

Machine	PRF / Velocity range	Wall filter	Doppler frequency
A	1.3 cm/s	Level 1	8 MHz
B	125 Hz	Level 1	10 MHz
C	150 Hz	15 Hz	R1 (Actual frequency not displayed on this machine)
D (no flow detected in this vessel)	200 Hz	Level 1	10 MHz
E (no flow detected in this vessel)	1000Hz	Low	12.5 MHz

Discussion

We showed that the sensitivity of the power Doppler modalities of five ultrasound machines (three machines used in clinic and two used for research) was very different, using a microvessel flow phantom. The very large differences found between the machines are only partly explained by each machine's Doppler frequency, lower limits of PRF and wall filter settings, but are most likely caused mainly by fundamental differences in processing of the power Doppler signal or internal settings inaccessible to users. There was no clear relation with price or technical sophistication of the machines: a lower-end machine (B) performed best for all three vessels, while mid-range and high-end research machines (D,E) did not detect any flow in the smallest vessel, against expectations.

Only one machine of the five (B) could detect the low flow velocity in capillaries that are based on previous research are estimated to be between 0.5 and 1 mm/s. Machine C came close to this limit, which underlines our conclusion that the observed differences are mainly caused by differences in processing of the signal, since the probe that was available for machine C had a bandwidth of only 3 to 9 MHz. When a high frequency probe would have been used with this machine, it might also have been able to detect less than 1 mm/s in the smallest vessel. The other machines did not perform appropriately according to this limit.

As mentioned above, flow phantoms have been published in literature before.[11, 12, 15-17] However, when comparing the power Doppler modalities of different ultrasound machines it is essential to use small, individual vessels. A positive power Doppler signal depends on the total detected Doppler signal power within the range gate (the colour Doppler "pixel size", typically <1 mm). This power depends on the number of particles that have a velocity above a certain threshold. This threshold is determined by the wall filter, the PRF/velocity range. Whether a power Doppler signal is actually detected/

displayed is also dependent on the noise level of the system and the system's ability to suppress clutter and signal from stationary targets. If the vessel diameter is larger than the gate size, the velocity threshold will determine the lowest detectable velocity. This explains why the minimum velocities found for 1 mm and 2 mm vessels are similar.
However, if the velocity is the same but the vessel is much smaller than the gate size, the number of moving particles will be lower and more stationary tissue will be inside the gate range. Then, the tissue suppression and noise level become more important and the minimal detectable velocity will be raised. This means that a phantom with a vessel that has a diameter that is too large[11, 12] may use a flow velocity similar to that in vessels in an inflamed joint, but more particles are inside one pixel in the phantom-situation (*in vitro*) compared to the situation in an inflamed joint (*in vivo*). This can possibly cause a positive power Doppler signal based on the large number of particles. In a flow phantom using a bundle of capillaries[16, 17] one can never know for sure what the flow velocity in each vessel is. So the possibility remains that the flow is very high in a few capillaries, causing a positive power Doppler signal solely based on the high flow velocity of particles in these few capillaries.
A study comparing machines A and B (older versions than in our study) on an 1000 micron flow phantom has been published in the past.[12] These older versions of the machines were ranked regarding sensitivity the same as in our study. However, in our study the machine B detected a considerably lower flow compared to their study; 0.06 mm/s in our study versus 1.3 mm/s in their study. Machine A detected a twofold lower flow in our study: 2.2 mm/s in our study versus 3.9 mm/s in their study.
Another study tested an earlier, single-element version of machine E (Vevo 770), on a microvessel flow phantom with vessel dimensions similar to ours (160 micron).[15] In this microvessel the Vevo 770 did detect flows as low as 0.5 mm/s. In our study machine E did not detect any flow in the smallest vessel (150 micron). A possible explanation for this higher sensitivity for low flows could be that the Vevo 770 uses a mechanically steered probe with a single element opposed to the array probe we used on machine E in our study. In general, the Doppler processing of a single-element system can be very different from an array system.
Some observations raised discussion within our research group. One of these discussions was about the very low flows detected by machine B in the 2000 micron vessel. To verify this finding the experiment was repeated several times by two observers (DTC and MvdV) which resulted in similar findings. When setting the flow slightly lower, the signal disappeared. Therefore, we think the measured flow is correct. A possible explanation for this low limit is that the PRF can be set to a very low level and

the wall filter cut-off frequency is probably also very low, in combination with a good clutter suppression. However, in in-vivo situations, normal tissue or probe motion will prevent detecting such extremely low flows.

Another observation that raised discussion is the lower flow detected in the 1000 micron vessel as compared to the 2000 micron vessel. A reason for this could be that the flow velocity profile in the 1000 micron vessel is shaped differently, as compared to the 2000 micron vessel, resulting in a larger difference between average flow and maximum flow. This may even have been reinforced by compression of the smaller vessel by the TMM. This means the average flow velocity is actually higher than estimated, since the calculation is quadratically dependent on the microvessel diameter. If the maximum velocity of the peak flow is slightly higher than the wall filter cut-off, this results in a positive power Doppler signal. This way the peak flow may be rather similar in the 2000 micron and the 1000 micron vessel, but due to the shape of the flow profile this corresponds to a lower average flow velocity in the 1000 micron vessel. While the true value for the flow velocities may differ from the calculated values, this difference is the same for all machines, so the comparison between machines is still valid per vessel.

A drawback of our study is that we have made assumptions on the capillary sizes and flow velocities in inflamed joints based on papers published on healthy subjects and periulcerous regions. This may not be entirely correct. Therefore, at present it is crucial to ascertain the flow velocities and capillary sizes in inflamed joints. With this information the minimal flows that rheumatological ultrasound machines need to be able to detect will be known.

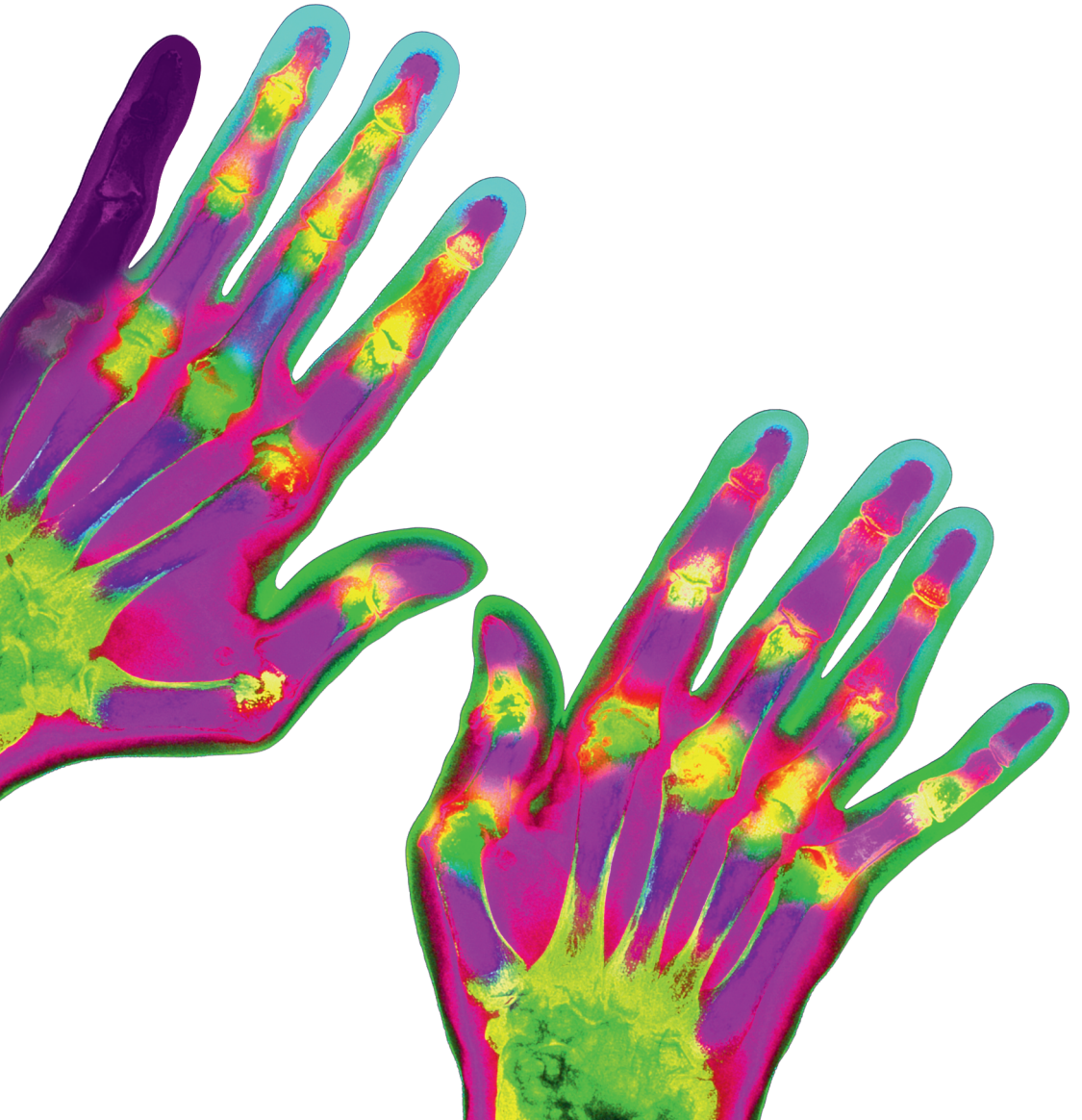
Nonetheless, for a reliable and reproducible detection of very low flows in inflamed joints, the choice of the ultrasound machine and its settings seems very important. Caution should be exercised when conducting a multi-machine trial or when making treatment decisions based on power Doppler ultrasound. Our flow phantom could be used to decide which ultrasound machine to use both in clinical practice and in clinical trials.

Conclusions

We created a flow phantom to test the sensitivity of ultrasound machines to very low flows in small vessels. We found that the sensitivity of the power Doppler modalities was very different between five ultrasound machines. Based on the results of our study it would be advisable to standardise and validate ultrasound machines both for rheumatological clinical practice and for clinical trials. Our phantom could be used for this purpose.

References

1. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4 Suppl 3:S265-72.
2. Gordon P, West J, Jones H, Gibson T. A 10 year prospective followup of patients with rheumatoid arthritis 1986-96. J Rheumatol. 2001;28(11):2409-15.
3. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum. 2002;46(4):894-8.
4. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S154-7.
5. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364(9430):263-9.
6. Filer A, De Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Annals of the Rheumatic Diseases. 2011;70(3):500-7.
7. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
8. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum. 2012;64(1):67-76.
9. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Annals of the Rheumatic Diseases. 2011;70(1):172-5.
10. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford). 2009;48(9):1092-7.
11. Browne JE, Watson AJ, Hoskins PR, Elliott AT. Validation of a sensitivity performance index test protocol and evaluation of colour Doppler sensitivity for a range of ultrasound scanners. Ultrasound Med Biol. 2004;30(11):1475-83.
12. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. Ann Rheum Dis. 2006;65(12):1590-5.
13. Stucker M, Baier V, Reuther T, Hoffmann K, Kellam K, Altmeyer P. Capillary blood cell velocity in human skin capillaries located perpendicularly to the skin surface: measured by a new laser Doppler anemometer. Microvasc Res. 1996;52(2):188-92.
14. Stucker M, Huntermann C, Bechara FG, Hoffmann K, Altmeyer P. Capillary blood cell velocity in periulcerous regions of the lower leg measured by laser Doppler anemometry. Skin Res Technol. 2004;10(3):174-7.
15. Pinter SZ, Lacefield JC. Detectability of small blood vessels with high-frequency power Doppler and selection of wall filter cut-off velocity for microvascular imaging. Ultrasound Med Biol. 2009;35(7):1217-28.
16. Kamishima T, Nishida M, Horie T, Narita A, Sagawa A, Henmi M, et al. Power Doppler signal calibration using capillary phantom for pannus vascularity in rheumatoid finger joint. A pilot study. Clin Exp Rheumatol. 2011;29(6):1057.
17. Veltmann C, Lohmaier S, Schlosser T, Shai S, Ehlgen A, Pohl C, et al. On the design of a capillary flow phantom for the evaluation of ultrasound contrast agents at very low flow velocities. Ultrasound Med Biol. 2002;28(5):625-34.
18. Teirlinck CJ, Bezemer RA, Kollmann C, Lubbers J, Hoskins PR, Ramnarine KV, et al. Development of an example flow test object and comparison of five of these test objects, constructed in various laboratories. Ultrasonics. 1998;36(1-5):653-60.
19. Ramnarine KV, Nassiri DK, Hoskins PR, Lubbers J. Validation of a new blood-mimicking fluid for use in Doppler flow test objects. Ultrasound Med Biol. 1998;24(3):451-9.



CHAPTER 9

High-frame rate power Doppler ultrasound is more sensitive than conventional power Doppler in detecting rheumatic vascularisation

Myrthe van der Ven
Jolanda J. Luime
Levinia L. van der Velden
Johannes G. Bosch
Johanna M.W. Hazes
Hendrik J. Vos

Ultrasound Med Biol. 2017 Sep;43(9):1868-1879

Abstract

Early recognition of joint inflammation will increase treatment efficacy in rheumatic arthritis (RA). Yet, conventional power Doppler (PD) ultrasound might not be sufficiently sensitive to detect minor inflammation. We investigated the sensitivity of high-frame rate Doppler, combined with Singular Value Decomposition technique to suppress tissue signals, for microvascular flow in a flow phantom setup and in a proof-of-principle study in healthy controls and in RA patients with different disease activities.

In the flow phantom, minimal detectable flow velocity was a factor three lower with high-frame rate PD than with conventional PD ultrasound. In the proof-of-principle study we detected a positive PD signal in all volunteers, diseased or healthy, with high-frame rate PD ultrasound. We saw a gradual increase of PD signal in RA patients depending on disease activity. In conclusion, high-frame rate Doppler is more sensitive to detect vascularisation than conventional PD ultrasound.

Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease with a prevalence of 1% worldwide.[1] RA leads to destruction of joints, severe disability and increased cardiovascular mortality.[2] Obligatory for the current diagnosis of RA is inflammatory arthritis of at least one joint.[3] Arthritis is assessed by manual palpation of swelling in joints. Treatment of RA is directed at suppressing inflammation and establishing a state of remission according to a treat-to-target protocol.[4, 5] Remission is regarded as the ultimate therapeutic goal for RA patients to prevent further joint damage and disability and to maintain function and quality of life. Therefore, it is important to ensure that the methods of assessing disease activity are accurate to diagnose and monitor RA. Current clinical measures rely on composite scores based on physical examination (swollen and tender joints) and laboratory assessments.[6, 7] These measures have the disadvantage of not directly measuring inflammation and may be subject to confounding influences and subjectivity. In addition, reports suggest a disparity between clinical status and outcome, with evidence of radiographic or cytoscopic progression despite apparent clinical remission.[8-10] This indicates ongoing subclinical inflammation. Data from several ultrasound studies indicate that subclinical disease lingers in joints which lack clinical signs of arthritis.[11-13] Presence of subclinical disease may explain why some patients still develop bone erosions or have a relapse of their disease, while clinically the disease is in remission.[11, 13-16]

A review from Ten Cate et al.[17] revealed that ultrasound imaging has added value in the diagnosis of RA and monitoring RA patients who are in remission, especially the use of the power Doppler (PD) mode. In conventional ultrasound, any PD signal in the joint indicates elevated vascularisation, which is an important sign of active inflammation. Conventional PD modes are able to detect flow velocities down to 0.05 mm/s in a flow phantom experiment in which the background tissue is motionless, although there is a large variability between ultrasound machines in the sensitivity to detect low flows.[18] In actual clinical application, the settings used in these phantom experiments produce flash artefacts -caused by unavoidable minor motion- which fully cover the blood signal. To be able to detect low flow velocities in actual clinical application there is a need for a sensitive PD ultrasound modality which reduces such flash artefacts.

