Imaging of Osteoarthritis and Rheumatoid Arthritis in Hand Joints

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Imaging of Osteoarthritis and Rheumatoid Arthritis in Hand Joints

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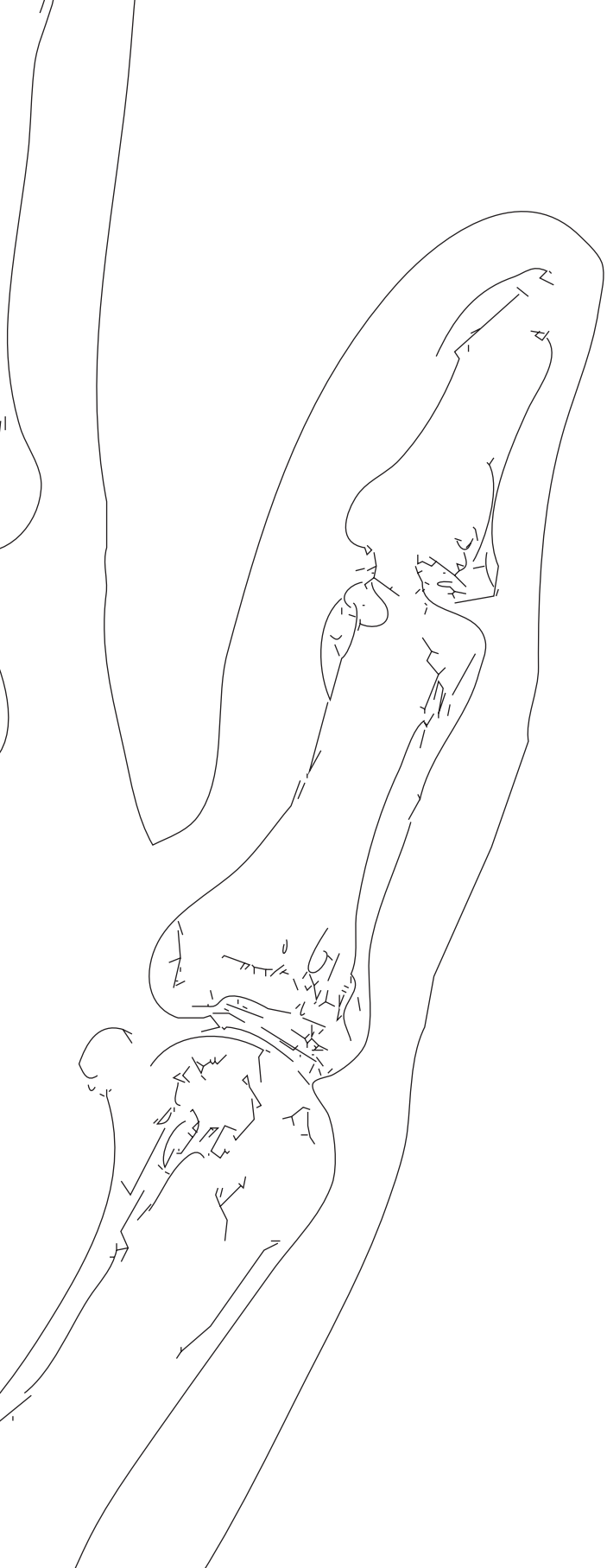
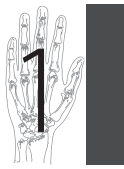


Chapter 1

General introduction



Joint diseases are a leading cause of pain and disability in developed countries, with hand joint diseases having large impact on normal daily activities. Osteoarthritis (OA) and rheumatoid arthritis (RA) are two prevalent joint disease of very different etiology, both affecting hand joints. The focus of this thesis lies on improving knowledge of radiological imaging techniques to detect features of OA and RA in hand joints. The following introduction will describe these joint diseases, the radiological imaging techniques, and how these techniques are used to image the hand joints and these joint diseases. Followed by the aims and outline of this thesis.

Background of osteoarthritis and rheumatoid arthritis

Osteoarthritis is the most common joint disease worldwide. The prevalence of osteoarthritis increases with age, and 10-18% of people aged over 50 have osteoarthritis.[1] Osteoarthritis occurs in the hand mainly in the distal interphalangeal (DIP) joints, the proximal interphalangeal (PIP) joints and the first carpometacarpal (CMC1)joint.[2] Other joints often affected are the knees, hips, and joints of the spine. The exact mechanisms of OA are unclear, but the disease affects the whole joint. Key aspects are the degradation of the cartilage leading to cartilage destruction, low grade inflammation of the synovium, and involvement of subchondral bone.[3, 4] With progression of disease, irregular outgrowth along the margin of the bone are created called osteophytes, probably because the body tries to reduce the stress on the bone by increasing the joint surface. Subchondral bone increases in cellularity and density, and can undergo cystic degeneration in advanced disease. While the joint degrades and gets inflamed, patients experience joint pain, and due to the bone remodeling the joint becomes deformed and loses range of motion.[5] Research into disease-modifying osteoarthritis drugs (DMAODs) is ongoing, but a usable drug has yet to be found. Currently, no treatment is available to halt or cure OA.[6] Treatment protocols for hand OA are focused on alleviating symptoms by subscribing pain medication, performing physiotherapy, and splinting of joints to decrease joint stress. In severe thumb base OA, joint surgery like trapeziectomy can be performed to alleviate symptoms and help restore some thumb movement.

Rheumatoid arthritis is the second most prevalent hand joint disease in the world. It is more prevalent in women and prevalence increases with age. The prevalence in women over 50 in Europe is 1- 2%.[1] RA is a systemic auto-immune disease with an unknown cause, which mainly targets the joints. The joints in

the hand affected mostly are the wrists, metacarpal (MCP) joints and proximal interphalangeal (PIP) joints, and the disease occurs also in metatarsophalangeal (MTP) joints, shoulders, elbows, knees and ankles. An immune reaction created by the body targets the joint synovium, starting synovitis.[7] This inflammation results in hypertrophy and neovascularization of the synovium, and production of excess synovial fluid. The inflammation then spreads to the adjacent bone and to the joint cartilage, ultimately resulting in bone and cartilage destruction (see fig. 1). Clinically, the affected joints usually become swollen, painful, and stiff in the morning. Over time, the cartilage and bone destruction results in deformity and further loss of function. The disease is not limited to the musculoskeletal system; RA patients also have increased risk of cardiovascular disease, and the disease affects lungs, brain, skin and liver, which are thought to be caused by byproducts of the inflammatory reaction.[7] While there is no treatment to cure the disease, available disease-modifying antirheumatic drugs (DMARDS) can slow or stop the progression of RA, improving symptoms and preventing joint deformity. Diagnosing RA is relatively easy in late stage disease. However, the goal is to treat RA as early as possible, to prevent this stage. In the early stage it is often difficult to diagnose RA, as typical clinical signs and symptoms may be absent and specific laboratory tests may be normal.

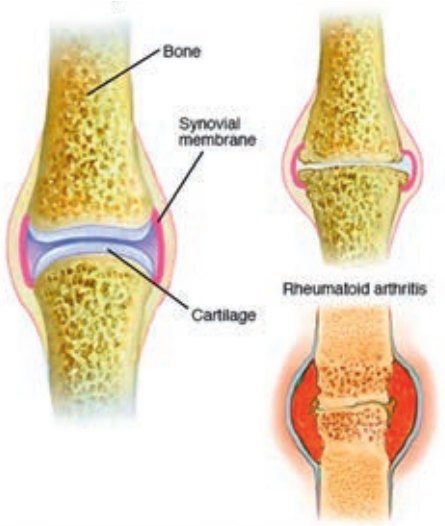
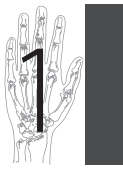


Figure 1. Schematic anatomical differences between a normal hand joint, a joint with osteoarthritis and a joint with rheumatoid arthritis. Note that there is cartilage loss and loss of joint space in both disease, but mainly proliferation of bone on the joint edges in osteoarthritis and destruction of bone in rheumatoid arthritis (Image duplicated from the Mayo foundation with permission).



Use of radiological imaging methods

Radiological imaging methods are used to depict the current anatomical status of joints. In clinical practice they can be used to help form a diagnosis, determine the current amount of joint damage, help decision-making for treatment by determining if there is current inflammation, and compare with previous images to determine progression. The radiological imaging methods are conventional radiology (CR), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). They use different physical properties, resulting in each method having its own advantages and disadvantages and specific uses. A short description of the underlying mechanism of each technique follows below to aid the understanding of their specific uses in hand joints, so that we can discuss how they may improve earlier detection of disease and help in treatment-trials for RA and OA.

Conventional radiography

The radiological imaging methods originate from the year 1895, in which Wilhelm Conrad Röntgen discovered the existence of x-rays, and created the first radiograph: an image of the hand of his wife (fig 2a). This technique was soon used for medical imaging and is mostly called conventional radiography (CR). Over the years the technique improved significantly, but the fundamentals stayed the same. Electromagnetic radiation with a wavelength of approximately 0.01 to 0.1 nm is produced in an x-ray tube creating a stationary beam of x-rays, which is then passed through the human body. Part of the x-rays are scattered and absorbed by the human body, with dense structures like bone absorbing more x-rays then soft-tissues. The unaltered x-rays are received on a detector on the other side of the patient, creating an image (fig 2b). As bone can be well differentiated from soft-tissues with this method, it is mostly used in joint imaging to detect bony pathology. Usually x-rays from two different directions are made to get a sense of the 3-dimensional aspect.

If CR is used to image the early stages of osteoarthritis, findings are likely normal. The earliest visible signs on CR are small osteophytes and joint space narrowing (JSN), which is an indirect measure of cartilage destruction and can only be seen when a sufficient amount of cartilage is destroyed.[8, 9] Later in the disease course the increase of density in the subchondral bone is seen as subchondral sclerosis, and subchondral cyst formation can be seen in

advanced disease. When imaging early RA, conventional radiographs may also be normal. The first symptom of RA on a radiograph is swelling of the peri-articular tissue, which however is non-specific, and usually also clinically visible. When the inflammative reaction has destroyed enough bone, juxta-articular lucency of the bone can be seen, and erosion of bone close to the attachment of the synovium to the bone becomes visible. The location of these erosions are specific for RA, but they are usually seen on a radiographs after 6-12 months of onset of the disease [10]. Ultimately the cartilage also gets destroyed and the whole joint becomes deformed.

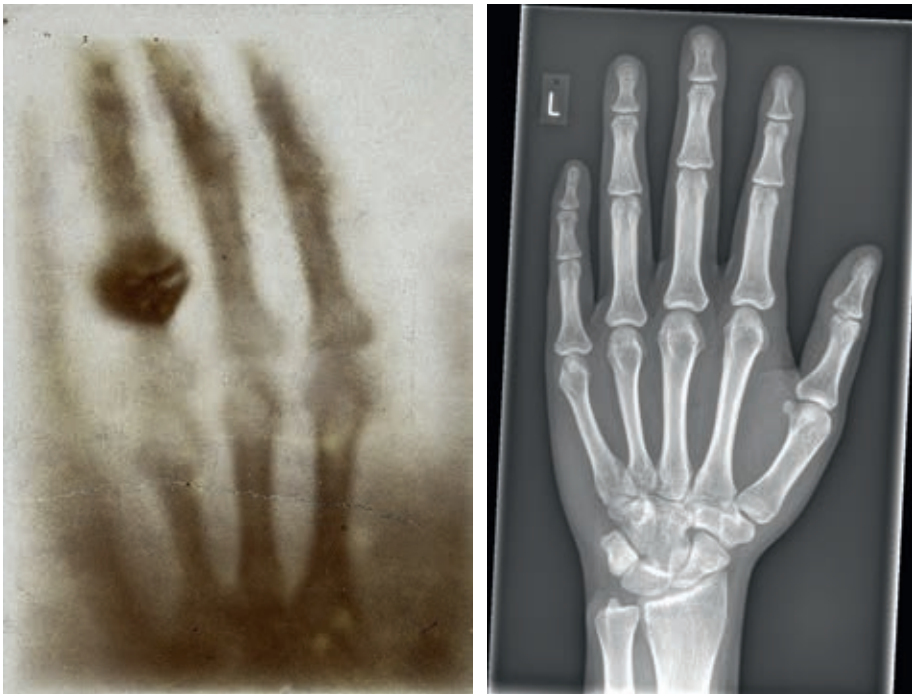


Figure 2. Progress of radiographic imaging through time. left: First radiograph ever acquired. Wilhelm Röntgen imaged the hand of his wife Anna Bertha Ludwig (Image duplicated from Wikimedia Commons - public domain). Right: A recently acquired x-ray of the left hand of a healthy person.

CT

The progress in processing power of computers made computed tomography possible since the 70's. The same x-rays as in conventional radiology are used, but the patient lies on a table while the x-ray tube and the detector rotate around

the patient during scanning. The detected signals from all the different angles are then processed by the computer to construct multiple thin image slices through the scanned human body. These slices can also be recalculated in any desired direction. In human hand joint scanning these 2d images in all planes eliminate the problem of overprojection from which conventional radiographs suffer, so the true 3d bony anatomy is visualized (fig3). This makes CT very good for detection of small ossal pathology like early erosions in RA patients and subtle osteophytes and subchondral cysts in OA patients, especially in areas of complex anatomy like the wrist. This increase in detail comes at the cost of increased monetary costs for a CT examination.

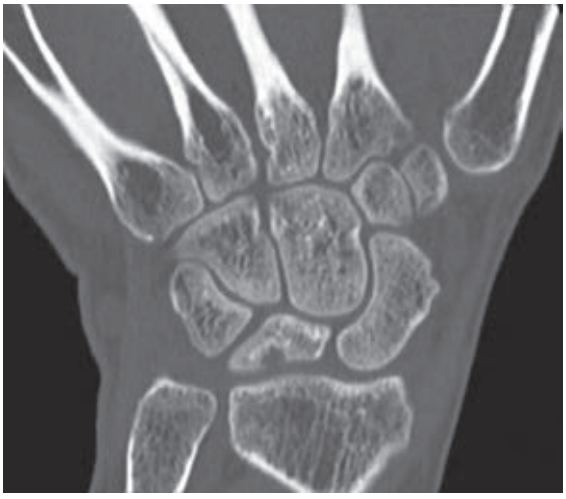


Figure 3. Single slice of a CT examination of the wrist. Notice, in comparison with figure 2, that there is no overprojection of bones with CT.

MRI

Magnetic resonance imaging does not use ionizing radiation, but uses strong magnetic fields and radiofrequency pulses to influence the magnetic spin of protons in the imaged subject. These spins create a small signal which is detected by specific antenna called coils. The received signals are then processed to images. Normal clinical MRI scanners are used to induce and measure differences in spins between hydrogen atoms. Hydrogen atoms are abundant in the human body, mostly in fat and water, and the proton spins behave differently depending on the molecule that they are in. These differences are the reason that MRI is very good in differentiating between soft

tissues like fat and water. As in CT, MRI is used to obtain slices through the human body in any desired direction. MRI has not only the 3d advantage for hand joint imaging, but it in contrast to previously mentioned methods it can also directly visualize the cartilage, synovium, tendons and ligaments (fig4) which are affected in RA and HOA.[11-13] Because of its sensitivity to water, MRI shows increased water content in the bone marrow when this gets involved in RA and OA, and it is easier to see joint hydrops and synovial proliferation. Additionally gadolinium contrast can be injected intravenously, which will enhance areas with increased blood flow like inflamed synovium. Contrast enhanced MRI is the most sensitive imaging method to detect this increased blood flow, and therefore the most sensitive method to detect synovitis.

All these advantages of MRI, however, come with higher examination times, increased monetary costs, and not every patient is a good candidate for an MRI examination, as the magnetic field may disrupt electrical implants, and metallic implants in the region of interest distort the images.