The past decade has shown that high-frame rate ultrasound has improved sensitivity to blood flow.[19, 20] With high-frame rate ultrasound, the entire field of view is imaged with a single transmission, enabled by advances in the electronic hardware of the ultrasound machines. The high-frame rate ensures high temporal correlation between

frames, which facilitates a good separation between relatively slow tissue motion, and blood flow.[20, 21] This has led to improved sensitivity of blood flow imaging in e.g. rheumatology[20, 21], brain vascular imaging[22, 23], and carotid flow velocity estimation[24-26]. The high temporal correlation between frames also allows for using spatial correlation to further discriminate blood flow in small localized vessels from global motion of soft tissue and bone, generally enabled with Singular Value Decomposition (SVD).[27, 28]

We applied the combination of high-frame rate Doppler ultrasound imaging and SVD filtering, which is expected to be more sensitive to low flow velocities than the conventional method[27], for perfusion imaging of finger joints. It is our premise that such a more sensitive technique can provide accurate detection of active inflammatory joint tissue in RA, enabling earlier diagnosis of RA and better treatment monitoring. Of note, an early diagnosis of RA assumes that the patient is frequently seen by a rheumatologist. This is the case, since the persons have inflammatory joint complaints, albeit without clinically apparent swollen joints -and so, according to clinical decision diagrams, do not get the diagnosis RA at that point. In such case, sensitive PD ultrasound would be able to improve diagnosis accuracy.

In this study, our first aim was to test in a flow phantom if the high-frame rate Doppler ultrasound technique is more sensitive in detecting low flows than a conventional clinical ultrasound machine. Our second aim was to perform a proof-of-principle study in RA patients with various disease activities to evaluate whether we are able to detect higher levels of vascularisation in affected joints with the new technique than with the conventional method. The proof-of-principle study was complemented with healthy volunteers to evaluate to what level healthy joints show vascularisation.

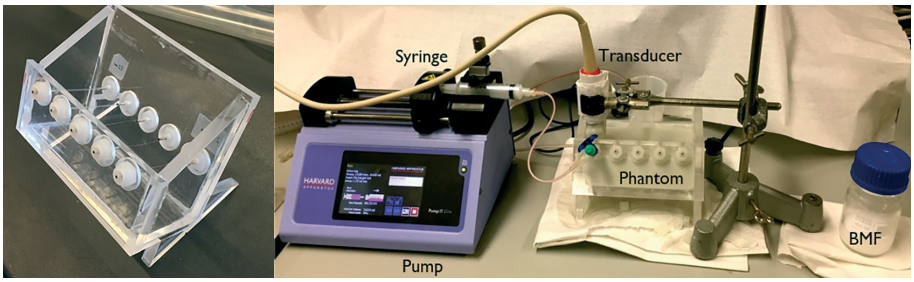


Figure 1. (A.) Flow phantom before actual filling the cavity with tissue mimicking material; (B.) Experimental phantom setup; BMF: blood mimicking fluid.

Methods

Flow phantom

The flow phantom [Figure 1] consisted of an acrylic (polymethyl methacrylate) container filled with tissue mimicking material, according to a previously published recipe.[29] In this tissue mimicking material we placed a 0.7 mm (inner diameter) microvessel made of silicone (Eriks bv, Alkmaar, the Netherlands). Evaluation of the vessels was at a depth of 8-10 mm, which would be the largest depth of possible vessels in the metacarpophalangeal (MCP) joint that we study. A blood-mimicking fluid (BMF) was prepared based on the recipe by Ramnarine et al.[30] The BMF contained 91% (w/w) demineralised water, 1% (w/w) dextran (average 150 kDa, D4876; Sigma-Aldrich, Zwijndrecht, the Netherlands), 1% (w/w) ICI supersonic N surfactant, 5% (w/w) glycerol, and 2% w/w Orgasol particles (5 µm in diameter; Arkema B.V., Rotterdam, The Netherlands). The BMF was mixed using a magnetic stirrer, filtered using a 40 µm sieve (352340; BD, Breda, the Netherlands) and degassed using a vacuum pump. Compared with the original recipe by Ramnarine and colleagues, our BMF contained half the amount of dextran and glycerol – this made our BMF less viscous, which was necessary to prevent blockage of the vessels. A syringe pump (Hugo Sachs Elektronik, March-Hugstetten, Germany) was used to generate flows. Flow settings were calculated that corresponded to average flow velocities ranging from 26 to 0.13 mm/s, using the following equation, where Q is flow (m^3/second), V_{avg} is the average flow velocity (m/second) and R is the inner radius (m):

$$Q = V_{avg} \times \pi R^2 \qquad (1)$$

By assuming a parabolic flow profile, the peak velocity is twice the average velocity in a circular tube.[31] Reported velocities are peak velocities.

Study population

Ten healthy controls and 14 RA patients were included in this proof-of-principle study. To be able to interpret ultrasound results we included RA patients with a broad spectrum of disease activity: i) RA patients in clinical remission (no clinically swollen or tender joints); ii) RA patients who were well controlled (low to medium disease activity, but with clinically swollen and/or tender joints); and iii) RA patients with a clinical flare (high disease activity with clinically swollen and/or tender joints). Disease activity was measured by physical examination of swollen and tender joints, and disease

activity score (DAS) in 28 joints was calculated.[6] A clinically swollen joint needed to be confirmed by the patient's treating rheumatologist. Written informed consent was obtained from the participants according to the declaration of Helsinki. The study was approved by the local medical ethics committee of Erasmus MC, University Medical Centre Rotterdam, the Netherlands (MEC-2015-179).

Ultrasound equipment and machine settings

Conventional ultrasound machine

The conventional ultrasound machine was an Esaote MyLab60 which is used in daily clinical practice, equipped with a high-frequency linear array probe (LA435, 10-18MHz). In both the phantom and clinical studies, the probe was mounted on a 4-degree-of-freedom mounting arm with a hydrostatic brake (442110/290 mm, NOGA, Israel) to reduce probe motion caused by the sonographer. To reduce the motion of the hand of the participant, the hand was positioned in a custom plate with pins to spread the fingers [Figure 2]. Participants were sitting on a chair, and were asked to hold breath (after breathing out) during the measurement to reduce residual motion as much as possible. The PD gain was set at the disappearance level of colour noise in the PD images. The Pulse Repetition Frequency (PRF) was set as low as possible to have maximum sensitivity for low flow, which was 125 Hz in the phantom study, and 750 Hz in the clinical pilot study. Further settings are shown in Table 1.

We adjusted the size and position of the colour box to include the subcutaneous tissue to recognise artefacts caused by vessels above the joint.[32]

Figure 2. Experimental set-up for the proof-of-principle study with the probe-mounting arms and the custom plate with pins to spread and fixate the fingers. Left machine: Esaote MyLab 60; right machine: Verasonics Vantage-256 on a custom trolley.

Table 1. Conventional ultrasound (Esaote MyLab60) settings for the phantom study and for the proof-of-principle study

	Phantom study	Proof-of-principle study
Doppler frequency (MHz)	10	10
Pulse repetition frequency (Hz)	125	750
Wall filter	Level 1	Level 3
Power Doppler persistence	Level 4	Level 4
Image depth (cm)	3.0	2.5

Research ultrasound machine

The research system was a Vantage-256 (Verasonics, Kirkland, WA USA) with a high-frequency probe (L40-8/12, Ultrasonix, Richmond BC, Canada) with a customized adapter to the Verasonics system. The specifications of this probe are equal to the Verasonics L22-14v probe. The system was programmed in high-frame rate mode, i.e. plane wave transmissions, and capturing and saving the full channel data.[21] One B-mode image and one Doppler ensemble were recorded per dataset. The Doppler ensemble consisted of 122 frames in In-Phase Quadrature (IQ) format. Each Doppler frame was composed by coherent summation of the images reconstructed from 11 angled plane wave transmit/receive events, transmitting over an angular range of -10 to +10 degree. The image reconstruction was performed by the internal Verasonics reconstruction algorithm. The ultrasound pulse was a 1-cycle tone burst at 12.5 MHz for the B-mode, and a 4-cycle tone burst at 12.5 MHz for the Doppler data. The PRF was set to 1375 pulses per second, leading to a rate of 125 frames per second in the Doppler ensemble. This led to the recording time of approximately 1 sec, i.e. one Doppler image per second. Given a general heart rate of one beat per second, this recording time implies that the PD signal is obtained over one complete heart cycle, and no diastolic or systolic difference will be observed, unlike regular PD which has image rates of a few per second.

The performance of the high-frame rate imaging was tested in a flow phantom. In this experiment we used a Doppler frame rate of 500 Hz and 62 frames, leading to a recording time of 124 ms. Such a Doppler ensemble recording time is closer to that of the image rate in the clinical scanner. This measurement served as initial test to show the higher sensitivity to low flow velocities of the high-frame rate imaging in a controlled environment.

To investigate the influence of wall filters, we tested both a conventional wall filter with static high-pass filtering characteristics, and a recent approach of Singular Value Decomposition (SVD) following the procedure of Demené et al.[27] In the phantom

study, the conventional wall filter (Verasonics built-in filter 'WeakFlowVLow') had -6dB and -20 dB cut-off frequencies of 12 Hz and 6 Hz, respectively, which results in a cut-off velocity of 0.4 - 0.8 mm/s. In the volunteers study, we used a 6th order zero-phase Butterworth filter with -6dB cut-off frequency of 37.5 Hz, which results in a cut-off velocity of 2.4 mm/s. Lower cut-off frequencies led to severe flash artefacts. The SVD filtering is a statistical approach in which high-amplitude tissue signals with large spatial coherency are separated from the low-amplitude local blood signals, and then removed. Moreover, electronic noise is separated and subsequently removed by the filter, since noise has low amplitude and very low spatial coherency. The lower separation threshold (for tissue suppression) was manually set to visually suppress tissue signals and quasi-static signals from the bone structure, while maintaining the blood signal in the PD image.[27] The higher separation threshold (for noise suppression) was manually set to suppress the noise signal in the deeper regions of the image, where no ultrasound echo would be expected from since that region is located inside bone. This led to SVD cut-off values of 18 and 32 respectively (of a set of 122 frames). The power Doppler signal is then normalized to the maximum Doppler power value in the image. In the images we overlay the Doppler power to the B-mode images; if the Doppler power in any pixel is larger than 12% of the maximum Doppler power in the image, then the pixel gets its Doppler power value, otherwise the pixel gets the B-mode grayscale value. Note that this procedure may be different from conventional power Doppler, in which the grayscale value determines the local power Doppler sensitivity in the image (so called colour priority) which enhances larger vessels in the power Doppler images that appear black on the grayscale images. Such power Doppler enhancement by colour priority is not meaningful when the vessel diameters are smaller than the image resolution, which is generally the case in scanning the fine vasculature in the hand.

Imaging protocols

Phantom study

In the flow phantom the lowest detectable flow for each machine and vessel was defined as the flow that still resulted in a continuous PD signal. First the pump was set to a high flow, and then decreased gradually until the PD signal disappeared. The value of the lowest flow was recorded, an image for each lowest detectable flow was stored, and we recorded the machine settings used to acquire this image. Between each change in pump flow we waited five minutes to reach stable flow velocities.

Proof-of-principle study

In the volunteer study, we used the experimental set-up in Figure 2 to position the probe and the hand of the patient. For the clinical proof-of-principle study, patient and probe positioning was according to EULAR guidelines.[33] In healthy controls, MCP2 (second metacarpophalangeal joint; dorsal aspect) was ultrasonographically evaluated in extended position. In RA patients two MCP joints were examined. In RA patients in clinical remission bilateral MCP2 joints were examined. In RA patients who had controlled disease, a clinically swollen joint (MCP2 or MCP3) was examined. In this group a clinically non-swollen joint (MCP2 or MCP3) was also examined to be used as an in-patient reference joint. In RA patients with a clinical flare two clinically swollen joints (MCP2 or MCP3) were examined. In all cases, each joint was evaluated three times by PD; the maximum score of three was the final score.

Ultrasound evaluation

The comparison of images by different modalities (conventional and high-frame rate) was evaluated semi-quantitatively, and the presence or absence of PD signal on each imaging modality was recorded. Synovial vascularisation was measured using PD. PD was graded as: 0=absent; 1=mild single vessel signal or isolated signal; 2=moderate confluent vessels; 3=marked vessel signals in more than half of the intra-articular area.[34]

The PD images acquired with high-frame rate ultrasound were scored by four raters independently. Raters were blinded to all clinical information. For each image the median of the PD scores was taken. To optimise inter-rater reliability, the raters followed a standardised protocol which stated to ignore any residual signal elicited at bone surface and to ignore flash artefacts.

Statistical analysis

Simple descriptives were used to describe baseline characteristics and the ultrasound findings. According to general convention of median values, if there is an even number of items in the data set, then the median is taken as the average of the two middle numbers after sorting. We calculated the kappa statistic[35] to determine the inter-rater reliability for scoring PD images acquired with high-frame rate imaging.

We analysed differences in PD scores between the conventional ultrasound method and high-frame rate imaging. Since the data were not normally distributed we used the Wilcoxon-Mann-Whitney test. Analyses were done using STATA 14.0, using a p-value $\leq$ 0.05 as the level of statistical significance.

RESULTS

Phantom study

Figure 3 shows the PD images obtained at the lowest detected velocities in the flow phantom. The high-frame rate ultrasound machine detected a minimal flow velocity of 0.5 mm/s with the conventional wall filter, and 0.26 mm/s with the SVD-based wall filter. The conventional ultrasound machine detected a minimal flow velocity of 0.8 mm/s. Since the phantom and probe both had a very low residual motion, the PRF and wall filter in the conventional ultrasound machine could be set extremely low, compared to regular clinical settings. In the current exam, the PRF was 125 Hz and the wall filter was set to 1, which is the lowest setting. In regular clinical ultrasound, the minimal PRF to avoid flash artefacts is 750 Hz, and wall filter 3. This implies that the lowest detectable flow velocity with the conventional ultrasound machine in clinical conditions is at least a factor of six higher (because of the factor of six increase in the PRF), which is 4.8 mm/s.

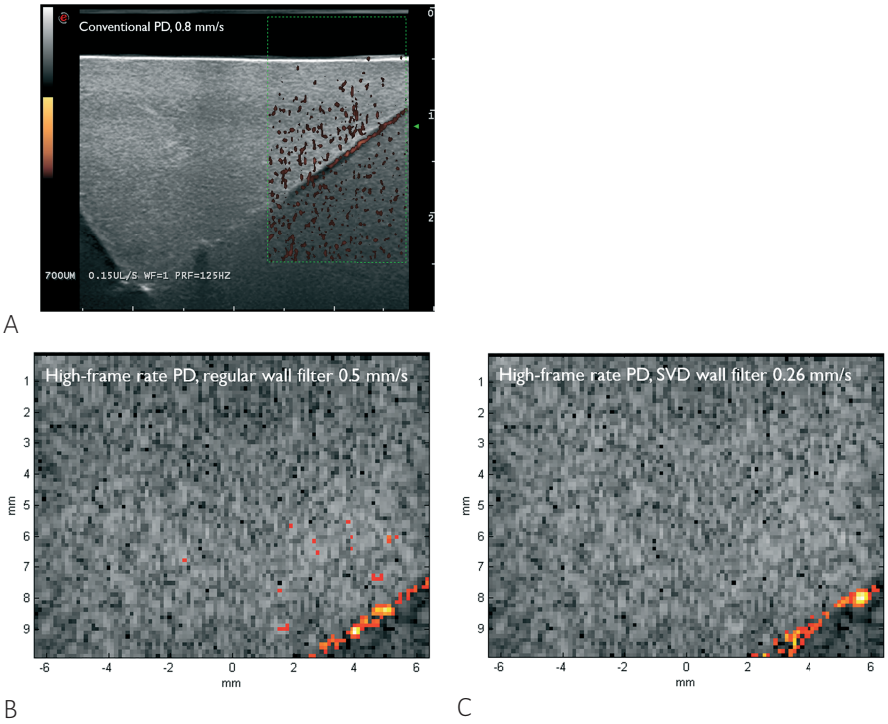


Figure 3. PD images obtained in the 700 µm vessel at the lowest detected velocity with the respective machines and wall filtering; (A.) Conventional PD ultrasound, lowest wall filter, and V_{peak} = 0.8 mm/s ; (B.) High-frame rate Doppler, conventional wall filter, and V_{peak} = 0.5 mm/s; (C.) High-frame rate Doppler, tissue filter based on Singular Value Decomposition (SVD), and V_{peak} = 0.26 mm/s. (PD = power Doppler).