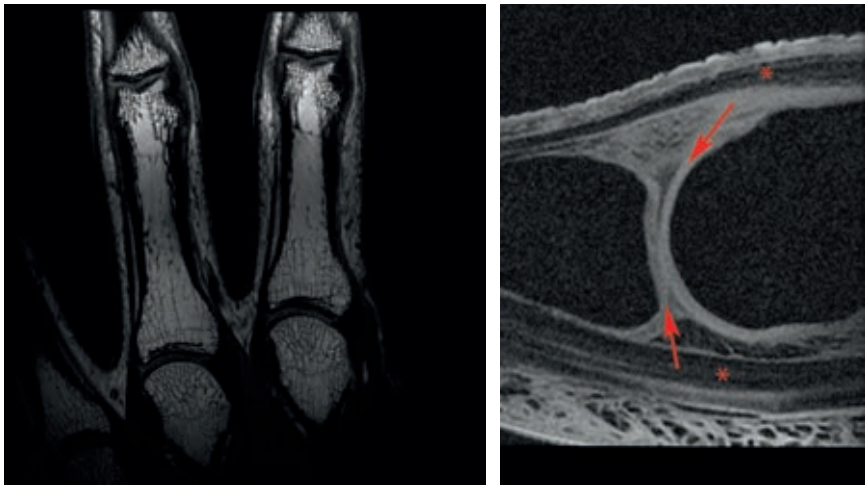


Figure 4. Left: Single slice in the coronal plane of an MRI examination of two proximal phalanx including the MCP and PIP joints right: Sagital image of an MRI examination of a single MCP joint, depicting the cartilage layers as bands of high signal intensity (arrows) and clear depiction of the tendons as a structure of low signal intensity(asterisk).

Ultrasound

Ultrasound is an imaging technique that also does not use ionizing radiation, but uses soundwaves above the threshold of human hearing. For hand joint imaging, typically waves of 8-17 Mhz are used. A transducer containing piezo-electric crystals is placed onto the anatomy of interest. These crystals generate ultrasound waves, which are sent into the patient. Depending on the properties of the underlying tissues some ultrasound waves travel through some of these tissues, while other soundwaves are bounced back to the transducer. These bounced back soundwaves are measured by the same piezo-electric crystals and multiple reflected soundwaves are used to compute the images. The travel speed of sound waves vary between different tissues. Sound waves are especially reflected back as the sound travels from one tissue to another tissue with a different sound speed. The travel speed of sound waves is approximately the same in most human tissues (1450-1580 m/sec) allowing the visualization of all these tissues at once. However, as the travel speed in bone is vastly different (4080 m/sec), all soundwaves are reflected at the bone cortex, and medical ultrasound can therefore not be used to look through bone. Images are generated very quickly, allowing for movement of the patient during examination. While ultrasound cannot look through the bone, views from different positions make it possible to look at the finger joint from a multitude of angles in a short time. However, the complex anatomy of the carpal bones makes this region harder to visualize with ultrasound.

In patients with RA and OA, ultrasound is mainly used to detect swelling of the joint and hypertrophy of the synovium (fig 5). It can be used to detect defects in the cortex of the bones. In addition Doppler ultrasonography can be used to detect movement within a scanned image. A moving object creates echoes with a slightly lower or higher velocity, which can be visualized within the image. In hand joint imaging this is mainly used to detect (increased) blood flow to the synovium in active synovitis.

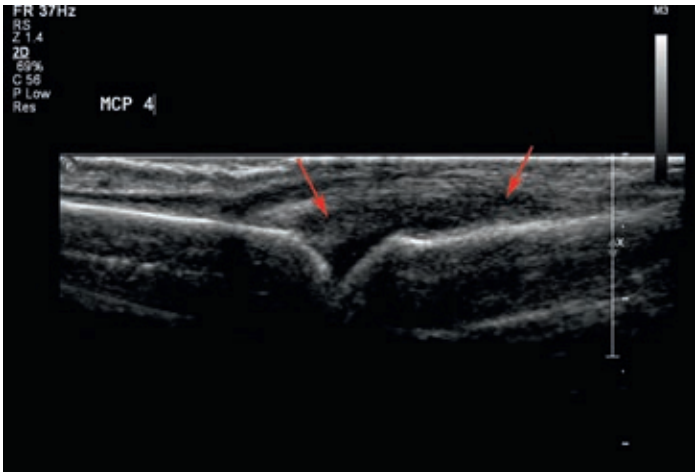


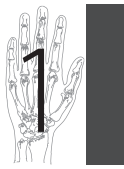
Figure 5. Sagital image of an MCP joint in a patient with arthritis, and an explanation below. The blue dotted lines represent the bones, on the left side the proximal phalanx, and on the right the metacarpal bone. There is hypertrophy of the synovium (red marked area)in the joint.

Thesis outline

Current role of imaging in OA

According to the 2006 EULAR recommendations for diagnosing hand OA, a confident clinical diagnosis can be made when typical features are present in patients aged over 40.[14] When complaints are not typical, imaging might be beneficial to confirm the diagnosis of HOA, or to exclude other diagnosis. According to these EULAR recommendations conventional radiographs are the gold standard for morphological assessment of hand OA, and the additive information of other imaging modalities is not well-researched and rarely yield additional diagnostic information.

Since these recommendations were created, multiple studies have investigated the use of ultrasound and MRI in hand OA yielding promising results. In **chapter 2** we therefore systematically reviewed the literature on imaging methods other than conventional radiology on their ability to detect features of HOA. Articles on validity, reliability and responsiveness of MRI, CT, ultrasound, and bone scintigraphy were reviewed.



For this thesis, we performed multiple imaging studies in hand OA with methods other than CR. While CT is a more accurate imaging method than CR, it usually results in little additional relevant clinical information when imaging finger joints with OA. In complex anatomical areas like the wrist, CT may have additional value, especially if the small anatomical details are relevant for treatment options, like surgery. In **chapter 3** we therefore compared CT with CR to detect osteoarthritis in the CMC1 and STT joint in possible pre-operative patients**.**

MRI is the only imaging method capable of imaging all the joint structures. Current MRI studies in hand OA are good in visualizing synovitis and bone lesions, but cartilage is not assessed directly. Joint space narrowing is used as a surrogate marker for cartilage damage, because the thin cartilage layer is hard to visualize. It is expected that direct visualization of cartilage will allow visualization of smaller cartilage defects, and improve sensitivity to change for cartilage damage. This may help further understand OA, and improve clinical trials for OA drug development. In **chapter 4 and 5** we therefore asses high-resolution MRI for direct cartilage imaging in hand osteoarthritis. In **chapter 4** we first assess the validity of high resolution cartilage MRI to detect cartilage damage in a small hand joint, specifically the thumb base of pre-surgical patients to compare with histological cartilage specimens of the same joint. In **chapter 5** we continue with high resolution MRI to asses patients with variable stages of OA and healthy controls, and investigate if high resolution MRI detects any additional damaged joints in comparison with currently used JSN measurements in MRI.

Current role of imaging for RA

Current ACR/EULAR guidelines for classification of RA[15] are mainly based on the presence of the serological markers anti-cyclic citrullinated protein antibody (ACPA) and rheumatoid factor (RF), and on the number of involved swollen or tender joints. While these criteria do not require medical imaging for classification, MRI and US detected joint swelling and synovial hypertrophy can be used to determine joint involvement. In longstanding suspected RA patients who do not meet the criteria, it is advised to make a conventional radiograph. Typical erosions as seen in progressive RA on a radiograph then also allow classification of RA. For clinical diagnosis and management of RA, imaging can be used as a problem solver. Recent EULAR recommendations

for clinical management of early RA advise the use of CR, US and MRI when in clinical doubt of diagnosing RA, as this can improve certainty of diagnosis. [16] However, the role of MRI and US in diagnosing RA is still unsure. They seem to raise sensitivity but decrease specificity.

Of these two methods MRI is considered to be the most sensitive method for imaging synovitis. A large variation of MRI machines is available with higher-end MRI machines creating better images. However it is still unclear how the diagnostic capability of lower-cost extremity MRI compares to normal clinical MRI in patients with early unclassified arthritis and arthralgia, or how these machines compare to ultrasound. In **chapter 6** we therefore compare normal high field MRI and low field extremity MRI for erosions, synovitis and bone marrow edema and compare with ultrasound for detection of synovitis and MCP erosions.

The aims of this thesis can be summarized as:

- to assess construct validity and reliability of direct cartilage imaging with MRI in hand OA.
- to asses if CT has better reliability and detection rate of thumb base OA than conventional radiography.
- to assess construct validity of low-field extremity MRI in early arthritis patients.

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Chapter 2

Metric properties of advanced imaging methods in osteoarthritis of the hand: a systematic review

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Galied S. R. Muradin, J. Henk Coert, Johan W. van Neck, Jolanda J. Luime

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Abstract

Objective To assess the value of advanced imaging techniques in the detection of hand osteoarthritis (OA) and hand OA progression.

Methods PubMed/Medline and Embase were searched until April 2012 for studies on imaging of hand OA that presented quantitative data on validity, reliability or responsiveness. Articles presenting only data on conventional radiography (CR) were excluded. Methodological quality was assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist for validity, the Quality Appraisal of Reliability Studies (QAREL) for reliability and the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) for responsiveness.

Results Of 627 citations, 25 studies on ultrasonography (US), MRI or scintigraphy were included. No studies on CT, positron emisission tomography or single photon emission computed tomography met our eligibility criteria. Validity was generally assessed against healthy controls, CR or clinical examination. Overall, US and MRI detected more disease than CR and found significant differences between patients and healthy controls. Scintigraphy detected fewer pathological joints than CR. Intra- and inter-reader reliability varied for US (κ=0.01-1.0) and MRI (κ=0.15-0.84 and ICC= 0.21-0.99), and were good for scintigraphy (κ=0.61-0.84). There were no responsiveness studies for MRI. US responsiveness studies showed a reduction of soft-tissue changes after treatment which correlated with decrease in pain (r=0.7-0.8). For scintigraphy, scores decreased over time while CR showed progression of hand OA.

Conclusions MRI and US seem to be the most promising candidates for early detection of hand OA and for future use in clinical trials. However, further research is needed to improve scoring methods, to compare US with MRI, to confirm reliability of MRI and to further determine the responsiveness of US and MRI.

Background

Hand osteoarthritis (OA) is a disabling disease, with prevalence of up to 70% among the elderly.[1, 2] Patients typically present with intermittent joint pain and stiffness,[3] loss of joint mobility, and loss of grip strength causing impairment in daily activities.[4-6] Hand OA is characterised by degradation of articular cartilage, synovial inflammation, and bone deformation. Possible treatments are limited, but new pharmacological treatments are being developed.[7]

Conventional radiography (CR) is the standard imaging method for assessing structural changes in OA.[8, 9] It can display joint space narrowing (JSN), an indirect measurement of cartilage destruction, and bone deformation. Although four major scoring systems are available for evaluating hand OA on CR,[10-13] there is no consensus on the optimal system. These scoring systems have demonstrated good reliability,[14, 15] but low sensitivity to change within one year.[14] CR does not show inflammation and seems unable to show beginning cartilage degradation.[16] CR is therefore not optimal for identifying early OA or for monitoring disease progression for time periods of <1 year.[17]

Several other imaging techniques can be considered for detecting and monitoring OA related changes, each with their own advantages and disadvantages. These include Computed Tomography (CT), ultrasonography (US), Magnetic Resonance Imaging (MRI), and nuclear imaging methods like Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and scintigraphy. CT is the best method for imaging structural bony changes, but cannot depict cartilage or the joint capsule. US can visualise cartilage and other soft tissues, but the ultrasonic waves may be blocked by bony structures, hindering imaging of the whole joint. MRI visualises both bone and the soft tissues, but has a lower resolution than other imaging techniques, is time consuming and relatively expensive. Nuclear imaging methods do not visualise structural anatomy, but show metabolic activity within the joints, which can often be detected before radiographic changes.

To assess the value of advanced imaging techniques for detection of hand OA detection and its progression, we performed a systematic review of the literature to assess validity, reliability and responsiveness for CT, US, MRI, PET, SPECT and scintigraphy.

Methods

Search strategy and selection

The electronic databases Medline and Embase were searched for articles up to April 2012. The search terms included keywords such as as "osteoarthritis", "hand joints" and "imaging techniques" (see online supplementary text S1). No language restrictions were used. Titles and abstracts were independently screened by two reviewers (MSS, JJL or RWS) to identify eligible articles. If one of the reviewers selected an abstract, the full-text article was retrieved, screened and, if eligible, selected for review. Selection disagreements were resolved by consensus. Reference lists of retrieved articles were checked for additional records.

Papers were eligible if (1) the paper was a full-length primary paper on hand OA; (2) CT, MRI, US, PET, SPECT or scintigraphy was used to image one or multiple hand joints in patients diagnosed with, or suspected of having, hand OA or if one of these techniques was used to assess hand OA-related characteristics in healthy controls; (3) one or more of the following joints were imaged: first carpometacarpal (CMC1), scapho-trapezio-trapezoidal (STT), metacarpophalangeal (MCP), proximal interphalangeal (PIP), or distal interphalangeal (DIP) joint; and (4) a quantification of validity, reliability, or responsiveness was presented.

Both criterion validity and construct validity studies were included. Criterion validity is determined by comparison with an optimal reference standard, which we considered to be a comparison against histology or arthroscopy. Construct validity is determined by comparison with other techniques measuring similar properties, and we therefore included comparisons against other imaging techniques, clinical examination and healthy controls. Reliability studies were included if any form of inter-reader or intra-reader reliability was reported. Responsiveness studies were included if they measured change and compared this change with another method.

We excluded articles if CR was the only imaging technique used or if descriptive data only were reported, without hypothesis testing. We also excluded articles that assessed a patient group of diverse arthritides, and data from patients with

hand OA was not reported separately. The primary reviewer (MSS), extracted all the data, which included study design, patient characteristics, details of imaging technique, method of image analysis, and outcome measures.

Quality assessment

Methodological quality was assessed using three checklists. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool with additional QUADAS items for validity,[18, 19] the Quality Appraisal of Reliability Studies (QAREL) checklist for reliability,[20] and the responsiveness checkbox of the Consensus-based Standards for the selection of health status Measurement Instrument (COSMIN) for responsiveness.[21] The checklists were adapted for our specific purpose (see online supplementary text S2). Questions were answered with "yes", "no", or "unclear". If studies investigated multiple outcome measures, then multiple quality assessments were performed. Quality assessment was performed independently by five reviewers (MSS, SMABZ and RWS for QUADAS; MSS, JJL and JWvN for QAREL; and MSS and JJL for COSMIN). Disagreements were resolved by discussion.

Results

Selection of studies

Our search identified 869 records, (313 Medline and 556 Embase) including 242 duplicates (figure 1). We considered 106 relevant and retrieved them in full text. Seventy-seven articles were excluded, including three because they were not in English.[22-24] Four articles[25-28] reported data about the same cohort, and we included the most informative article.[28] Two other articles also reported data from the same study population,[29, 30] of which one was kept.[29] Reference checking did not result in any additional records.

Study characteristics

Twenty-five articles were included in this review:[28, 29, 31-53] Fourteen articles on US, five on MRI, five on scintigraphy, and one on both US and MRI. Abstract screening yielded two PET and one SPECT article on hand OA, which were excluded because no quantification of validity, reliability, or responsiveness was presented,[54, 55] or because patients with diagnoses other than hand OA

were included.[56] We did not identify any CT study. The characteristics of the included studies are summarised in table 1.

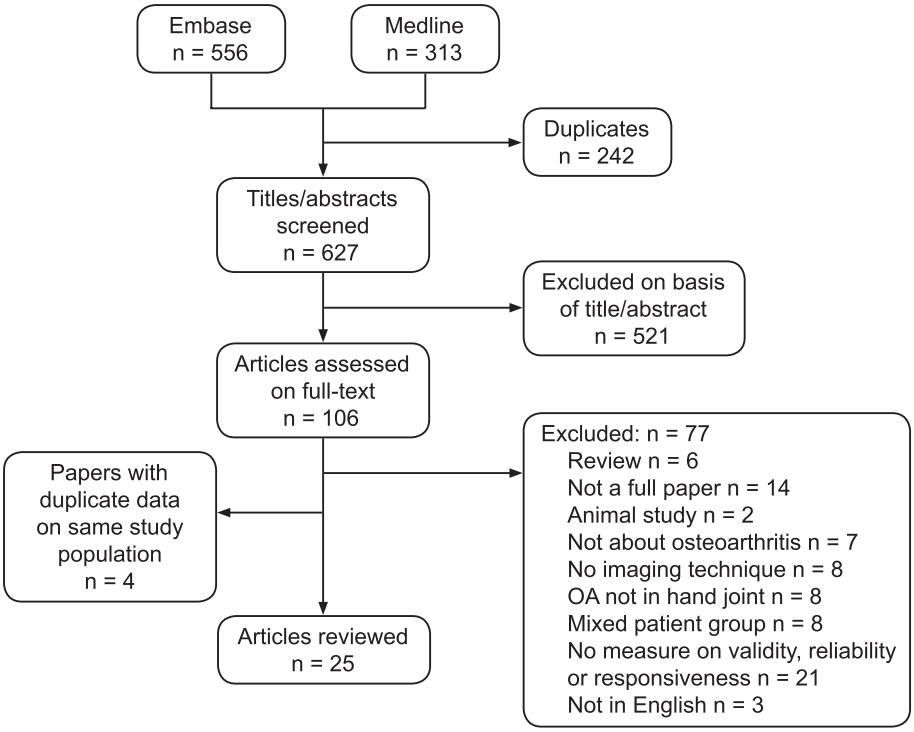

Figure 1. Results of systematic search and selection process.