Proof-of-principle study

We included ten healthy controls (mean age (range): 32 (22-59) years) and 14 RA patients (58 (31-70) years), of whom three patients were in clinical remission, nine patients were well controlled, and two patients had a clinical flare. Baseline characteristics are presented in Table 2.

Example images are presented in Figure 4. The left images show the screen shot of the conventional PD ultrasound, while the right images are the high-frame rate Doppler ultrasound.

Images are taken from a healthy control [Figure 4A & 4F] and RA patients in different disease states [Figure 4B-4E & 4G-4K]. The bone edges are identified by the bright inclined structures in the images at depths between 2–5 mm. The joint is presented by the V-shape of the bone, and the synovium of healthy joints is located at the top of the area bounded by the V-shape. In healthy joints, the synovium is very thin and thus not visible in ultrasound images; however, it may contain a minor amount of blood vessels since the synovial fluid (inside the synovium) is fed from the synovium. In case of rheumatoid arthritis, the synovium is thick and highly perfused because of inflammation of the surrounding area. In that case, PD ultrasound should be able to measure significant blood signal.

Figure 4 illustrates these effects. The high-frame rate Doppler images show more PD signal with increasing disease severity, whereas the conventional Doppler only shows a PD signal for the swollen joint and with clinical flare. Moreover, the high-frame rate Doppler images also show a significant signal at the bone surfaces, where the cartilage is located. We presume that this is a PD artefact, caused by minor motion of the bone in combination with very large amplitude of the reflection signal. When scoring the PD signal, we neglected this signal at the location of the cartilage / bone surface.

Figure 4 also shows that the conventional imaging system has a high-quality grey scale image, presumably caused by an interleaved ultrasound sequence to generate a grey scale image and the Doppler image quasi-simultaneously. In our current implementation of the high-frame rate sequence, we did not optimise for the grey scale image quality; we used a quick angular plane wave compounding technique to produce the grey scale image, at a quality which is sufficient to align the transducer in real time, and sufficient to interpret the anatomic landmarks. In further clinical studies this grey scale acquisition sequence can be further optimised to reach regular clinical quality, in order to also score the disease state based on the grey scale images.

With reference to Table 2, conventional PD ultrasound in healthy controls and in RA patients in clinical remission showed no PD signal in MCP2 joints, and either no

or minimum signal in the non-swollen joints of RA patients. In the swollen joints of controlled RA patients and RA patients with a clinical flare, median PD score was 1 (IQR: 0-2).

With high-frame rate PD ultrasound median PD score was 2 (IQR: 2-2) in healthy controls, 1.5 (IQR: 1-2) in RA patients in remission, 2 in controlled RA patients in both non-swollen (IQR: 2-2) and swollen MCP joints (IQR: 1.5-2), and 2 (IQR: 2-3) in RA patients with a flare [Table 2]. PD scores with high-frame rate ultrasound were significantly different ($p<0.001$) from PD scores with conventional ultrasound.

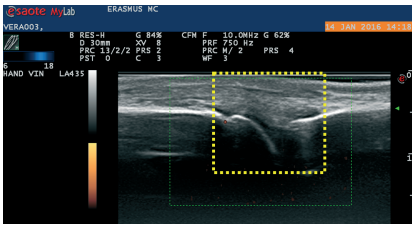
Table 2. Baseline characteristics, and ultrasonographic findings

	Controls (n=10)	RA – remission (n = 3)	RA – controlled (n = 9)		RA – flare (n= 2)
Age, mean (range)	32 (22-59)	53 (48-59)	59 (31-70)		56-67
Female, %	60	100	78		100
DAS28, mean (range)		2.8 (2.7-3.0)	3.1 (1.3-4.2)		4.3-5.7
SJC, median (range)		0 (0-0)	5 (3-6)		1-11
TJC, median (range)		0 (0-0)	2 (0-3)		7-16
			non-swollen MCP	*swollen MCP*	
Conventional US					
PD score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	1 (0-2)	1 (0-2)
High frame rate US					
PD score, median (IQR)	2 (2-2)	1.5 (1-2)	2 (2-2)	2 (1.5-2)	2 (2-3)

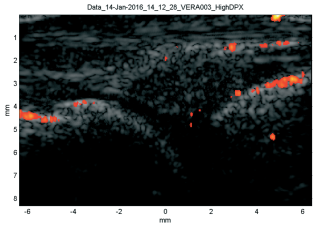
DAS28: disease activity score in 28 joints; SJC: swollen joint count; TJC; tender joint count; MCP: metacarpophalangeal joint; US: ultrasound; PD: power Doppler; IQR: interquartile range

If any PD signal was detected with conventional ultrasound, this was also detected with high-frame rate ultrasound and scored the same PD grade or higher. If no PD signal was detected with conventional ultrasound, high-frame rate ultrasound showed either no or mild PD signal detection. Moreover, the largest difference between conventional and high-frame rate ultrasound is observed in the controls, and in the non-swollen joints in the controlled-RA patient group. Apparently, the high-frame rate ultrasound detects increased microvasculature in the joint, compared to the control group. This increased microvasculature is detected neither by the physical examination, nor by the conventional power Doppler technique.

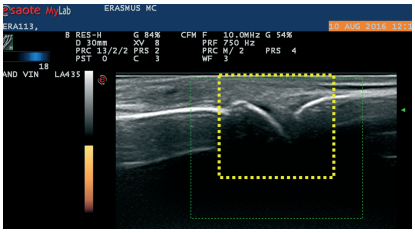
PD images acquired with high-frame rate ultrasound were scored by four observers independently. The kappa statistic for inter-rater reliability was $\kappa=0.55$, which means the agreement between the four observers was moderate.[35]



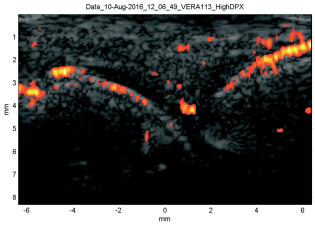
A



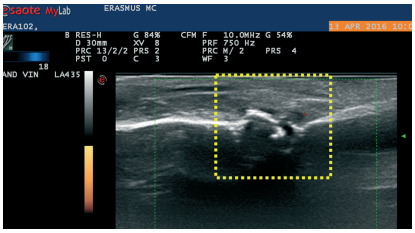
F



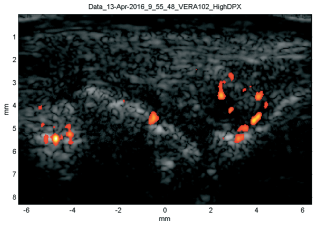
B



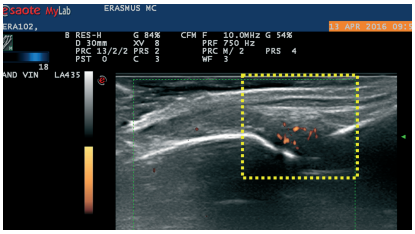
G



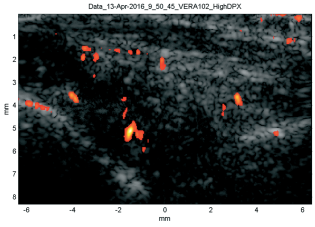
C



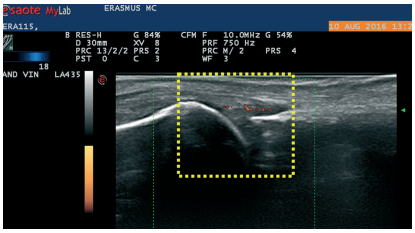
H



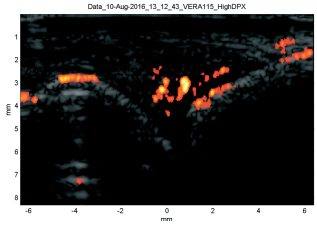
D



I



E



K

Figure 4. MCP joints of healthy controls and RA patients were scanned with conventional PD ultrasound (A.-E.) and high-frame rate Doppler imaging (F.-K.). Images (A. & F.) healthy control; (B. & G.) RA in remission; (C. & H.) RA controlled (non-swollen MCP); (D. & I.) RA controlled (swollen MCP); (E. & K.) RA flare. The dashed yellow box in A-E depicts the region of interest in F-K with the metacarpal bone (left hand side) and the proximal phalanx. (MCP = metacarpophalangeal; RA = rheumatoid arthritis)

To investigate the potential grading power of high-frame rate Doppler, we plotted the distribution of PD scores (range 0-3) in all subjects for each different disease state in Figure 5. Note that, for each subject, all three measurements per examined joint were scored, and the median value was taken for the data shown in Figure 5. In all cases at least one out of the three recordings showed a PD score 1. In correspondence with the median values shown in Table 2, this plot shows a gradual shift of PD score from healthy controls to flaring joints, implying that the high-frame rate Doppler can indeed stage the vascularisation. On the other hand, we observe no difference in vascularisation between the swollen and non-swollen joints with controlled disease.

Discussion

Summary

This study investigated the sensitivity of high-frame rate PD ultrasound for use in rheumatology practice. In a flow phantom, we could detect lower velocities with the high-frame rate ultrasound machine (0.26 mm/s) than with the conventional ultrasound machine (0.8 mm/s) in a 0.7 mm vessel with the clinically unrealistic but optimal settings to detect low flow velocities with the clinical scanner. In the proof-of-principle study we detected a positive PD signal in all volunteers, diseased or healthy, with high-frame rate PD ultrasound. This was opposite to the measurements with conventional PD ultrasound, where no PD signal was observed in the healthy volunteers and in RA patients in clinical remission. In controlled RA patients we found higher PD scores in both clinically swollen MCP joints and in non-swollen MCP joints with high-frame rate PD. In RA patients with a clinical flare, PD scores were higher as well with high-frame rate Doppler than with conventional PD ultrasound. For all groups, PD scores were significantly higher for high-frame rate ultrasound compared to conventional ultrasound. Therefore, high-frame rate PD ultrasound is a more sensitive tool to detect vascularisation than conventional PD ultrasound.

Clinical implications

There are several clinical implications of the findings. Firstly, in healthy controls conventional ultrasound could not detect any PD signal, but with high-frame rate imaging we found at least median grade 1 PD signal in all controls. These PD signals might refer to normal vascularisation of the synovium, which consists of low velocities not detectable by conventional imaging methods. This finding is consistent with

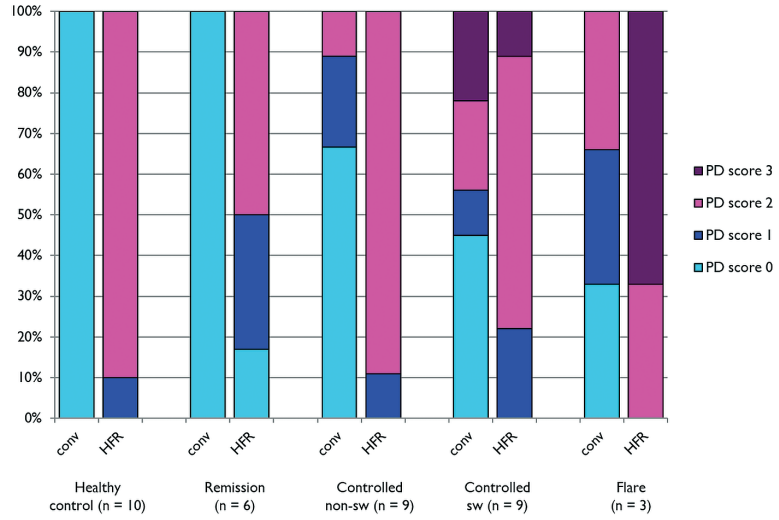


Figure 5. The distribution of PD scores (range 0-3) for healthy controls and the RA patient groups for both conventional PD and high-frame rate PD. More active RA coincides with increasing PD score. (conv = conventional; HFR = high-frame rate; PD = power Doppler; sw = swollen)

previous research with high-frame rate Doppler imaging in healthy volunteers by Maresca et al.[21], although in that study the perfusion was increased by use of a warm water bath in which the hand was held. PD signals in healthy subjects in normal clinical circumstances were not included in the conventional grading system.[34] Hence, a new grading system which includes PD signals in healthy controls is needed. Such grading system could be based on estimating the vessel density[21], although such method needs careful consideration of the used thresholds. A new grading system could also improve interobserver agreement, which is important when a new method is introduced into clinical practice. In our study, the agreement was moderate, which could be explained by the semi-quantitative scoring scale which could introduce subjectivity regarding interpretation especially between grade 1 and grade 2 power Doppler. Anyhow, a study with larger population is needed to fine-tune the grading of signals on a scale ranging from healthy, through (early) inflammation, to full flare.

Overall, high-frame rate PD ultrasound was more sensitive to detect vascularisation, but with some loss of discrimination between healthy controls and RA patients. Further research with high-frame rate PD ultrasound to improve discrimination might lead to more knowledge regarding the physiology of inflammation, especially the relation between symptoms, clinical swelling, vascularisation and inflammation.[8,10]

Secondly, in the clinical experiment we clamped the transducers and mildly fixated the probe to reduce motion from both the ultrasound examiner and the participant.

The mechanical arm in which the probe is held may complicate the dissemination. To assess its need, we performed an additional test in which we compare the high-frame rate PD images recorded with the mechanical arm, with those of manual scanning by an expert (MvdV). Figures 6 (A,B) shows two recordings made with the mechanical arm, and Figures 6 (C,D) show manual scanning. There, the bone reflections lead to residual Doppler signals, because of a much higher relative motion of bone, and no vasculature detection in the synovium. We quantified a peak-to-peak axial motion of 6 µm per recording when scanning with the mechanical arm, and 20 µm with manual scanning (mean of 10 recordings each). The different appearances in Figure 6 indicate the need for mechanical stabilization. In the future, the rather large mechanical arm may be replaced by e.g. a dedicated wearable rheumatology probe which is very gently clipped onto the finger of interest.

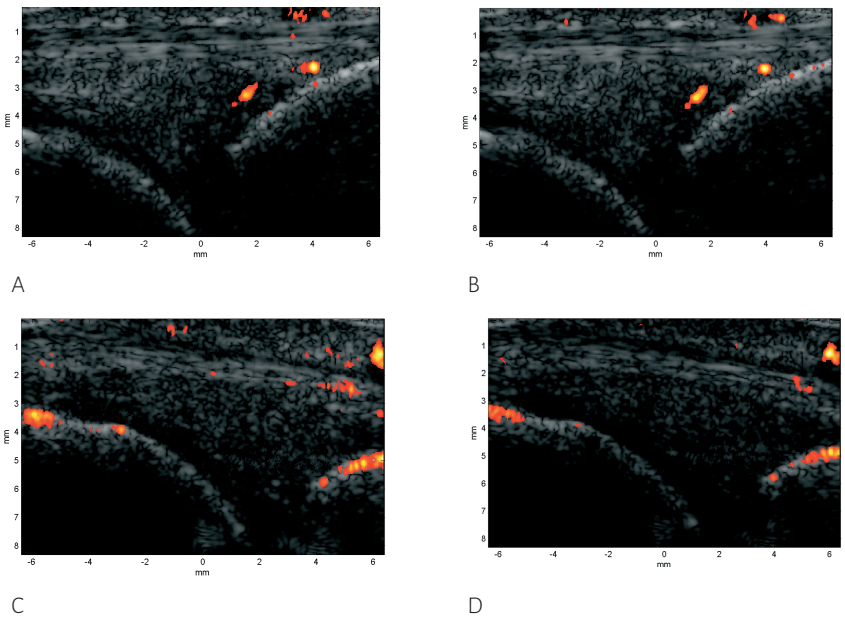


Figure 6. Variability of power Doppler signals when the probe was held in the hydrostatic arm (A, B) and when manually held (C, D).

We used the mechanical arm also for our *in-vivo* measurements with conventional ultrasound to obtain comparable results. In the reported results, we used the same settings (PFR 750 Hz, wall filter 3) as in daily clinical practice, leading to presumed equal sensitivity to flow as in daily routine. Yet, with this clamping and hand fixation, we also tested more optimal settings to detect low-flow PD signal (PRF 370 Hz, wall filter 2) without the risk of flash artefacts. Scoring of those images did not lead to other

results than shown in the main study. Therefore, we only showed the results with the regular clinical settings.