The inclusion criteria varied between studies from symptomatic hand OA without abnormalities on CR or positive American College of Rheumatology criteria[57], to erosive hand OA on CR. This heterogeneity in patient populations reflects the variation in disease duration, which ranged from a few months to more than 10 years. Age and sex distributions were consistent among most studies (mean or median age of patients > 55, and 61-100% being female). The scored joints ranged from a single CMC1, DIP or PIP joint to a 30-joint examination of thumb base, DIP, PIP, and MCP joints of both hands. One scintigraphic study also included the radial and ulnar part of the wrist.[28]

Table 1. Characteristics of the included studies

Author (year)	hand OA patients	healthy controls	inclusion criteria for hand OA diagnosis	Age mean (range)	Female %	Symptom duration Mean (range)	scored joints[§]	scoring system (REF)[¶]
US studies								
Arrestier (2011)[31]	55	46	ACR'90	61 (51-89)	93	5 yrs (0-30)	PIP + DIP	R[58]
Iagnocco (2000)[37]	57	20	ACR'90	61 (57-71)	76	1 yrs (0-3)	CMC1 (1H)	U
Iagnocco (2005)[38]	110	-	Symptomatic and CR	65 (44-88)	100	4 yrs (1-12)	PIP + DIP	[59]
Keen (2008)[40]	7	-	NR	NR NR	NR	NR	CMC1 + MCP + PIP + DIP (1H)	U
Keen (2008)[41]	37	-	Symptomatic and CR *or* ACR'90	57* (53-66)°	83	4 yrs* (3-8)°	CMC1 + MCP + PIP + DIP	R[40]
Keen (2008)[42]	36	19	Symptomatic and CR *or* ACR'90	58* (53-66)°	86	NR	CMC1 + MCP + PIP + DIP	[40, 41]
Keen (2010)[43]	36	-	Symptomatic and CR *or* ACR'90	58* (53-66)°	86	4 yrs* (2-9)°	CMC1 + MCP + PIP + DIP (1H)	[40]
Klauser (2012)[44]	33	-	ACR '90	64 (46-76)	85	6 yrs (2-11)	CMC1 + MCP + PIP + DIP (1H)	R[40]
Kortekaas (2010)[45]	55	-	ACR'90	62 (8)•	87	5 yrs* (0-55)	CMC1 + MCP + PIP + DIP	[40, 58]
Kortekaas (2011)[46]	55	-	ACR'90	61 (9) •	86	5 yrs* (0-55)	CMC1 + MCP + PIP + DIP	R[40]
Koutroumpas (2010)[47]	18	-	ACR'90 *and* erosion on CR	61 (46-71)	89	5 yrs (1-18)	CMC1 + MCP + PIP + DIP	U
Mancarella (2010)[60]	25	10	ACR'90	65 (8)•	92	7 yrs* (3-13)°	MCP + PIP + DIP	[40, 61]
Vlychou (2009)[51]	22	-	ACR'90 *and* CR	62 (51-71)	91	4 yrs (NR)	CMC1 + MCP + PIP + DIP	R[62]
Wittoek (2010)[52]	38	-	ACR'90	61 (6)•	87	10 yrs (5)•	PIP + DIP	U

Table 1. Characteristics of the included studies

Author (year)	hand OA patients	healthy controls	inclusion criteria for hand OA diagnosis	Age mean (range)	Female %	Symptom duration Mean (range)	scored joints[§]	scoring system (REF)[¶]
MRI & US Studies								
Wittoek (2011)[53]	14	-	ACR'90	61* (49-73)	67	10 yrs* (2-25)	PIP + DIP	R[63]
MRI Studies								
Grainger (2007)[33]	15	-	ACR'90	59 (51-68)	93	9pt: <1 yrs 6pt: ≥1 yrs	1 DIP or PIP (1H)	[63]
Haugen (2011)[34]	10	-	Symptomatic	70 (6)•	90	NR	PIP + DIP (1H)	U
Haugen (2011)[35]	85	-	ACR'90 *or* CR	69 (6)•	91	NR	PIP + DIP (1H)	R[34]
Haugen (2012)[36]	106	-	ACR'90 *or* CR	69 (6)•	92	NR	PIP + DIP (1H)	[34, 35]
Tan (2005)[29]	30	18	Symptomatic	58 (49-68)	80	3 yrs	1 DIP or PIP (1H)	U
Scintigraphy studies								
Balblanc (1995)[32]	15	-	Symptomatic *and* CR	59 (42-69)	93	NR	PIP + DIP	U
Jónsson (1998)[39]	all patients[‡]: 297	-	-	NR NR	64	NR	CMC1+ MCP PIP + DIP	U
Macfarlane (1993)[28]	35	-	CR	62 (9)•	91	11 yrs (9)•	TB + MCP + PIP+ DIP	U
McCarthy (1994)[49]	Knee OA: 67	-	-	62 (10)•	61	NR	TB + MCP + PIP + DIP	U
Olejárova (2000)[50]	52	-	Symptomatic *and* CR	67 (8)•	88	15 yrs (NR)	CMC1+ MCP PIP + DIP	U

[§] Both hands were scored in all studies, except for the studies indicated with: (1H)

[¶]This column shows the reference to the scoring method that was used in the study.

R = The referenced method was used, but it was revised or had new additions U= No hand OA article has previously used the method, or it is unclear if this is a new or previously used method.

[‡]All patients undergoing bone scanning were included, not just those with hand OA.

* = median, ° = Inter quartile range, • =standard deviation, OA = osteoarthritis, NR = not reported, CR = conventional radiography, m = months, yrs = years, DIP = distal interphalangeal joint, PIP = proximal interphalangeal joint, MCP = metacarpal joint, CMC1 = first carpometacarpal joint, TB = first carpometacarpal + scaphotrapezotrapezoidal joint scored as one joint.

Methodological quality

The results of the presented studies pose some limitations and should be interpreted with caution (see online supplementary text S2 for details). The optimal spectrum of patients should consist of a mix of patients who are likely to undergo imaging for diagnosis or follow-up of hand OA. However, some studies only included patients with severe OA, while others added healthy controls to the patient group. Other general limitations included insufficient description of sample size determination, and lack of information about the training and experience of the examiner.

In the validity studies, the use of only severely affected patients might have increased sensitivity, while the use of healthy volunteers as reference standard might have increased specificity or overestimated correlations.[19] In the reliability studies, agreement might have been inflated in samples where results are obvious, for example in patients with extreme disease status or healthy controls.[20] Examiner blinding was insufficiently described in reliability studies. As incomplete blinding may affect reliability results,[20] it should be described extensively. Responsiveness studies often lacked a-priori hypotheses of the expected change, which are recommended as it is easy to retrospectively create alternative explanations for low correlations or differences between changes.[21] It was also often unclear whether raters could review their prior ratings. This is important as not knowing previous results minimizes expectation bias, but gives a higher measurement error.[64]

Validity

Eleven US, five MRI and three scintigraphy articles examined validity (table 2). None of the studies determined criterion validity by comparing with histology or arthroscopy. Construct validity was determined by using different comparators as healthy controls, CR, joint pain, joint swelling, or MRI.