Furthermore, the fact that any exam should give a minor PD signal is highly beneficial for the confidence of the sonographer in the measurement. If no signal is detected, then this is a sign of failure of the measurement, such as malfunctioning (caused by, e.g., broken crystals in the probe), wrong settings, or poor acoustic contact between the probe and skin. This is unlike the conventional method, where 'no PD signal' always is interpreted as 'no or very minor vascularisation'. The conventional ultrasound machine (Esaote MyLab60) is used in daily clinical practice. Although the machine can be considered as mid-range equipment, we selected this machine for comparison as it performed best in detecting low flows in an earlier phantom study.[18] We realise that the use of a more recent high-end clinical ultrasound machine might have led to a different result in the comparison. Yet, in a preliminary test with the ultrafast Doppler mode on a Supersonic Imagine Aixplorer with SL15-4 probe, no vascularisation was observed in the metacarpophalangeal joints of a healthy volunteer. As both the Aixplorer ultrafast Doppler and the proposed high-frame rate ultrasound technique presumably have similar data acquisition schemes, the difference in sensitivity may be sought in either the choice of probe (the currently used probe has a more shallow elevation focus than the used probe of the Aixplorer) or the use of the SVD scheme to cancel tissue signals, thus allowing for more sensitive settings.

Methodology

As there is no gold standard for imaging the microvasculature in finger joints in RA patients, we first investigated the technique with the flow phantom, establishing actual detection of very slow flows. Second, to investigate whether the Doppler signal is 'real' ***in-vivo***, we repeated the measurement ten times at the same location of the MCP joint of one healthy volunteer. It appeared that the same vessels always appeared, and no other appeared, except for isolated pixels at the level of the bone reflection. See Figures 6 (A, B) for two example images. The pixel difference would certainly not change the scoring of such image. The use of SVD to suppress tissue signals has been introduced before in high-frame rate Doppler[27,28], and similar to Demené et al. we have optimised the choice of the singular values which are supposed to contain blood flow information. By visual inspection of the resulting PD images, we found that most blood flow information was contained in the SVD singular values 5 to 32 (of 122 maximum). Yet, minimal bone motion also led to a PD signal in the lower values (range 5 to 15, roughly). In such case, minimal motion of a large scattering object such as the hard

boundary of bone produces similar PD signal as blood flow, which is characterised by a large motion of a low scattering object. Therefore we analysed the PD frames obtained with singular values 18 to 32. Different sets of SVD components, in which the pixel colouring threshold and colour priority was also manually varied, showed minor difference in appearance in terms of noise and bone signal. Yet, this did not lead to a different staging, since the observer in this series (MvdV) was used to interpret bone signal and noise as artefacts. Any automated analysis algorithms that may be used to stage the vascularisation should be devised to perform this discrimination based on the anatomical landmarks present in the grayscale images and PD data.

Retrospectively, we also processed the high-frame rate raw data with a conventional wall filter with relatively low cut-off frequency (37.5 Hz, corresponding to 2.4 mm/s flow velocity). This resulted in very large signal from bone, and no detection of blood flow in cases where filtering with SVD resulted in minor but persistent detection. Lower cut-off values resulted in large flash artefacts and bone signals. This result is consistent with that provided by Demené et al. on the comparison between SVD and conventional wall filtering.[27] The SVD filtering technique removes the tissue motion that is spatially coherent in the images, independent of the typical Doppler frequency of that motion. Since spatial coherency has no influence on the conventional wall filtering, the bone signal is not sufficiently suppressed by that wall filter.

In conventional applications the Doppler power is scaled by the local B-mode intensity (so-called colour priority). Although this suppresses the spurious Doppler signal from bone, it may also enhance Doppler signal from hypo-echoic regions in the joint such as those shown in Figure 4E, thus resulting in a blooming effect and perhaps overestimating tissue motion. We therefore did not apply the scaling of the Doppler power by the B-mode intensity in the final data analysis.

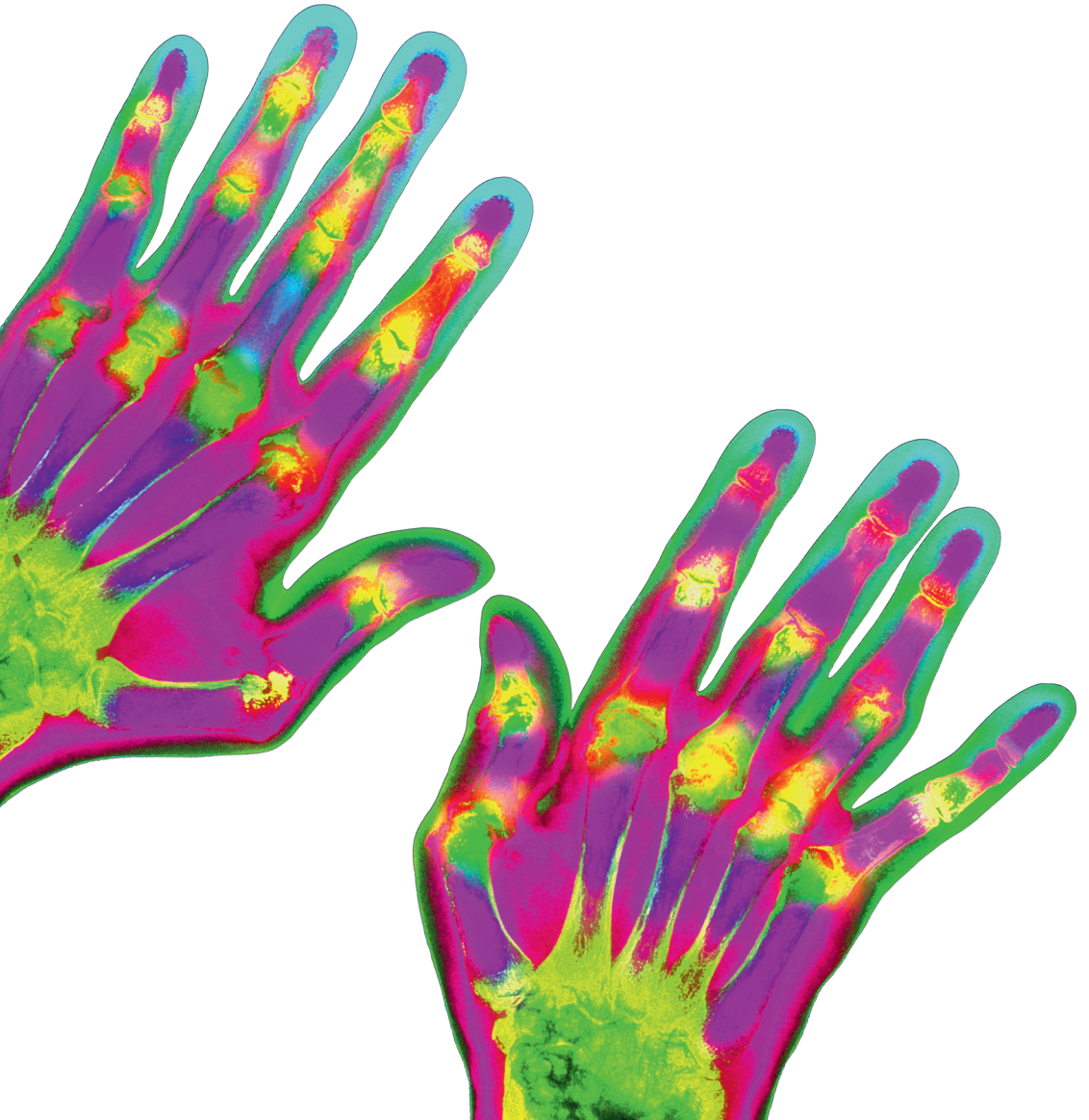
Since we are processing the data in 'power Doppler' mode in which, basically, any signal variation (after tissue removal) is integrated and imaged, there is no intrinsic limitation of maximum detectable blood flow. Therefore, 125 Hz will not limit the maximum detectable flow velocities. Note that this is opposite to colour Doppler or pulsed wave Doppler, in which aliasing (caused by too low PRF) affects the sign and magnitude of flow velocity estimation dramatically.

Our relatively quick implementation of the complementary grayscale images led to a poor grayscale resolution compared to conventional ultrasound imaging. This shortcoming can be solved in the future by increasing the number of angles of plane waves for reconstructing the grayscale image, or even by using conventional line scanning, without dramatic increase of the overall recording time.

References

1. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4 Suppl 3:S265-72.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580-8.
4. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis. 2014;73(5):861-70.
5. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis. 2016;75(1):16-22.
6. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8.
7. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38(1):38-43.
8. Andersen M, Ellegaard K, Hebsgaard JB, Christensen R, Torp-Pedersen S, Kvist PH, et al. Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. Ann Rheum Dis. 2014;73(4):678-83.
9. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54(12):3761-73.
10. Kitchen J, Kane D. Greyscale and power Doppler ultrasonographic evaluation of normal synovial joints: correlation with pro- and anti-inflammatory cytokines and angiogenic factors. Rheumatology (Oxford). 2015;54(3):458-62.
11. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
12. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis. 2011;70(3):500-7.
13. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456-65.
14. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis. 2011;70(1):172-5.
15. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis. 2012;71(8):1316-21.
16. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford). 2009;48(9):1092-7.
17. Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM, et al. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis - a systematic review of the literature. Arthritis Res Ther. 2013;15(1):R4.
18. Ten Cate DF, Luime JJ, van der Ven M, Hazes JM, Kooiman K, de Jong N, et al. Very different performance of the power Doppler modalities of several ultrasound machines ascertained by a microvessel flow phantom. Arthritis Res Ther. 2013;15(5):R162.
19. Bercoff J, Montaldo G, Loupas T, Savery D, Meziere F, Fink M, et al. Ultrafast compound Doppler imaging: providing full blood flow characterization. IEEE Trans Ultrason Ferroelectr Freq Control. 2011;58(1):134-47.

20. Tanter M, Fink M. Ultrafast imaging in biomedical ultrasound. IEEE Trans Ultrason Ferroelectr Freq Control. 2014;61(1):102-19.
21. Maresca D, Tanter M, Pernot M, editors. Ultrasound microangiography of the metacarophalangeal joint using ultrafast Doppler. IEEE International Ultrasonics Symposium, IUS; 2014.
22. Demene C, Pernot M, Biran V, Alison M, Fink M, Baud O, et al. Ultrafast Doppler reveals the mapping of cerebral vascular resistivity in neonates. J Cereb Blood Flow Metab. 2014;34(6):1009-17.
23. Demene C, Tiran E, Sieu LA, Bergel A, Gennisson JL, Pernot M, et al. 4D microvascular imaging based on ultrafast Doppler tomography. Neuroimage. 2016;127:472-83.
24. Ekroll IK, Voormolen MM, Standal OK, Rau JM, Lovstakken L. Coherent compounding in doppler imaging. IEEE Trans Ultrason Ferroelectr Freq Control. 2015;62(9):1634-43.
25. Hasegawa H, Kanai H. Simultaneous imaging of artery-wall strain and blood flow by high frame rate acquisition of RF signals. IEEE Trans Ultrason Ferroelectr Freq Control. 2008;55(12):2626-39.
26. Lenge M, Ramalli A, Boni E, Liebgott H, Cachard C, Tortoli P. High-frame-rate 2-D vector blood flow imaging in the frequency domain. IEEE Trans Ultrason Ferroelectr Freq Control. 2014;61(9):1504-14.
27. Demene C, Deffieux T, Pernot M, Osmanski BF, Biran V, Gennisson JL, et al. Spatiotemporal Clutter Filtering of Ultrafast Ultrasound Data Highly Increases Doppler and f Ultrasound Sensitivity. IEEE Trans Med Imaging. 2015;34(11):2271-85.
28. Song P, Manduca A, Trzasko JD, Chen S. Ultrasound Small Vessel Imaging With Block-Wise Adaptive Local Clutter Filtering. IEEE Trans Med Imaging. 2017;36(1):251-62.
29. Teirlinck CJ, Bezemer RA, Kollmann C, Lubbers J, Hoskins PR, Ramnarine KV, et al. Development of an example flow test object and comparison of five of these test objects, constructed in various laboratories. Ultrasonics. 1998;36(1-5):653-60.
30. Ramnarine KV, Nassiri DK, Hoskins PR, Lubbers J. Validation of a new blood-mimicking fluid for use in Doppler flow test objects. Ultrasound Med Biol. 1998;24(3):451-9.
31. Evans DH, McDicken WN. Doppler Ultrasound: Physics, Instrumentation and Signal Processing. Second ed: John Wiley and Sons Ltd; 1999. 456 p.
32. Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann Rheum Dis. 2008;67(2):143-9.
33. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60(7):641-9.
34. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
35. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37(5):360-3.



CHAPTER 10

General discussion

With the ability of treating rheumatic disease with more precision than we ever could, the questions is raised whether physical examination reached its maximum to identify joint inflammation in its earliest phases. And we know that physical examination is of limited value in detecting inflamed entheses unless the inflammation is visible as for example enthesitis of the Achilles tendon.

Over the last years ultrasound has become an important tool in the assessment of rheumatic diseases, as it accurately detects many essential lesions including joint effusion, synovial hypertrophy, enthesopathy, bursitis and bone erosions. Especially the power Doppler mode is of clinical interest, since presence of power Doppler signal indicates elevated vascularisation, which is an important sign of active inflammation.

In this general discussion, the two aims of this thesis will be discussed separately. The first part will focus on our results regarding the added value of ultrasound in clinical decision making in rheumatology. In the second part I will elaborate on technological developments in ultrasound machines which could increase the sensitivity of power Doppler ultrasound.

Ultrasound in clinical practice

Disease onset – inflammatory arthritis

Many of the first outpatient clinic visits in rheumatology are taken by patients who initially only present with arthralgia. Most of them will have benign symptoms unrelated to inflammatory arthritis (IA). However, a small part will develop IA over time. If left unobserved we miss the opportunity to treat them in very early stages of disease. Previous studies in ACPA and/or RF positive patients who were still in the arthralgia phase showed that 35% will develop IA and in seronegative patients 12% developed IA over one year.[1] Until now it has been fairly difficult to identify those arthralgia patients who will develop IA at first consultation to see whom would benefit from close observation by a rheumatologist.

In our cohort of early arthralgia patients the presence of power Doppler signal had the strongest association with the development of IA within a year. This suggests that power Doppler ultrasound could be of diagnostic value to predict progression to IA. Ultrasound could be of specific use in the seronegative arthralgia patients, as they have few prognostic factors. Additionally, our findings endorse the use of ultrasound to rule out development of IA. If no joints were ultrasound positive, the negative predictive value was 89% (positive predictive value of ultrasound was 26%). It can be debated

whether ultrasound has added value in clinical practice in these patients, since they are also negative at physical examination. Since ultrasound is a time-consuming tool, routine assessment of early inflammatory arthralgia patients would not be recommended.

Our findings correspond well with previous research. Auto-antibody positive arthralgia patients with a positive ultrasound had an increased risk for developing IA.[2, 3] In patients with very early hand symptoms, the presence of power Doppler signal was associated with developing IA.[4] These studies do not mention a negative predictive value or discuss the use of ultrasound to rule out development of IA, therefore further research regarding the added value of ultrasound to rule out development of IA is recommended.

To identify which arthralgia patients progress to IA, power Doppler ultrasound could be useful, but our findings need to be validated. Besides ultrasound, other imaging modalities (e.g. MRI) or biomarkers might help us to predict development of IA in arthralgia patients. If an arthralgia patient is clinically (and ultrasonographically) suspect for developing arthritis, the question arises whether and when to start treatment. Intervention trials are needed to evaluate the efficacy of DMARD treatment in these patients. It has been shown that early treatment of RA is beneficial and improved outcomes (e.g. mortality rates) can still be seen after 20 years[5], so these results encourage to strive for even earlier detection and treatment. For now, it is recommended to follow-up early inflammatory arthralgia patients who are suspect for developing arthritis by clinical expertise. It has been observed that these patients do not consider themselves as patients, so it would not be harmful with respect to their perception of symptoms or identity.[6] Including ultrasound assessments in the follow-up of these patients might increase the identification of patients who develop IA.