Four of 11 US studies compared hand OA patients with healthy controls and reported significant differences in JSN,[42] osteophytes,[42] synovitis,[31, 42, 60] Power Doppler signal (PD),[31,42,60] and joint effusion,[31,37,60] while no significant differences were found for tendon effusion.[31] Five studies compared structural US changes with CR, and US generally detected more osteophytes,[41, 46, 51, 52] erosions,[51, 52] and JSN.[41] Only one study detected less erosions with US (sensitivity=0.72,

specificity=1.0).[38] Joint pain, tender joints and swollen joints were used as comparator in four studies and agreed poorly with US greyscale measurements of synovitis, effusion, PD measurements, JSN and osteophytes.[31, 42, 45, 46]

One out of five MRI studies compared hand OA patients with healthy controls, reporting significantly more ligament abnormalities, tendon abnormalities, cartilage abnormalities, joint effusion, osteophytes, bone marrow lesions (BML), erosions and cysts in patients.[29] Two other studies compared MRI with CR, and found that MRI detected significantly more osteophytes and erosions, while CR detected significantly more cases with malalignment.[33, 36] A fourth study investigated associations between MRI and joint pain on palpation, and found the highest associations for synovitis (OR 2.4 95%CI=1.6-3.8) and bone attrition (OR 2.5 95%CI=1.5-4.1).[35] One study compared US with MRI, and reported moderate agreement between these modalities (k=0.41-0.55). US detected more osteophytes and effusion, while MRI detected more erosions and synovitis.[53]

Three scintigraphy studies compared isotope uptake in bone with joint pain and CR. Isotope uptake was correlated with joint pain (τ=0.24),[28] and OA on CR (r=0.50-0.61).[32, 50] Scintigraphy detected less pathological joints than CR.

Table 2. Validity of US, MRI and scintigraphy studies for hand OA.

Author (year)	Pathology examined (joints scored)	positive joints (mean)	positive joints comparator (mean)	Statistics		
US studies			**healthy controls**			
Arrestier (2011)[31]	synovitis (16)	0.0	0.0	-		
	effusion PIP (8)	2.1	1.7	p>0.05		
	effusion DIP (8)	2.1	0.2	p<0.05		
	subtendinous effusion PIP (8)	1.9	-	p>0.12		
	PD PIP (8)	0.1	0.0	-		
	PD DIP (8)	0.3	0.0	-		
Iagnocco (2000)[37]	effusion (1)	3.55[a]	2.89	p<0.001		
Keen (2008)[42]	JSN (30)	12.1	8.2	p<0.001		
	osteophytes (30)	12.2	8.8	p<0.001		
	synovitis (30)	13.7	10.2	p<0.001		
	PD (30)	2.0	0.9	p=0.002		
Mancarella (2010)[60]	synovitis (28)	3.2	2.1	p=0.06		
	effusion (28)	3.0	1.9	p=0.08		
	PD (28)	2.3	0.1	p<0.0001		
	cartilage thickness (mm)	0.35[a]	0.41	p<0.0001		
US studies			**CR**			
Arrestier (2011)[31]	effusion (16)	4.1	[c]	κ=0.03		
	PD (16)	0.4	[c]	κ=0.01		
Iagnocco (2005)[38]	erosions (1)	0.15	0.20[d]		Se=0.73	Sp=1.00
Keen (2008)[41]	osteophytes (30)	12.1	8.9e	κ=0.54	*Se=0.83*	*Sp=0.76*
	JSN (30)	12.2	7.1e	κ=0.44	*Se=0.82*	*Sp=0.72*
Vlychou (2009)[51]	erosions (30)	10.5	5.2[d]	p<0.05		
	osteophytes (30)	16.4	14.1[d]	p<0.05		
Wittoek (2010)[52]	erosions (18)	3.1	1.9[f]		Se=0.94	Sp=0.92
	osteophytes (18)	11.0	8.1[f]		Se=0.95	Sp=0.66
Kortekaas (2011)[46]	osteophytes (30)	20.7	13.8[g]			
US studies			**pain on palpation**			
Kortekaas (2011)[46]	osteophytes (30)	20.7	NR	OR 4.8 (3.1 – 7.5)		
Kortekaas (2010)[45]	synovitis (30)	6[b]	9[b]	OR 4.0 (1.9 – 8.2)		
	joint effusion (30)	6[b]		OR 3.7 (1.8 – 7.6)		
	synovial thickening (30)	2[b]		OR 2.5 (1.1 - 6.3)		
	PD (30)	2[b]		OR 2.0 (0.8 - 4.9)		
US studies			**joint pain with swelling**			
Arrestier (2011)[31]	effusion (16)	4.1	2.0	κ=0.14		
	PD (16)	0.4	2.0	κ=0.06		
US studies			**joint pain (VAS)**			
Keen (2008)[42]	JSN (30)	12.1	65	ρ=0.13		
	osteophytes (30)	12.2		ρ=0.05		
	synovitis (30)	13.7		ρ= 0.001		
	PD (30)	2.0		ρ=-0.31		

Table 2. Validity of US, MRI and scintigraphy studies for hand OA.

Author (year)	Pathology examined (joints scored)	positive joints (mean)	positive joints comparator (mean)	Statistics		
US studies			**MRI**			
Wittoek (2011)[53]	US erosion (8)	2.9	3.9	κ=0.55	*Se=0.67*	*Sp=0.93*
	US osteophytes (8)	5.1	4.4	κ=0.51	*Se=0.87*	*Sp=0.55*
	US synovitis (8)	1.2	1.5	κ=0.55	*Se=0.65*	*Sp=0.93*
	US effusion (8)	5.3	5.1	κ=0.41	*Se=0.83*	*Sp=0.57*
MRI studies			**healthy controls**			
Tan (2005)[29]	cartilage defects (1)	1.0	0.0	p<0.001		
	erosions (1)	0.6	0.0	p<0.001		
	osteophytes (1)	0.9	0.1	p<0.001		
	bone sclerosis (1)	0.7	0.0	p<0.001		
	cysts (1)	0.2	0.0	p<0.05		
	joint effusion (1)	0.7	0.0	p<0.001		
	BML (1)	0.9	0.1	p<0.001		
	ligament abnormalities (1)	1.0	0.3	p<0.001		
	tendon abnormalities (1)	0.8	0.0	p<0.001		
MRI studies			**CR**			
Grainger (2007)[33]	erosions (8)	2.5	0.6[d]	p<0.05	*Se=1.00*	*Sp=0.34*
Haugen (2012)[36]	osteophytes (8)	7[b]	3[b,h]	p<0.001	*Se=1.00*	*Sp=0.22*
	JSN (8)	7[b]	7[b,h]	p<0.001	*Se=0.78*	*Sp=0.72*
	erosions (8)	4[b]	1[b,h]	p=0.001	*Se=0.95*	*Sp=0.63*
	cysts (8)	0[b]	0[b,h]	p=0.66	*Se=0.16*	*Sp=0.96*
	malalignment (8)	0[b]	0[b,h]	p<0.001	*Se=0.43*	*Sp=0.98*
MRI studies			**pain on palpation**			
Haugen (2011)[35]	osteophytes (8)	8[b]	4[b]	OR 1.4 (0.9-2.1)		
	JSN (8)	7[b]		-		
	erosions (8)	4[b]		OR 1.4 (1.0-1.9)		
	bone attrition (8)	1[b]		OR 2.5 (1.5-4.1)		
	cysts (8)	0[b]		-		
	malalignment (8)	0[b]		-		
	synovitis (8)	6[b]		OR 2.4 (1.6-3.8)		
	BML (8)	1[b]		OR 1.5 (1.0-2.3)		
Scintigraphy studies			**CR**			
Balblanc (1995)[32]	isotope uptake (18)	9.5	14.1[i]	r=0.61	*Se=0.53*	*Sp=0.86*
Olejárova (2000)[50]	isotope uptake (30)	16.1[j]	64[k]	r=0.50		
Scintigraphy studies			**pain on palpation**			
Macfarlane (1993)[28]	isotope uptake (34)	21.9	9.7	τ = 0.24		
Scintigraphy studies			**joint pain (VAS)**			
Macfarlane (1993)[28]	isotope uptake (34)		39.7	τ = 0.02		

Results of validity shown per study. The mean scores were extracted from the article or calculated from available results. *italic* sensitivity and specificity were calculated from results and not reported in the primary articles.