Disease onset – enthesitis

With the introduction of the CASPAR (Classification criteria for psoriatic arthritis) criteria for psoriatic arthritis (PsA), psoriasis patients can classify as PsA with only enthesitis as inflammatory involvement.[7] Up to now no consensus has been achieved on its measurements in the diagnostic setting and entheseal inflammation is difficult to assess by clinical examination only.[8-10] Clinical examination by assessing tender points at entheseal sites tend to overestimate entheseal inflammation.[11] With ultrasound we were more specific in detecting enthesitis, since we were able to visualise active inflammatory involvement at the enthesis. By combining ultrasound with clinical data we reduced the number of patients with enthesitis who should be evaluated

in screening psoriasis patients by a rheumatologist. This could help to differentiate patients with non-inflammatory entheseal pain from patients with entheseal involvement related to inflammation, helping physicians to make informed decisions about whether the entheseal tenderness might be related to PsA and in whom to start anti-inflammatory treatment.

One of the difficulties we came across was the absence of general accepted definitions for both the clinical presentation as well as the ultrasound presentation of enthesitis. The first steps towards agreement on ultrasound definitions and elementary lesions were taken by the OMERACT Ultrasound Task Force on enthesitis.[12] However, consensus still needs to be reached on what exactly is defined as inflammatory components since they did not reach consensus on entheseal thickness. Besides that it would help if a generally accepted definition for enthesitis would be available for daily clinical work. In addition, the mismatch between clinical and ultrasound findings especially needs further investigation. Some of our patients showed explicit signs of ultrasound and did not experience any pain or stiffness.

We showed that entheseal abnormalities detected by ultrasound are very common in psoriasis patients (95% had structural ultrasound abnormalities), but it is debatable if ultrasound needs to added to routine clinical practice to identify enthesitis in psoriasis patients since it time-consuming. However, Wervers et al. showed in an early PsA cohort that health-related quality of life across both physical and mental scales was lower in patients with tender entheses compared to those patients with no tender enthesis.[13] These results emphasise that the entheses are important in the assessment of PsA.

Whether ultrasound is the right method to detect enthesitis, needs further investigation since ultrasound abnormalities are also frequently found in healthy controls.[14] Ultrasound features (e.g. altered signal, erosions, cysts) which are regarded specific for enthesitis are also seen in posttraumatic, degenerated entheses or could be related to mechanical stress. Poggenborg et al. confirmed this statement by assessing entheses of patients with PsA and of healthy controls with whole body MRI and found no statistically significant difference.[15] The drawback of whole body MRI is the thicker image layers compared with conventional MRI causing low readability for distal peripheral joints. With MRI it is possible to detect bone marrow oedema, but this could also be found in the healing phase of trauma.[16] This emphasises that proper evaluation of lifestyle, history of trauma and body weight are needed to differentiate between truly enthesitis and microtrauma-enthesopathy.

To conclude, I would not endorse to introduce ultrasound as a screening tool for enthesitis in psoriasis patients. Ultrasound might have added value in patients who

clinically present themselves with inflammatory entheseal complaints to confirm diagnosis of enthesitis.

Monitoring – rheumatoid arthritis

Feet involvement

The goal of treat-to-target strategies is to achieve clinical remission. For accurate assessment of inflammation in RA patients, physical examination is important but difficult to perform in the feet. Although the first disease activity score (DAS) contains the feet, quickly after its introduction simplified disease activity scores were introduced (DAS28, SDAI/CDAI), excluding the feet. Due to less joints, these scores made it easier to be applied in clinical practice but in the era of achieving disease remission may not suffice as the feet may still show signs of inflammation while other joints are in remission.

Two definitions of remission were redefined in 2011, both based on 28-joint counts.[17] Several studies showed that these reduced 28-joints count overestimates the original DAS remission. This discrepancy can be explained by inflammation in joints not captured by the DAS28, mainly by residual inflammation in ankles and feet.[18, 19] For monitoring disease activity in RA patients it is recommended to perform a full joint assessment, including the feet. However, physical examination of the feet to identify synovitis is more difficult than that of other joints.[20, 21] Ultrasound could be a useful tool to monitor inflammation of the feet.

In newly diagnosed RA patients we found that 29% of all MTP joints were swollen at physical examination and 14% had ultrasound synovitis at baseline. The agreement at joint level was poor between physical examination and ultrasonographic evaluation (K=0.02). Positive percent agreement between physically swollen MTP joints and positive ultrasound was low (<16%). Negative percent agreement (non-swollen MTP joint at physical examination and no ultrasound synovitis) was high (>85%). This indicates there is a role for ultrasound in monitoring inflammation in the feet in RA patients in clinical remission to assess whether the feet are really in remission and treatment could be tapered.

Quality of life

Due to treat-to-target strategies, many RA patients are able to reach a state of clinical remission.[22] Patient-reported outcomes are becoming more important in monitoring RA patients, but the association between health status and (ultrasound) remission has not been investigated thoroughly.[23-26] We found that one-third of RA patients in clinical

remission were also in ultrasound remission. This is slightly lower, but still comparable with other studies which found ongoing ultrasound synovitis in 48-73% of RA patients who were in clinical remission.[27-31]

The presence of ultrasound synovitis may indicate that patients still experience problems in their daily live even when they are in clinical remission. Therefore, we compared RA patients in clinical remission with and without ultrasound synovitis. In general, all patients in clinical remission reported good health, with low scores for pain, functional disability, anxiety, depression and fatigue and higher scores for general health. There were small differences between the two groups, although in opposite direction of what we had expected. We found that patients in ultrasound remission experienced more pain (VAS pain, range 0-10; 3 vs 1) and anxiety (HADS anxiety, range 0-21; 5 vs 3). We could not find a clear association between health status and being in ultrasound remission. Our results implicate that ultrasound does not add extra clinical information that may identify lingering subclinical disease.

Tapering

Previous research has shown that ultrasound, especially the presence of power Doppler signal, can be used as a predictor of disease relapse in RA patients in clinical remission who tapered or discontinued their medication.[32-34] Our results in a relatively large group of RA patients in clinical remission showed less promising results and indicate that there is limited value in scanning every patient every three months to identify patients who will have a disease relapse. This was also found by Lamers-Karnebeek et al. in RA patients who discontinued TNFi.[35] Baseline ultrasound was informative at group level for predicting disease relapse, but at patient level ultrasound had little added value over easy available clinical variables.

We found a high negative predictive value, which is more interesting since that makes it possible to identify which patients could go to the next step in tapering their medication.

Several studies showed that ultrasound synovitis predicts short-term relapse and erosions, but do we need to treat-to-target (T2T) with ultrasound monitoring and aim for ultrasound remission? Whether the incorporation of ultrasound in a T2T strategy would improve clinical and imaging outcomes has been investigated by Dale et al. Patients were randomised either to a DAS28-driven T2T strategy or to a ultrasound-driven T2T strategy. Ultrasound-driven T2T therapy led to more intensive treatment and more patients achieved DAS44 remission after 18 months, but ultrasound-driven

T2T therapy was not associated with better clinical or imaging outcomes compared with DAS-driven T2T therapy.[36] These results were also found in the ARCTIC trial.[37] Their results support our opinion that an ultrasound assessment should not be introduced as a regular imaging tool in routine clinical practice. There is a role for ultrasound in monitoring RA patients and is especially informative in treatment decision making when clinical disease activity status is not apparent. However, added value of routine use of ultrasound as part of a T2T strategy is not yet demonstrated.

Experimental technical research

Power Doppler and its variation

The importance of accurate monitoring of inflammation in rheumatic diseases has contributed to the increasing interest in ultrasound.[38] Especially power Doppler seems to have a lot of potential. The presence of power Doppler signal in RA patients in clinical remission predicts disease relapse at group level and radiographic progression.[26, 29, 39-41] However, besides being operator-dependent, power Doppler ultrasound is dependent of type of ultrasound machine used.[42, 43] The performance of the power Doppler modality of several ultrasound machines was compared by a flow phantom. We found large differences in sensitivity of the power Doppler modality between the machines. Since power Doppler signal is regarded very valuable in detection of (subclinical) inflammation, correct assessment of presence or absence of power Doppler signal is important in clinical decision making in rheumatology. This study also showed that not every ultrasound machine was capable to detect low flow velocities which could indicate subclinical inflammation. Our results regarding different sensitivities to low flows emphasize the significance of testing the power Doppler modality of ultrasound machines. In clinical practice it could lead to a patient being identified as having ultrasound inflammation and possible escalation of medication assessed by one machine, whereas the same patient could be identified as being in ultrasound remission by another machine and possible tapering of medication. Therefore, we recommend to pay extra attention to the sensitivity of the power Doppler modality when purchasing an ultrasound machine.

Improvement of power Doppler signal detection

To provide more accurate detection of active inflammation we studied a more sensitive ultrasound technique. We compared conventional ultrasound with high-frame rate

Doppler ultrasound in the same flow phantom and detected lower flow velocities with high-frame rate Doppler. With high-frame rate Doppler we found power Doppler signal in MCP2 joints of all healthy controls. These power Doppler signals are likely to represent normal vascularisation of the synovium. This of course can be seen as an advantage but also as a disadvantage. As an advantage in the sense that we are able to detect physiological flows, as a disadvantage in the sense that it makes discrimination between healthy and diseased more difficult.

To make use of high-frame rate ultrasound a new grading system is needed. This should take into account that power Doppler signals are also seen in healthy controls and needs to fine-tune grading of power Doppler signals on a scale ranging from healthy, through (early) inflammation, to full flare. A new grading system could be based on objective estimation of the vessel density as proposed by Maresca et al.[44] It would be recommended to incorporate grayscale findings in this grading system, which could be helpful to differentiate between healthy and diseased. Another option would be an adaptation of the semi-quantitative power Doppler grading system of Naredo et al.[45] by adding extra grade(s) around power Doppler score 2, since power Doppler score 2 was mostly detected in healthy controls.[46]

Overall, high-frame rate Doppler was more sensitive in detecting vascularisation, but with some loss of discrimination between healthy controls and RA patients. Therefore, further research with high-frame rate Doppler ultrasound is needed to improve discrimination and to increase our knowledge of the physiology of inflammation, especially the relation between symptoms, clinical swelling, vascularisation and inflammation.[47, 48]

Questions arise when searching for a more sensitive imaging technique are: How sensitive for low flows is technically possible? And is it still clinically relevant? From a technological perspective, it is of interest to investigate which flow velocities are still detectable in vivo. From a clinical perspective, the rheumatologist wants a feasible valid method to determine for each individual patient if treatment alteration is needed. Remission is the ultimate therapeutic goal for RA patients to prevent (further) joint damage and disability and to maintain function and quality of life. With more a more sensitive imaging technique to detect relapsing disease at an earlier time point treatment intensification could be initiated. Therefore, it is very important to be able to distinguish healthy tissue from and inflamed joint or tendon. In addition, with the use of a more sensitive imaging method, it could be possible to identify patients in the preclinical phase of RA before clinically detectable arthritis develops. The persons

who will progress to develop arthritis need to be identified with high accuracy and risk stratification needs to be developed and investigated in preventive trials.

Further imaging possibilities in rheumatology

The research presented in this thesis showed added value in decision making of ultrasound assessment to clinical practice in certain situations, but does not demonstrate added value of routine use of ultrasound. However, in the research domain you want to have valid imaging methods and ideally an automated objective scoring system. Technological developments in ultrasound machines are promising, like the implementation of high-frame rate Doppler ultrasound. Other developments in ultrasound are 3D ultrasound and shear wave imaging, which both provide overcome the largest disadvantage of conventional ultrasound which is operator-dependency.

3D Ultrasound

3D ultrasound showed good to excellent agreement with conventional 2D ultrasound.[49, 50] Advantages of 3D ultrasound over conventional ultrasound is the reduction of the operator dependence in assessing synovitis, because of the automatic image acquisition and shortening of the examination time.[49-51] The evaluation of the acquired images can be done after the ultrasound assessment, with or without the presence of the patient. This feature is also interesting for clinical trials or observational studies, since assessors can be blinded for evaluation of the acquired ultrasound images. A pilot study by Naredo et al. suggests that 3D ultrasound can be responsive and repeatable in multicentre cohort studies.[51]

Shear wave ultrasound[52]

Sonoelastographic techniques provide extra information to conventional ultrasound related to tissue properties. Shear wave elastography is being increasingly used in the evaluation of musculoskeletal tissues and complements diagnosis obtained at grayscale ultrasound and power Doppler ultrasound. In rheumatology, shear wave imaging could be used especially in the assessment of tendons and ligaments. Shear waves propagate faster healthy tendons than in those which are tendinopathic, and faster in contracted tendons than in those which are relaxed. In case of tendinopathy, shear wave velocity is lower than in normal tendons. The basic physics of shear wave imaging is explained in Figure 1. Shear wave elastography is considered to be more

operator independent and reproducible, since there is no need for manual compression of the tissue.

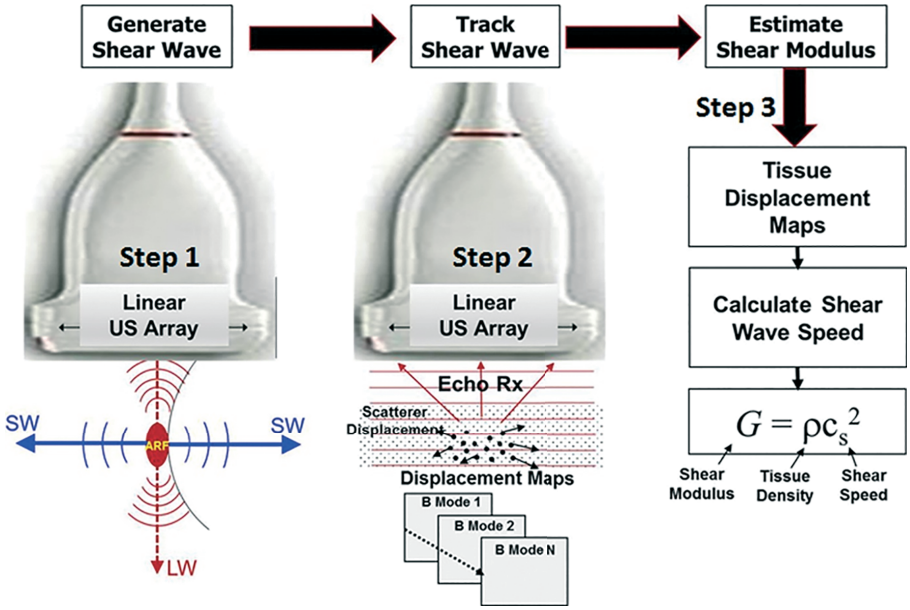


Figure 1. Basic physics of shear-wave elastography. In step 1, shear waves are generated using acoustic radiation force; they propagate perpendicularly to the primary ultrasound wave at a lower velocity. In step 2, fast plane wave excitation is used to track displacement and velocity as shear waves propagate, and tissue displacement is calculated using a speckle tracking algorithm. In step 3, tissue displacements are used to calculate shear-wave velocity (c_s) and shear modulus (G). [Adapted from Taljanovic et al.[52]]

New insights

- The absence of ultrasound synovitis is of diagnostic value in clinically suspect arthralgia patients to rule out development to inflammatory arthritis.
- Adding ultrasound of the entheses to clinical information reduced the number of primary care psoriasis patients with enthesitis who should be evaluated by a rheumatologist.
- In monitoring disease activity in RA patients ultrasound confirms that a patient has no ongoing inflammation and is therefore of diagnostic value to identify RA patients who can taper their medication.
- High-frame rate Doppler imaging is more sensitive than conventional power Doppler in detecting vascularisation in RA patients and healthy controls.

Implications for clinical practice

Overall, clinical examination of joints is adequate in most situations and therefore I would not recommend to add a routine ultrasound assessment to clinical examination in daily practice. However, we found 3 subsamples of patients who would benefit from the addition of ultrasound to clinical examination. The absence of ultrasound rules out development of arthralgia to arthritis and the absence of ultrasound rules out disease relapse in RA patients in clinical remission who are tapering their medication. Evaluating the entheses by ultrasound in psoriasis patients may provide information about the presence of entheseal inflammation. I would recommend to use ultrasound as a tool in case of doubt to ensure if there is ongoing inflammation or not.
The results from this thesis highlight the importance of conducting clinical trials to evaluate the added value of new imaging technologies or new treatment strategies including imaging before wide adaption in clinical practice.

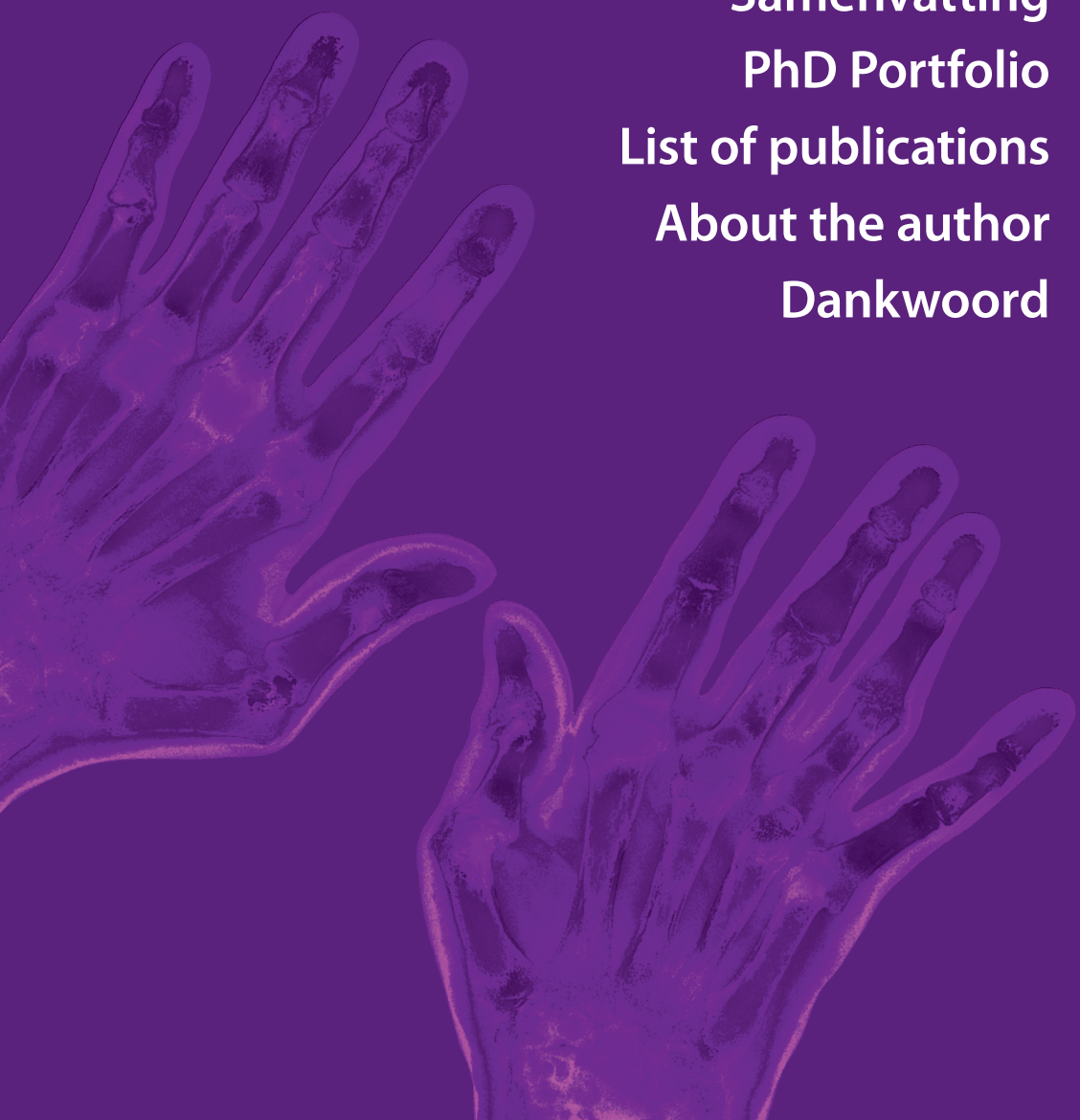
References

1. Alves C. Early detection of patients at risk for rheumatoid arthritis - A challenge for primary and secondary care. Erasmus University Rotterdam; 2015, February 6. p. Retrieved from http://hdl.handle.net/1765/78432.
2. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis 2015;74(9):1659-66.
3. van de Stadt LA, Bos WH, Meursinge Reynders M, Wieringa H, Turkstra F, van der Laken CJ, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther 2010;12(3):R98.
4. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis 2010;69(2):417-9.
5. Zink A, Albrecht K. Rheumatoid arthritis: The benefits of early treatment after decades. Nat Rev Rheumatol 2017;13(8):458-9.
6. Newsum EC, van der Helm-van Mil AH, Kaptein AA. Views on clinically suspect arthralgia: a focus group study. Clin Rheumatol 2016;35(5):1347-52.
7. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54(8):2665-73.
8. Mandl P, Niedermayer DS, Balint PV. Ultrasound for enthesitis: handle with care! Ann Rheum Dis 2012;71(4):477-9.
9. McGonagle DG, Helliwell P, Veale D. Enthesitis in psoriatic disease. Dermatology 2012;225(2):100-9.
10. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. J Rheumatol 2006;33(7):1435-8.
11. Freeston JE, Coates LC, Helliwell PS, Hensor EM, Wakefield RJ, Emery P, et al. Is there subclinical enthesitis in early psoriatic arthritis? A clinical comparison with power doppler ultrasound. Arthritis Care Res (Hoboken) 2012;64(10):1617-21.
12. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al. Defining enthesitis in spondyloarthritis by ultrasound: results of a delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken) 2014;66(5):741-8.
13. Wervers K, Luime JJ, Tchetverikov I, Gerards AH, Kok MR, Appels CWY, et al. Quality of life at baseline in early psoriatic arthritis related to initial presentation of mono-, oligo-, and polyarthritis and tender enthesis: results from the DEPAR study. Ann Rheum Dis 2016;75(Suppl 2):1155.
14. Gandjbakhch F, Terslev L, Joshua F, Wakefield RJ, Naredo E, D'Agostino MA, et al. Ultrasound in the evaluation of enthesitis: status and perspectives. Arthritis Res Ther 2011;13(6):R188.
15. Poggenborg RP, Eshed I, Ostergaard M, Sorensen IJ, Moller JM, Madsen OR, et al. Enthesitis in patients with psoriatic arthritis, axial spondyloarthritis and healthy subjects assessed by 'head-to-toe' whole-body MRI and clinical examination. Ann Rheum Dis 2015;74(5):823-9.
16. Sudol-Szopinska I, Pracon G. Diagnostic imaging of psoriatic arthritis. Part II: magnetic resonance imaging and ultrasonography. J Ultrason 2016;16(65):163-74.
17. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/ European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-13.
18. Landewe R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65(5):637-41.
19. Wechalekar MD, Lester S, Proudman SM, Cleland LG, Whittle SL, Rischmueller M, et al. Active foot synovitis in patients with rheumatoid arthritis: applying clinical criteria for disease activity and remission may result in underestimation of foot joint involvement. Arthritis Rheum 2012;64(5):1316-22.
20. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32(5):531-7.
21. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38(1):38-43.

22. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75(1):3-15.
23. Bingham CO, 3rd, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, et al. Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. J Rheumatol 2011;38(8):1751-8.
24. Bingham CO, 3rd, Alten R, de Wit MP. The importance of patient participation in measuring rheumatoid arthritis flares. Ann Rheum Dis 2012;71(7):1107-9.
25. Bykerk VP, Lie E, Bartlett SJ, Alten R, Boonen A, Christensen R, et al. Establishing a core domain set to measure rheumatoid arthritis flares: report of the OMERACT 11 RA flare Workshop. J Rheumatol 2014;41(4):799-809.
26. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71(8):1316-21.
27. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54(12):3761-73.
28. Ozgocmen S, Ozdemir H, Kiris A, Bozgeyik Z, Ardicoglu O. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial inflammation in clinical remission. South Med J 2008;101(3):240-5.
29. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70(1):172-5.
30. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum 2009;60(7):1915-22.
31. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol 2013;23(3):456-65.
32. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Bahlas S, Hegazi M, et al. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. Clin Rheumatol 2016;35(12):2915-23.
33. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka S, Norimoto A, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. Arthritis Care Res (Hoboken) 2014;66(10):1576-81.
34. Naredo E, Valor L, De la Torre I, Montoro M, Bello N, Martinez-Barrio J, et al. Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. Rheumatology (Oxford) 2015;54(8):1408-14.
35. Lamers-Karnebeek FB, Luime JJ, Ten Cate DF, Teerenstra S, Swen N, Gerards AH, et al. Limited value for ultrasonography in predicting flare in rheumatoid arthritis patients with low disease activity stopping TNF inhibitors. Rheumatology (Oxford) 2017.
36. Dale J, Stirling A, Zhang R, Purves D, Foley J, Sambrook M, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 2016;75(6):1043-50.
37. Haavardsholm EA, Aga A-B, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in the management of rheumatoid arthritis: results from the randomized controlled ARCTIC trial. Ann Rheum Dis 2016;75(Suppl2):123.
38. Brown AK. Using ultrasonography to facilitate best practice in diagnosis and management of RA. Nat Rev Rheumatol 2009;5(12):698-706.
39. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58(10):2958-67.
40. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum 2012;64(1):67-76.

41. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford) 2009;48(9):1092-7.
42. Browne JE, Watson AJ, Hoskins PR, Elliott AT. Validation of a sensitivity performance index test protocol and evaluation of colour Doppler sensitivity for a range of ultrasound scanners. Ultrasound Med Biol 2004;30(11):1475-83.
43. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. Ann Rheum Dis 2006;65(12):1590-5.
44. Maresca D, Tanter M, Pernot M, editors. Ultrasound microangiography of the metacarophalangeal joint using ultrafast Doppler. IEEE International Ultrasonics Symposium, IUS; 2014.
45. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis 2005;64(3):375-81.
46. van der Ven M, Luime JJ, van der Velden LL, Bosch JG, Hazes JMW, Vos HJ. High-Frame-Rate Power Doppler Ultrasound Is More Sensitive than Conventional Power Doppler in Detecting Rheumatic Vascularisation. Ultrasound Med Biol 2017;43(9):1868-79.
47. Andersen M, Ellegaard K, Hebsgaard JB, Christensen R, Torp-Pedersen S, Kvist PH, et al. Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. Ann Rheum Dis 2014;73(4):678-83.
48. Kitchen J, Kane D. Greyscale and power Doppler ultrasonographic evaluation of normal synovial joints: correlation with pro- and anti-inflammatory cytokines and angiogenic factors. Rheumatology (Oxford) 2015;54(3):458-62.
49. Acebes C, McKay N, Ciechomska A, Alcorn N, Harvie JP, Robson B, et al. Level of agreement between three-dimensional volumetric ultrasound and real-time conventional ultrasound in the assessment of synovitis, tenosynovitis and erosions in rheumatoid arthritis patients. Rheumatol Int 2017;37(2):197-205.
50. Filippucci E, Meenagh G, Delle Sedie A, Salaffi F, Riente L, Iagnocco 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. Clin Exp Rheumatol 2009;27(2):197-200.
51. Naredo E, Acebes C, Brito E, de Agustin JJ, de Miguel E, Mayordomo L, et al. Three-dimensional volumetric ultrasound: a valid method for blinded assessment of response to therapy in rheumatoid arthritis. J Rheumatol 2013;40(3):253-60.
52. Taljanovic MS, Gimber LH, Becker GW, Latt LD, Klauser AS, Melville DM, et al. Shear-Wave Elastography: Basic Physics and Musculoskeletal Applications. Radiographics 2017;37(3):855-70.

ADDENDUM



Summary

The importance of early diagnosis and accurate monitoring of inflammation in rheumatic diseases has contributed to the increasing interest in ultrasound. Since ultrasound is more sensitive than physical examination in the detection of synovitis, it is increasingly used in daily clinical practice. Yet, the position of ultrasound regarding the already existing diagnostic and monitoring tools needs to be established. Therefore, the aims of this thesis were:

1. to evaluate the added value of ultrasound in clinical decision making in:
   a. Patients with arthralgia
   b. Patients with psoriasis
   c. Monitoring rheumatoid arthritis patients
2. to increase sensitivity of power Doppler ultrasound for MCP joints.

The introduction, **chapter 1**, starts with a short background in ultrasound physics. This is followed by current perspectives of ultrasound in early recognition, diagnosis and monitoring in rheumatology and the challenges which are faced.

With the introduction of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) we are able to classify patients as having RA at an earlier stage (≥6/10 points). The developers of the 2010 criteria suggest that there is a scope for using other cut points for different purposes. In **chapter 2** we evaluated which cut point of the 2010 criteria would enable us to identify more early RA patients among early inflammatory arthritis (IA) patients at first consultation. Early arthritis patients with at least one joint with clinical synovitis and symptoms less than one year were included. After one year follow-up they were classified as case or non-case (i.e. methotrexate initiation). Diagnostic performance of the 2010 criteria was determined. By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify 15% more RA patients at a cost of 8% more false-positive patients. This could be used as a simple tool to initiate early treatment in RA patients.

This thesis is divided in two parts; ultrasound in clinical practice and experimental technical research.

Part one – Ultrasound in clinical practice

Since physical examination reached its maximum to identify synovitis, the first part of this thesis focussed on the added value of ultrasound in daily clinical practice. Chapter

3 and chapter 4 focus on the diagnostic value of ultrasound. Chapters 5, 6 and 7 focus on the value of ultrasound in monitoring of RA patients.

Previous research showed that 15% of arthralgia patients who present themselves without clinical signs of inflammation at baseline will develop IA within one year. Up to now it has been fairly difficult to identify those arthralgia patients who develop IA. In chapter 3 we aimed to identify arthralgia patients developing IA within a year using ultrasound to detect synovitis at first consultation. We included 196 arthralgia patients without clinical synovitis of whom 37% had ultrasound synovitis at baseline. We observed that 16% of the arthralgia patients developed IA within a year. Ultrasound did perform well in ruling out IA in arthralgia patients who did not have ultrasound synovitis. Factors associated with the development of IA were age, morning stiffness >30 minutes and the presence of power Doppler signal. The presence of power Doppler had the strongest association. Our findings suggest power Doppler ultrasound could be of diagnostic value to predict progression to IA in early arthralgia patients, but this needs further evaluation.

The diagnostic performance of ultrasound to detect enthesitis in primary care psoriasis patients is studied in chapter 4. Part of the psoriasis patients who have musculoskeletal complaints will have inflammation of the entheses. Entheseal inflammation is difficult to assess by clinical examination only. Therefore, we combined data from ultrasound, clinical examination and patient-reported questionnaires to define active inflammation at the enthesis. Active ultrasound inflammation contained positive power Doppler signal at the enthesis or in case of the plantar fascia increased thickness. Clinically, an enthesis was scored positive by a tender enthesis at clinical examination, reported pain in the history or self-reported pain in the questionnaires. In 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites (n=111) enthesitis was present. By adding ultrasound to the clinical evaluation of entheses we were able to visualise the presence of active inflammatory involvement of the enthesis. This reduced the frequency of entheseal lesions that should be evaluated by the rheumatologist compared to clinical exam only.

In RA patients the metatarsophalangeal (MTP) joints are frequently affected early in the course of the disease. Physical examination of the feet is more difficult than that of other joints. To enhance knowledge about the value of monitoring the feet in RA patients, we investigated the agreement of ultrasound findings at the MTP joints

with physical examination in newly diagnosed RA patients (n=174) who were treated to target in chapter 5. At baseline, 63% of the patients had at least one ultrasound positive MTP joint. After one year follow-up 62% reached DAS28 remission of whom a quarter still had at least one ultrasound positive MTP joint. At joint level, the presence of ultrasound synovitis in the MTP joints correlated poorly with physical examination. Conversely, we found high agreement between physically non-swollen or non-tender MTP joints and a negative ultrasound. The clinical implications of monitoring the feet at patient level in an era aiming for remission may be vast and need to be further investigated.

In chapter 6, we evaluated the frequency of ultrasound remission in RA patients who were in clinical sustained remission. Our second objective was to compare the health status of RA patients in clinical remission with RA patients who were also in ultrasound remission. Given the association between ultrasound synovitis and increased risk of flare, it is of clinical interest whether these patients with ultrasound synovitis report a different health status regarding pain, fatigue and general health. This could be used by physicians to adapt their treatment different in these patients compared to patients who are both in clinical and ultrasound remission. Eighty-nine RA patients in clinical remission were examined by ultrasound and patient reported outcomes were recorded. One-third of the RA patients in clinical remission were in ultrasound remission. We could not find a clear association between the health status of RA patients and being in ultrasound remission. We did find that patients in ultrasound remission experienced more pain and anxiety, but this was in the direction opposite to what was expected. We recommend that our results need to be confirmed in other cohorts with RA patients who are in clinical remission.