[a]mean thickness in mm; [b] median instead of mean; Se = Sensitivity; Sp = Specificity; PD = Power Doppler; JSN = Joint Space Narrowing; CR = Conventional Radiography; OR = Odds Ratio; CI = Confidence Interval VAS = Visual Analogue Score; HOA= patients with hand osteoarthritis; HC = Healthy Controls.
[c]compared with Kellgren and Lawrence score>2
[d]CR scoring not according to previous known system
[e]CR definitions according to Altman atlas 2004
[f]CR definitions according to Verbruggen scoring system
[g]CR definitions according to Altman atlas 1995
[h]CR definitions according to Altman atlas 2007
[i] CR scored according to Altman atlas , if any feature was detected, the joint was scored as positive
[k]mean score on the Kallman scale, (maximum of 300 per patient);
[j]mean score instead of affected joints, score range per joint was 0-3

Reliability

Eight US, four MRI and two scintigraphy studies examined reliability (table 3). Four US studies assessed inter-reader reliability. In two studies agreement was good (κ=0.83-0.99) for synovitis, PD, effusion, osteophytes and erosions,[52, 53] while in one study this varied for synovitis, PD and osteophytes (κ=0.229-0.530).[40] Intra-reader reliability was assessed in five studies. In four studies, intra-reader reliability assessed by one reader was moderate to good (κ=0.62-0.94) for synovitis, PD, JSN, effusion and osteophytes, and good for cartilage thickness (ICC=0.96).[42, 46, 51, 60] The fifth study reported intra-reader reliability for seven readers, ranging from poor to good (κ=0.172-1.0) for synovitis, PD, and osteophytes.[40]

Three MRI studies reported that inter-reader reliability was high for erosions, JSN, BML, malalignment and ligament absence (κ=0.76-0.84 and ICC=0.79-0.97); moderate to good for synovitis and tenosynovitis (κ=0.58 and ICC=0.48-0.51); low for cysts (ICC=0.21); and variable for osteophytes (κ=0.15 and ICC=0.88).[33, 34, 53] MRI Intra-reader reliability was assessed in two studies and was high for synovitis, osteophytes, erosions, JSN, BML, malalignment and ligaments (κ=0.71-0.84 and ICC=0.84-0.99); moderate for cysts (κ=0.66 and ICC=0.59); and variable for tenosynovitis (κ=0.30 and ICC=0.63).[34, 35]

One scintigraphy study reported high inter-reader reliability (κ=0.61-0.82),[49] and one scintigraphy study reported high intra-reader reliability (κ=0.84).[39]

Table 3. Reliability of US, MRI and scintigraphy studies for Hand OA

Author (year)	no. of raters	Pathology examined	Scoring system	Inter-reader reliability	Intra-reader reliability
US studies					
Iagnocco (2005)[38]	2	erosions	0-1	[a]	
Keen (2008)[40]	7	synovitis	0-1	κ= 0.40	κ= 0.07-1.0
			0-3	κ= 0.25	κ= 0.17-1.0
		PD	0-1	κ= 0.33	κ= 0.21-1.0
			0-3	κ= 0.23	κ= 0.09-1.0
		osteophytes	0-1	κ= 0.53	κ= 0.09-1.0
			0-3	κ= 0.38	κ= 0.17-0.91
Keen (2008)[42]	1	osteophytes	#		κ= 0.83
		JSN	0-1		κ= 0.64
		synovitis	0-3		κ= 0.62
		power Doppler	0-3		κ= 0.87
Kortekaas (2011) [45, 46]	1	osteophytes	0-3		ICC= 0.71
		effusion	0-3		ICC= 0.73
		synovial thickening	0-3		ICC= 0.73
		PD	0-3		ICC= 0.57
Mancarella (2010)[60]	1	synovial hypertrophy	0-1		κ= 0.91
		joint effusion	0-1		κ= 0.94
		PD	0-1		κ= 0.86
		cartilage thickness	mm		ICC= 0.96
Vlychou (2009)[51]	1	erosions	0-1		κ= 0.81[c]
		osteophytes	0-1		
		synovitis	0-1		
		joint effusion	0-1		
		PD	0-1		
		tenosynovitis	0-1		
Wittoek (2010)[52]	2	erosions	0-1	κ= 0.91	
		osteophytes	0-1	κ= 0.98	
		effusion	0-1	κ= 0.93	
		synovitis	0-1	κ= 0.99	
		PD	0-1	κ= 0.94	
Wittoek (2011)[53]	2	erosions	0-1	κ= 0.90	
		osteophytes	0-1	κ= 0.83	
		synovitis	0-1	κ= 0.93	
		effusion	0-1	κ= 0.84	

Table 3. Reliability of US, MRI and scintigraphy studies for Hand OA

Author (year)	no. of raters	Pathology examined	Scoring system	Inter-reader reliability	Intra-reader reliability
MRI studies					
Grainger (2007)[33]	2	erosions	0-1	κ= 0.84	
Haugen (2011)[34]	3	synovitis	0-3	ICC= 0.48 (0.09-0.70)	ICC= 0.84 (0.50-0.96)[d]
		flexor tenosynovitis	0-3	ICC= 0.51 (0.49-0.65)	ICC= 0.64 (0.05-0.90)[d]
		erosions	0-3	ICC= 0.92 (0.91-0.96)	ICC= 0.94 (0.74-0.99)[d]
		cysts	0-1	ICC= 0.21 (0.00-0.57)	ICC= 0.59 (-0.04-0.88)[d]
		osteophytes	0-3	ICC= 0.88 (0.86-0.89)	ICC= 0.91 (0.58-0.98)[d]
		joint space narrowing	0-3	ICC= 0.97 (0.93-0.99)	ICC= 0.99 (0.95-1.00)[d]
		malalignment frontal	0-1	ICC= 0.79 (0.77-1.0)	ICC= 0.95 (0.85-0.99)[d]
		malalignment sagittal	0-1	-	ICC= 0.0 (-1.93-0.73)[d]
		BML	0-3	ICC= 0.89 (0.65-0.89)	ICC= 0.83 (0.51-0.96)[d]
		Collateral ligament absence	0-1	ICC= 0.81 (0.61-0.81)	ICC= 0.79 (0.42-0.94)[d]
		BML at CL site	0-1	ICC= 0.81 (-0.07-0.83)	ICC= 0.42 (-0.29-0.82)
Haugen (2011)[35, 36]	1	Synovitis			κ= 0.78
		Flexor tenosynovitis			κ= 0.30
		Erosions			κ= 0.84
		Bone attrition			κ= 0.78
		Cysts			κ= 0.66
		Osteophytes			κ= 0.71
		Joint space narrowing			κ= 0.77
		Malalignment			κ= 0.79
		BML			κ= 0.77
		Collateral ligament Absence/discontinuity			κ= 0.73
		BML at CL site			κ= 0.76
Wittoek (2011)[53]	2	osteophytes	0-1	κ= 0.15	
		erosions	0-1	κ= 0.76	
		synovitis	0-1	κ= 0.58	
		effusion	0-1	κ= 0.50	
Scintigraphy studies					
Jónsson (1998)[39]	2	isotope uptake DIP	0-2	κ= 0.75	
		isotope uptake PIP		κ= 0.73	
		isotope uptake MCP		κ= 0.82	
		isotope uptake CMC1		κ= 0.61	
McCarthy (1994)[49]	1	isotope uptake	0-1		κ= 0.84

PD = Power Doppler; JSN = Joint Space Narrowing; BML = Bone Marrow Lesions; DIP = distal interphalangeal joint; PIP = proximal interphalangeal joint; MCP = metacarpal joint; CMC1 = first carpometacarpal joint; ICC = intraclass correlation coefficient

[a] no kappa or ICC value was calculated; reliability was reported as: "interobserver variation 5% (Not Significant)"

[b] count for total number of osteophytes

[c] overall kappa over all findings was reported as: "erosions and other findings"

[d] Reported is the median score of three readers

Table 4. Change and responsiveness of US and Scintigraphy studies for Hand OA

Author (year)	Intervention	Time between examinations	Imaging feature examined			Comparator		Responsiveness (comparison between both changes)
			Type	Score range	Mean scores baseline — follow-up	Type and score range	Mean scores baseline — follow-up	
US studies								
Keen (2010)[43]	i.m. prednisolon	4 weeks	synovitis	0-14	6.5 — 6.1	Pain VAS 0-100	65 — 29	NA
				0-42	9.4 — 9.0			
			PD	0-14	1.1 — 0.9			
				0-42	1.9 — 1.5			
Klauser (2011)[44]	i.a. hyaluronic acid	4 weeks	effusion	mm*	15.6 — 13.2	Pain VAS 0-100	68 — 37	r=0.7 (p<0.001)
			PD	0-3	2.7 — 1.4		68 — 37	r=0.8 (p<0.001)
Scintigraphy Studies								
Balblanc (1995)[32]	No intervention	4 years	isotope uptake	0-18	7.2 — 4.7	OA CR score 0-135	11.9 — 13.8	r=0.13 (p<0.05)
Olejárova (2000)[50]	No intervention	2 years	isotope uptake	0-90	16.1 — 9.10	OA CR score 0-300	64.0 — 68.7	NA
Macfarlane (1993)[28]	No intervention	1 year	isotope uptake	0-34	21.9 — 20.0	Pain VAS 0-100	39.7 — 48.4	NA
				0-136	41.9 — 37.8			

Results are given as the values at baseline and the values at the second measurement.