To improve individual tapering decision in RA patients who are in clinical remission we need to know which risk factors for disease relapse play a role. In chapter 7, we monitored RA patients every three months with ultrasound to determine if ultrasound synovitis preceded disease relapse. We included 125 RA patients in clinical remission who started tapering their medication (synthetic DMARD or TNF inhibitor). After one year follow-up 36% of the patients had had a disease relapse of whom 60% had ultrasound synovitis at baseline. In our study population, increasing number of joints with ultrasound synovitis was not significantly associated with disease relapse. Increasing number of joints with a positive power Doppler signal did significantly increase the risk for having a disease relapse within three months. Monitoring RA patients who started

tapering their medication every three months by ultrasound showed limited value for ultrasound to identify patients who will have a disease relapse. Given the high NPV, ultrasound might have added value to identify which patients could go to the next step in tapering their medication. This could be of special importance in monitoring disease activity in those patients in whom it was hard to achieve remission and who might have lost their therapeutic response after re-initiation of biologic treatment.

Part two – Experimental technical research

The second part of this thesis focussed on experimental technical research, since technological developments in ultrasound machines could also improve early detection of inflammation.

It has been shown that power Doppler ultrasound is highly dependent of the type of ultrasound machine used. The performance of the power Doppler modality of five ultrasound machines was compared by a flow phantom and described in chapter 8. Power Doppler settings were optimised to determine the lowest detectable flow for each ultrasound machine. The sensitivity of the power Doppler modalities of the five machines was very different. Only two of the machines were able to detect very low flows in the flow phantom. The differences found between the machines could be caused by fundamental differences in processing of the power Doppler signal or by internal settings inaccessible to users. In conclusion, the choice of ultrasound machine and its settings seems very important. Caution should be taken when conducting a multi-machine trial or when making treatment decisions based on power Doppler ultrasound.

Developments in high frame rate imaging are very promising, since this technique allows detection of slow flow in very small vessels. High frame rate Doppler ultrasound imaging is more sensitive to low flow than conventional ultrasound. Therefore, it might provide accurate detection of active inflammation in joints of RA patients. This could enable earlier diagnosis of RA and better treatment monitoring. In chapter 9 the sensitivity of high frame rate Doppler for microvascular flow in a flow phantom was investigated and a proof-of-principle study in healthy controls and RA patients with different disease activities was executed. In the flow phantom, minimal detectable flow velocity was a factor three lower with high frame rate power Doppler than with conventional power Doppler ultrasound. In the proof-of-principle study a positive power Doppler signal was detected in all volunteers, diseased or healthy, with high

frame rate power Doppler ultrasound. This was opposite to the measurements with conventional power Doppler ultrasound, where no power Doppler signal was observed in the healthy volunteers and in RA patients in clinical remission. With high frame rate power Doppler ultrasound a gradual increase of power Doppler signal in RA patients was seen depending on disease activity. For all groups, power Doppler scores were significantly different between high frame rate ultrasound and conventional ultrasound. Further research with high frame rate power Doppler ultrasound to improve discrimination between healthy controls and RA patients and might lead to more knowledge regarding the physiology of inflammation.

In chapter 10 our results are summarised and discussed considering methodological issues and current literature. This thesis ends with the clinical applicability of our results and recommendations for future research.

Samenvatting

In de reumatologie zijn vroege diagnosestelling en accurate monitoring van ziekteactiviteit belangrijk. Dit heeft er mede voor gezorgd dat de interesse in echografie is toegenomen. Aangezien is aangetoond dat echografie sensitiever is in het detecteren van synovitis dan lichamelijk onderzoek, wordt het ook steeds meer in de klinische praktijk toegepast. Echter is de plaats van echografie in verhouding tot de bestaande diagnostiek en monitoring nog niet geheel duidelijk. Daarom zijn de doelstellingen van dit proefschrift als volgt:

1. Bepalen wat de toegevoegde waarde is van echografie in de klinische besluitvorming bij:
   a. Patiënten met artralgie
   b. Patiënten met psoriasis
   c. Monitoren van patiënten met reumatoïde artritis (RA)
2. Verbeteren van de sensitiviteit van power Doppler echografie van de MCP gewrichten.

Hoofdstuk 1 geeft in het kort een introductie van de achterliggende natuurkunde van de gebruikte technologie. Daarna volgt de huidige plaats van echografie in vroegherkenning, diagnosestelling en monitoring in de reumatologie en welke vragen er momenteel nog liggen.

In 2010 zijn nieuwe classificatiecriteria voor RA opgesteld door de Europese en Amerikaanse reumatologie verenigingen, waardoor het mogelijk is om patiënten al op een eerder moment te classificeren als RA patiënt (≥6/10 punten). De auteurs van de 2010 criteria hebben aangegeven dat andere afkappunten gebruikt kunnen worden voor andere doeleinden. In hoofdstuk 2 hebben we onderzocht welk afkappunt van de 2010 criteria ons in staat zou stellen om tijdens een eerste poliklinisch bezoek meer RA patiënten te identificeren binnen een studiepopulatie van vroege inflammatoire artritis (IA) patiënten. Voor deze studie hebben we vroege artritis patiënten geïncludeerd. Zij hadden minimaal één klinisch gezwollen gewricht en korter dan één jaar klachten. Patiënten werden gedurende een jaar gevolgd, waarna werd vastgesteld of ze met methotrexaat waren gestart (case) of niet (non-case) binnen dit jaar. De diagnostische waarde van de 2010 criteria hebben we daarna vastgesteld. Bij het verlagen van het afkappunt van de 2010 criteria van 6 naar 5 punten, konden we 15% meer RA patiënten identificeren ten koste van 8% meer vals-positieve patiënten. Dit toont aan dat

verlaging van het afkappunt gebruikt kan worden als een simpele methode om in een vroeg stadium medicatie te kunnen starten in RA patiënten.

Het proefschrift is hierna verdeeld in twee delen; echografie in de klinische praktijk en experimenteel technisch onderzoek.

Deel 1 – Echografie in de klinische praktijk

Lichamelijk onderzoek heeft zijn grenzen bereikt met betrekking tot het ontdekken van synovitis, daarom richt het eerste deel van dit proefschrift zich op de toegevoegde waarde van echografie in de dagelijkse klinische praktijk. Hoofdstukken 3 en 4 behandelen de diagnostische waarde van echografie. In hoofdstukken 5, 6 en 7 hebben we de waarde van echografie in de monitoring van RA patiënten onderzocht.

Eerder onderzoek heeft aangetoond dat van patiënten met artralgie zonder klinische symptomen van ontsteking bij het eerste bezoek aan de reumatoloog, toch 15% IA ontwikkelt binnen een jaar. Het is echter nog steeds lastig deze patiënten te identificeren. Het doel van **hoofdstuk 3** was om artralgie patiënten te identificeren die binnen één jaar follow-up IA ontwikkelen door middel van het detecteren van synovitis met echografie tijdens het eerste bezoek. Honderd zes-en-negentig artralgie patiënten zonder klinische synovitis werden geïncludeerd van wie 37% op het eerste bezoek echografische synovitis had. Binnen één jaar follow-up ontwikkelde 16% van de artralgie patiënten IA. De negatief voorspellende waarde van echografie was hoog, met andere woorden, als een patiënt geen echografische synovitis had, was de kans klein dat hij IA zou ontwikkelen. Factoren die geassocieerd waren met het ontwikkelen van IA waren leeftijd, ochtendstijfheid >30 minuten en de aanwezigheid van power Doppler signaal. De aanwezigheid van power Doppler signaal had de sterkste associatie. Deze resultaten geven aan dat power Doppler van diagnostische waarde zou kunnen zijn in vroege artralgie patiënten om de ontwikkeling van IA te voorspellen, maar dit moet worden vastgesteld in verder onderzoek.

De diagnostische waarde van echografie in het detecteren van enthesitis in eerstelijns psoriasis patiënten wordt beschreven in **hoofdstuk 4.** Een deel van psoriasis patiënten met musculoskeletale klachten heeft een ontsteking van de entheses (peesaanhechtingen). Ontsteking van de enthesis is moeilijk vast te stellen met lichamelijk onderzoek. Daarom hebben wij de informatie verkregen uit de anamnese en vragenlijsten met echografie en lichamelijk onderzoek gecombineerd om zo een

actieve ontsteking van de enthesis vast te kunnen stellen. Actieve echografische ontsteking was gedefinieerd als de aanwezigheid van power Doppler signaal bij de enthesis of in het geval van de fascia plantaris een verdikking van de enthesis. Klinisch werd een ontsteking vastgesteld door drukpijn op de enthesis, door gerapporteerde pijn van de enthesis in de voorgeschiedenis of door pijn aangegeven in de vragenlijsten. Door deze data te combineren had 36% van de eerstelijns psoriasis patiënten (n=111) die aangaven pijn te hebben aan één of meer entheses, ontsteking van minimaal één enthesis. Door echografie toe te voegen aan de het lichamelijk onderzoek en de anamnese konden we de aanwezigheid van een actieve ontsteking van de enthesis visualiseren. Door de combinatie van klinische gegevens neemt het aantal patiënten met mogelijke enthesitis die door de reumatoloog moet worden gezien af.

De metatarsophalangeale (MTP) gewrichten zijn vaak aangedaan in pas gediagnosticeerde RA patiënten. Lichamelijk onderzoek van de voeten is lastiger dan dat van andere gewrichten. In hoofdstuk 5 hebben we de overeenstemming van echografische bevindingen van de MTP gewrichten vergeleken met lichamelijk onderzoek in pas gediagnosticeerde RA patiënten (n=174). Patiënten werden gedurende één jaar gevolgd en treat-to-target behandeld. Tijdens het eerste bezoek had 63% van de patiënten minimaal één positief MTP gewricht op echo. Na één jaar follow-up was 62% van de patiënten in remissie volgens de DAS28, een kwart van deze patiënten had nog minimaal één positief MTP gewricht op echo. Op gewrichtsniveau was de correlatie tussen aanwezigheid van echografische synovitis in een MTP gewricht en een klinisch gezwollen gewricht slecht. Aan de andere kant vonden we wel hoge mate van overeenkomst tussen klinisch niet gezwollen of niet pijnlijke gewrichten en een negatieve echo. De klinische waarde van het monitoren van de voeten op patiëntniveau waarbij remissie het behandelingsdoel is, moet nog verder onderzocht worden.

In hoofdstuk 6 hebben we geëvalueerd hoeveel RA patiënten in klinische remissie ook echografisch in remissie waren. In deze patiëntenpopulatie hebben we bepaald of er verschil in gezondheidsstatus bestond tussen RA patiënten die alleen in klinische remissie waren en RA patiënten die ook in echografische remissie waren. Aangezien is aangetoond dat er een associatie bestaat tussen echografische synovitis en verhoogd risico op flare, is het vanuit klinisch oogpunt interessant om te weten of patiënten met echografische synovitis anders naar hun gezondheid kijken met betrekking tot pijn, vermoeidheid en hun algemene gezondheid. Hierdoor zouden reumatologen de behandeling in RA patiënten met echografische synovitis kunnen veranderen ten

opzichte van RA patiënten die in klinische en echografische remissie zijn. Bij 89 RA patiënten in klinische remissie is een echo gemaakt van de polsen en de kleine hand- en voetgewrichten. Deze patiënten hebben daarnaast meerdere vragenlijsten ingevuld. Eén-derde van de patiënten in klinische remissie waren ook in echografische remissie. We hebben geen duidelijke associatie gevonden tussen de gezondheidsstatus van RA patiënten in klinische remissie en het wel of niet in echografische remissie zijn. Patiënten in echografische remissie rapporteerden meer pijn en angst, maar dit was de tegengestelde richting van wat verwacht was. Als aanbeveling moeten onze resultaten bevestigd worden in andere cohorten met RA patiënten in klinische remissie.

Om op patiëntniveau te kunnen bepalen of een RA patiënt in klinische remissie zijn medicatie af kan bouwen is het belangrijk om te weten welke risicofactoren een rol kunnen spelen bij het krijgen van een flare (toename van de ziekteactiviteit). In hoofdstuk 7 hebben we RA patiënten die medicatie (conventionele DMARD of TNF inhibitor) aan het afbouwen waren iedere drie maanden gemonitord met echografie om te bepalen of de aanwezigheid van echografische synovitis vooraf gaat aan een flare. Honderd vijf-en-twintig RA patiënten zijn geïncludeerd die gestart zijn met afbouwen van de medicatie. Binnen één jaar follow-up had 36% van de patiënten een flare meegemaakt, van hen had 60% op baseline echografische synovitis. In onze studiepopulatie was het aantal gewrichten dat op echo positief was niet significant geassocieerd met het ontstaan van een flare. Het aantal positieve power Doppler gewrichten was significant geassocieerd met het ontstaan van een flare binnen drie maanden, maar deze associatie was zwak. Het iedere drie maanden monitoren van RA patiënten met echografie die starten met afbouwen van medicatie heeft weinig toegevoegde waarde om een flare te voorspellen. Echter was negatief voorspellende waarde wel hoog, wat kan betekenen dat het mogelijk zou zijn om met echografie patiënten te identificeren die hun medicatie verder kunnen afbouwen. Dit kan met name van belang zijn in de behandeling van RA patiënten bij wie het lastig was om remissie te bereiken en voor wie nog maar een gelimiteerde keuze van andere DMARDs bestaat om opnieuw remissie te bereiken in geval van een flare.

Deel 2 – Experimenteel technisch onderzoek

Het tweede deel van dit proefschrift richt zich op experimenteel technisch onderzoek, aangezien technologische ontwikkelingen in echomachines vroege detectie van ontstekingen kunnen verbeteren.

Het is aangetoond dat het wel of niet zien van signaal zeer afhankelijk is van de echomachine die wordt gebruikt. De prestaties van de power Doppler modaliteit van vijf echomachines zijn onderzocht met behulp van een flow fantoom en de resultaten zijn beschreven in hoofdstuk 8. De power Doppler instellingen van iedere machine waren zo ingesteld om de laagst detecteerbare snelheid te kunnen bepalen. De power Doppler sensitiviteit van de vijf machines verschilde onderling veel. Slechts twee van de machines waren in staat om zeer lage snelheden te detecteren in het flow fantoom. Het verschil tussen de machines kan deels verklaard worden door verschillen van signaalanalyse van het power Doppler signaal of door instellingen die niet te veranderen zijn door de gebruiker. Concluderend kan gezegd worden dat de keuze van een echomachine en de daarbij behorende power Doppler instellingen zeer belangrijk is. Hier moet men zeker op bedacht zijn in het geval van een multi-machine trial of bij het aanpassen van behandeling gebaseerd op de aan- of afwezigheid van power Doppler signaal.

De ontwikkelingen in high frame rate echografie zijn veelbelovend, aangezien deze techniek het mogelijk maakt om zeer lage snelheden in kleine vaten te detecteren. High frame rate Doppler echografie is namelijk sensitiever voor lage snelheden dan conventionele power Doppler echografie. Hierdoor is accurate detectie van gewrichtsontstekingen in RA patiënten denkbaar. Met deze nieuwe methode zou het mogelijk zijn eerder de diagnose RA te stellen en behandeling beter te monitoren. In hoofdstuk 9 is de sensitiviteit van high frame rate Doppler voor microvasculaire flow in een flow fantoom onderzocht. Daarnaast werd een proof-of-principle studie uitgevoerd in gezonde vrijwilligers en in RA patiënten met verschillende mate van ziekteactiviteit. In het flow fantoom was de minimaal detecteerbare flowsnelheid een factor drie lager met high frame rate Doppler vergeleken met conventionele power Doppler echografie. In de proof-of-principle studie werd met high frame rate Doppler een positief power Doppler signaal in alle deelnemers gedetecteerd, gezond en ziek. Dit was tegenovergesteld aan de resultaten met conventionele power Doppler echografie, waarmee geen power Doppler signaal werd gedetecteerd in gezonde vrijwilligers en in RA patiënten in klinische remissie. Met high frame rate Doppler werd een geleidelijke toename in power Doppler signaal gezien in RA patiënten gerelateerd aan hun ziekteactiviteit. Voor gezonden en patiënten was er een significant verschil in power Doppler score tussen high frame rate Doppler echografie en conventionele power Doppler echografie. Verder onderzoek naar high frame rate Doppler echografie

is nodig om discriminatie tussen gezond en afwijkend te verbeteren en om meer kennis te vergaren over ontstekingsfysiologie in gewrichten van RA patiënten.

In hoofdstuk 10 zijn onze resultaten samengevat en worden deze bediscussieerd aan de hand van methodologische kwesties en huidige stand van zaken. Dit proefschrift eindigt met de klinische relevantie van onze resultaten en aanbevelingen voor verder onderzoek.

PhD portfolio

Name	Myrthe van der Ven
Erasmus MC Department	Rheumatology
Research School	NIHES
PhD period	2012-2017
Promotor	Prof. dr. J.M.W. Hazes
Copromotor	Dr. J.J. Luime

General academic skills	4 ECTS
2014	Biomedical English Writing and Communication, Erasmus MC, Rotterdam
2012	BROK ('Basiscursus Regelgeving Klinisch Onderzoek'), Erasmus MC, Rotterdam

Biostatistical courses – NIHES	15 ECTS
2015	Missing values in clinical research
2014	Repeated measurements
2013	Intervention research and clinical trials
2013	Advanced analysis of prognosis studies
2013	Biostatistical methods II: Classical regression models
2012	Biostatistical methods I: Basic principles
2012	History of epidemiology

In depth courses	3 ECTS
2017	PCDI course 'Employability outside academia', Utrecht
2012	Ultrasound 'hands on' course, Houten

Teaching tasks	5 ECTS
2015 – 2016	Mentor course KBP ('Kennismaking met de Beroepspraktijk') to 1st and 2nd year medical students, Erasmus MC, Rotterdam
2015	Supervising master internship Technical Medicine
2015	Supervising research internship Medicine
2014 – 2015	Teaching course 'Clinical Trials' to 4th year medical students, Erasmus MC, Rotterdam
2013 – 2014	Teaching course 'Kritisch lezen' to 1st year medical students, Erasmus MC, Rotterdam

(Inter)national conferences	18 ECTS
2016	American College of Rheumatology Annual Meeting (ACR), Washington, USA [oral presentation]
2016	Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [2x poster presentation]
2016	European Congress of Rheumatology (EULAR), London, UK [poster presentation in tour]
2015	Congress Reumatologie op Ameland [2x poster (1x Top 3 – Presentation)]
2015	American College of Rheumatology Annual Meeting (ACR), San Francisco, USA [2x poster presentation]
2015	Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [oral presentation and poster presentation]
2015	4th World Psoriasis & Psoriatic Arthritis Conference (IFPA), Stockholm, Sweden [poster presentation]
2015	European Congress of Rheumatology (EULAR), Rome, Italy [poster presentation and 2x poster presentation in tour]

(Inter)national conferences

2015	Congress Nederlandse Vereniging voor Technische Geneeskunde, Amsterdam [poster pitch and poster presentation]
2014	American College of Rheumatology Annual Meeting (ACR), Boston, USA [poster presentation and poster presentation in tour]
2014	GRAPPA Fellow's symposium, Geneva, Swiss [oral presentation]
2014	Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [2x oral presentation]
2014	European Congress of Rheumatology (EULAR), Paris, France [oral presentation]
2013	American College of Rheumatology Annual Meeting (ACR), San Diego, USA [oral presentation]
2013	Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [poster presentation]

Seminars and workshops 3 ECTS

2012 – 2017	Department Journal club Rheumatology (attendance & presentations)
2012 – 2017	VENA workshops
2012 – 2017	Cicero meetings

Other 8 ECTS

2014 – now	Board member Nederlandse Vereniging voor Technische Geneeskunde
2015 – 2016	Study management TARA study
2015 – 2016	Workshop ultrasound Girlsday, Erasmus MC, Rotterdam
2015	Organising Masterclass Ultrasound, Erasmus MC, Rotterdam
2014	Organising Girlsday, Erasmus MC, Rotterdam
2014	Organising and invited speaker Masterclass enthesitis Nijmegen
2012	Member congress committee Nederlandse Vereniging voor Technische Geneeskunde

Grants

2017	Erasmus MC grant PCDI course
2016	Erasmus Trustfonds travel grant EULAR London
2015	Pfizer travel grant IFPA Stockholm
2015	Reumafonds travel grant EULAR Rome
2014	Pfizer travel grant ACR Boston
2014	Erasmus Trustfonds travel grant ACR Boston
2014	GRAPPA travel grant Geneva
2014	EULAR travel grant Paris
2013	Reumafonds travel grant ACR San Diego

List of publications

This thesis

M. van der Ven, M. van der Veer-Meerkerk, D.F. Ten Cate, N. Rasappu, M.R. Kok, D. Csakvari, J.M.W. Hazes, A.H. Gerards, J.J. Luime. *Absence of ultrasound inflammation in patients presenting with arthralgia rules out the development of arthritis.* Arthritis Res Ther. 2017 Sep 15;19(1):202. doi: 10.1186/s13075-017-1405-y.

M. van der Ven, J.J. Luime, L.L. van der Velden, J.G. Bosch, J.M.W. Hazes, H.J. Vos. *High-frame rate power Doppler ultrasound is more sensitive than conventional power Doppler in detecting rheumatic vascularisation.* Ultrasound Med Biol. 2017 Sep;43(9):1868-1879

M. van der Ven, T.M. Kuijper, A.H. Gerards, I. Tchetverikov, A.E. Weel, D. van Zeben, J.M. Hazes, J.J. Luime. *No clear association between ultrasound remission and health status in RA patients in clinical remission.* Rheumatology (Oxford). 2017 Aug 1;56(8):1276-1281

M. van der Ven, M.C. Karreman, A.E.A.M. Weel, I. Tchetverikov, M. Vis, T.E.C. Nijsten, J.M.W. Hazes, J.J. Luime, *Adding ultrasound to clinical examination reduced frequency of enthesitis in primary care psoriasis patients with musculoskeletal complaints.* Clin Exp Rheumatol. 2016 Nov-Dec;34(6):1020-1025

M. van der Ven, C. Alves, J.J. Luime, A.H. Gerards, P.J. Barendregt, D. van Zeben, B. van Schaeybroeck, P.B.J. de Sonnaville, B.A. Grillet, J.M.W. Hazes, *Do we need to lower the cut point of the 2010 ACR/EULAR classification criteria for diagnosing rheumatoid arthritis?* Rheumatology (Oxford). 2016 Apr;55(4):636-9

Ten Cate DF, Luime JJ, van der Ven M, Hazes JM, Kooiman K, de Jong N, Bosch JG, *Very different performance of the power Doppler modalities of several ultrasound machines ascertained by a microvessel flow phantom.* Arthritis Res Ther. 2013 Oct 24;15(5):R162

Other publications

K. Wervers, M. Vis, N. Rasappu, **M. van der Ven**, I. Tchetverikov, M.R. Kok, A.H. Gerards, J.M.W. Hazes, J.J. Luime. *Sonographic changes suggestive of enthesitis seen in young, healthy volunteers: modifications in ultrasound scores needed for use in psoriatic arthritis.* Scand J Rheumatol. 2017 [accepted]

Karreman MC, Weel AE, **van der Ven M**, Vis M, Tchetverikov I, Nijsten TE, Wakkee M, Hazes JM, Luime JJ. *Performance of screeningtools for psoriatic arthritis: A cross-sectional study in primary care.* Rheumatology (Oxford). 2017;56:597-602

M. van der Ven, P. Veldt-Kok, A.H.M. van der Helm-van Mil, J.M.W. Hazes, A.E.A.M. Weel. *Wat is de waarde van echografie voor het stellen van de diagnose reumatoïde artritis bij een patiënt die zich presenteert met inflammatoire gewrichtsklachten of artritis?* Nederlands Tijdschrift voor Reumatologie. 2016 September

Karreman MC, Weel AE, **van der Ven M,** Vis M, Tchetverikov I, Nijsten TE, Wakkee M, Hazes JM, Luime JJ. *Prevalence of psoriatic arthritis in primary care patients with psoriasis.* Arthritis Rheumatol. 2016 Apr;68(4):924-31

M. van der Ven, A. Pasma. *Symposium 'Therapie-ontrouw; het hoe en waarom'*. Nederlands Tijdschrift voor Reumatologie. 2016 Maart

Schon BS, Schrobback K, **van der Ven M**, Stroebel S, Hooper GJ, Woodfield TB, *Validation of a high-throughput microtissue fabrication process for 3D assembly of tissue engineered cartilage constructs*. Cell Tissue Res. 2012;347:629–642

About the author

Myrthe van der Ven was born on the 6th of August in 1985 in Roosendaal. She grew up in Rucphen and she graduated in 2003 at the Katholieke Scholengemeenschap Etten-Leur.

She moved to Enschede where she finished the Master program Technical Medicine with the specialisation on Tissue Reconstruction at the University of Twente in 2011. For her internships she visited MST Enschede, UMC Utrecht, Radboudumc Nijmegen and Christchurch Hospital in New Zealand. Her specialisation internship was completed at the Burns Centre in Beverwijk. In September 2011 she obtained her master degree under supervision of prof. dr. P.P.M. van Zuijlen with thesis title "Cellular processes during mechanical load: Development of an in vitro model to validate splinting strategies".

In January 2012 she started to work at the research projects described in this thesis at the department of Rheumatology of the Erasmus MC, Rotterdam under the guidance of prof. dr. J.M.W. Hazes and dr. J.J. Luime at the department of Rheumatology at Erasmus MC.

Since 2014 she is board member of the Dutch Association for Technical Medicine (NVvTG).

She lives together with Gregor in Eindhoven. Since October 2016 they have a lovely boy named Tijmen.

Dankwoord

"Je kunt er niet vroeg genoeg aan beginnen" heb ik vaak gehoord, dus de eerste letters van mijn dankwoord staan een jaar van tevoren al op papier. In de hoop dat ik op deze manier niemand ga vergeten en het na alle hoofdstukken geen vertragende factor wordt voor het afronden van mijn proefschrift. Daarnaast blijven deze paar pagina's nu eenmaal de meest gelezen pagina's van dit hele boekwerk en daar wil ik natuurlijk genoeg tijd aan besteden.

Ik loop hier alleen in een te stille stad
Ik heb eigenlijk nooit last van heimwee gehad
Maar de mensen ze slapen de wereld gaat dicht
En dan denk ik aan Brabant want daar brandt nog licht

In 2012 begon ik mijn PhD avontuur in het grootse Rotterdam, niet wetend wat me te wachten zou stond, maar van zulke mooie jaren had ik alleen kunnen dromen. Daarom wil ik graag een aantal mensen die daar een essentiële bijdrage aan hebben geleverd, hierbij bedanken.

Wij moeten samen, wij zijn, groots zijn met elkaar
Wij moeten samen, wij zijn, iedereen is nodig, allemaal

Geachte professor Hazes, beste Mieke, met jou als promotor was ik er zeker van dat de klinische relevantie van mijn stukken altijd goed in het achterhoofd werd gehouden. Ik vond het erg fijn dat je in de afrondende fase iedere week tijd voor me had om de laatste stukken nog eens door te nemen. Daarnaast bedankt voor je oprechte interesse, zowel voor mijn onderzoek als voor mij persoonlijk.

Jolanda, mijn copromotor, met je kritische blik en je onuitputtende stroom van andere invalshoeken heb je er mede voor gezorgd dat ik trots kan zijn op het resultaat. Ook moedigde je mij aan om mijn technisch geneeskundige achtergrond niet uit het oog te verliezen en de samenwerking voort te zetten met de afdeling biomedical engineering. We zullen elkaar in Eindhoven vast nog vaker tegenkomen.

Zonder enthousiaste reumatologen, reumaverpleegkundigen en doktersassistenten is het uitvoeren van wetenschappelijk onderzoek onmogelijk. Daarom wil ik jullie

bedanken voor de tijd en inspanning die jullie in de verschillende onderzoeken hebben gestoken. Lieve Anke en Sjaan, bedankt voor jullie inzet en de maandelijkse autoritjes via Delft naar Utrecht vond ik erg gezellig.

David, echo-goeroe, bij ieder echoplaatje dat ik heb gemaakt was jij er stiekem bij. Mooie strakke witte botlijnen in beeld voordat ik tevreden mocht zijn met het resultaat. Veel dank voor het overbrengen van al jouw echografische kennis! Ik hoop dat je als je reumatoloog bent weer veel tijd aan deze passie kunt besteden.

Voor statistische vragen kon ik altijd bij jou terecht Martijn en je was altijd zeer geduldig om alles uit te leggen. Ik ben nog steeds trots op mijn STATA-diploma ☺. Daarnaast hebben we het toch maar voor elkaar gekregen de TARA-studie vol te krijgen, ik ben benieuwd naar de resultaten!

Graag wil ik ook mijn technische collega's bedanken van de 23e verdieping. En dan met name Rik. Ik weet niet hoeveel geduld je met mij moest hebben, maar ik vond het in ieder geval erg fijn dat ik jou had om mijn Matlab deficiëntie op te vullen. Ik ben er trots op dat wij samen een mooi artikel hebben gepubliceerd.

We zijn met vrienden, alleen met vrienden
Hou je niet in, niet als je huilt, niet als je lacht

Lieve meiden van de reumatologie, jullie hebben mijn jaren in Rotterdam echt tot een feestje gemaakt! Het was soms een kippenhok en soms wat minder productief, maar ik ga de lunches, etentjes, congressen en natuurlijk de babypraat enorm missen.
In het bijzonder Maren, wat hebben we samen veel van de wereld gezien. Blauwbekken op het dak van het hotel in New York, mini-Happy Socks kopen in Stockholm en de voorraad handtassen aanvullen in Rome, wat een heerlijke tijd! En nu gaan we beiden in 2018 ons wetenschappelijke avontuur afronden en ik vind het erg fijn dat je op 14 februari naast mij staat.

Marleen en Marjolein, lieve vriendinnetjes, vanaf onze studententijd hebben we het keigezellig en we hebben al heel wat samen meegemaakt. Nu zijn we alle drie mama en beginnen we weer aan een volgend avontuur. Ik kijk uit naar nog vele mokken thee, wijntjes en toastjes met brie.

Lieve Karin, weekendjes weg, heerlijk uit eten, een gezellig dagje shoppen of een optreden van Guus, we hebben altijd wel een reden voor een feestje ☺. We kunnen sparren over onze (werk)problemen, bevindingen, maar gelukkig ook over iets anders praten dan alleen werk. Dit houden we al ruim 20 jaar vol, dus op naar de volgende 20 jaar!

Mama vraagt of ik blijf eten, papa hoe het leven staat
Ik weet dat jullie weten, hoe het werkelijk met me gaat

Lieve papa en mama, het is altijd heerlijk thuiskomen bij jullie en jullie staan altijd voor me klaar. Ik vind het erg fijn dat jullie straks op de eerste rij zitten. Rutger, MBB, het gaat nu toch echt gebeuren, YLS gaat promoveren, daar drinken we samen een biertje op! Een klein voorproefje voor het grote feest in juni van Cathelijne en jou. Door jullie zal ik altijd weer terugkeren naar mijn Rucphense roots.

Ik glimlach tevreden, ik ben tevreden, ik glimlach verlegen, wat zie ik je graag
In het verleden, nog niet lang geleden, hoopte ik zo op een dag als vandaag

Mijn twee mannen als laatst. Lieve Gregor, ik leerde je kennen net voordat ik in Rotterdam begon aan dit promotietraject, dus je hebt van begin tot eind alle ups en downs meegemaakt. Je hebt me altijd gesteund en jij had het grootste vertrouwen in mij dat ik alles tot een goed einde zou brengen. Jouw coverontwerp maakt het geheel helemaal af. Nog meer wil ik je bedanken voor onze prachtige zoon Tijmen, wat hebben we een heerlijk mannetje. Lieve Tijmen, ik smelt iedere keer weer bij jouw gulle lach!

"Ik heb tranen gelachen, onnozel gedaan en tenslotte tevreden het licht uit gedaan"
(Guus Meeuwis)