*= scored in millimetres, no range predefined.

i.m. = intramuscular; i.a. = intra-articular; PD = Power Doppler ; CR = conventional radiography; VAS = visual analogue scale; NA = not available

Responsiveness

Two US and three scintigraphy studies assessed change scores over time, and included a comparator. Only two of these studies assessed true responsiveness by calculating a correlation coefficient between the changes (Table 4).

One US study reported a significant decrease in PD and effusion in patients treated with intra-articular hyaluronic acid injections. These decreases correlated with a significant reduction of pain (r=0.7 and r=0.8).[44] The other US study reported a small non-significant decrease in greyscale synovitis and PD in patients treated with intramuscular methylprednisolone injections, while there was a significant decrease in pain.[43]

In the scintigraphy studies, no interventions were used, but change during disease progression was measured. In all three studies scintigraphic scores decreased over time while the disease progressed and radiographic and pain scores increased.[28, 32, 50] Changes in the radiographic scores were weakly correlated with changes in the scintigraphic scores (r=0.13).[32]

Discussion

This systematic review shows that there is growing evidence on validity, reliability and responsiveness of advanced imaging methods in hand OA. US and MRI seem the most promising candidates, with US being the most investigated modality. Few studies have compared US directly with MRI. Wittoek et al. reported that MRI was more sensitive for synovitis and erosions, but US detected more effusion and osteophytes.[53] This last finding, however, is in contrast with a recent publication by Mathiessen et al. in which osteophytes were more often detected with MRI (87% vs 75%).[65] According to Mathiessen, the MRI might have underperformed in the study by Wittoek, as they did not use standardised scoring methods and had poor inter-reader reliability.

US and MRI were both more sensitive for detecting osteophytes and erosions than CR, with the exception of one US study. US and MRI also showed significant differences between patients and healthy controls for structural and soft-tissue changes, including ligament abnormalities, which were only investigated

with MRI, and cysts and BML which cannot be assessed with US. Correlations between US and clinically assessed synovitis were low, as also found in hip and knee OA studies.[66] Reported reliabilities were mostly moderate to good for US and MRI, although some variability was seen in the few MRI studies for synovitis, tenosynovitis, cysts and osteophytes. Responsiveness was only evaluated in US, which demonstrated that reduction of soft tissue lesions was correlated with pain decrease. More studies should therefore focus on reliability of MRI, responsiveness of US and MRI, and comparison of US and MRI.

Bone scintigraphy seems less promising for detection and follow-up of hand OA. Scintigraphy was weakly correlated with clinical symptoms and detected less pathological joints than CR. Reliability of scintigraphy was good, but scintigraphy scores decreased over time, while the disease progressed clinically and radiographically. This responsiveness pattern is comparable to results from a systematic review about knee OA,[67] and inherent to the technique. Scintigraphy shows increased uptake of bone tracers, representing osteophyte and cyst formation.[68] As the new osteophytes become visible on imaging techniques showing structural damage, they will relieve stress on the joint, and scintigraphic findings will diminish.[68]

No studies on CT, PET or SPECT reported validity, reliability or responsiveness. However, these may be less optimal than US and MRI. Although CT is more sensitive than MRI and US for detecting erosions,[69-71] it does not visualise cartilage or other soft tissues. PET and SPECT use radiopharmaceutical agents that target bone, and these imaging techniques may therefore have similar limitations as described for scintigraphy. However, this may change when cartilage-specific tracers become available.[72, 73]

A variety of scoring methods was used in the reviewed studies. These methods were often newly devised by the authors (based on rheumatoid arthritis literature), or not properly described. In both US and MRI literature only a single scoring method was used in multiple studies. The US method by Keen et al.[40] was used in eight articles, although mostly with additions or alterations to the original method. The MRI scoring method by Haugen et al.[34] has so far been used in articles by the author's own study group, and has undergone one change in subsequent studies. As seen in knee OA,[74] scoring methods can

improve over time and with new insights into OA. These improvements may lead to shorter scoring times, further improvement of reliability, validity and responsiveness, and hopefully a widely accepted consensus method.

A number of issues should be taken into account when interpreting the results of this review. Our search was extensive but we might still have missed publications. Three articles were excluded because of language difficulties,[22-24] as we could not reliably determine methodological quality and extract data. We found no criterion validity studies in which histology or arthroscopy was used as a reference standard, probably because these are not easily obtained for hand OA. Not all included validity studies were primarily designed to assess validity, which might have limited their methodological quality. Comparison of construct validity studies was hindered by differences in pathology definition, statistical analysis, and comparators. Homogeneity of study design and reporting should therefore be improved in future studies.

We included data on DIP, PIP, MCP, CMC1 and STT joints, but did not asses differences between these joints. However, anatomical differences may affect imaging performance. For example, limited resolution of MRI may hamper assessment of the smaller DIP joints,[34] while US may not fully assess the third and fourth MCP joints, due to a restricted acoustic window.[75] Both MRI and US have technologically advanced in recent years, and results from older studies might therefore not be comparable with those of the newer studies. This may also explain why the only study in which US was less sensitive than CR, was also the oldest study that compared the two methods.[38]

In conclusion, MRI and US seem to be the most promising candidates for early detection of hand OA and for future use in clinical trials. However, further research is needed to improve scoring methods, compare US with MRI, confirm reliability of MRI, and better determine responsiveness of US and MRI.

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Chapter 3

Computed tomography for the detection of thumb base osteoarthritis, comparison with digital radiography.

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Abstract

Objective To compare Computed Tomography (CT) with digital radiography for the detection of osteoarthritis (OA) of the first carpometacarpal (CMC1) and scaphotrapeziotrapezoid (STT) joint.

Materials and Methods We retrospectively identified patients who were assessed for CMC1 OA or STT OA at our hand surgery outpatient clinic between January 2008 and March 2011, and who had both a digital radiograph and a CT-scan of the hand within a three-month period. CT and radiographic images were scored independently by two musculoskeletal radiologists for joint space narrowing (JSN), osteophytes, subchondral sclerosis, bone cysts, and erosions in the CMC1 and STT joint.

Results Thirty patients were identified. The inter-reader reliability of CT for the detection of CMC1 OA (ICC 1.00) and STT OA (ICC 0.80) was higher than radiography (ICC's 0.15 and 0.45). In comparison with their own radiographical scoring, both readers detected with CT three more patients with CMC1 OA, and 13 and 5 more patients with STT OA.

Conclusion CT had a higher inter-reader reliability and detection rate for both CMC1 and STT OA, compared to radiography. As surgical treatment selection of thumb base OA depends on the presence of pathology in the CMC1 and STT joints, CT may improve treatment selection and surgical planning.

Introduction

Osteoarthritis (OA) of the first carpometacarpal (CMC1) joint is a very common and burdensome disease, and often co-exists with OA in the scaphotrapeziotrapezoid (STT) joint. Patients are usually treated in primary care to alleviate symptoms with nonsteroidal anti-inflammatory drugs, splints, and steroid injections. However, persistent pain or severe functional impairment are indications for surgical intervention.[1]

Various surgical procedures have been described to treat CMC1 OA, but no optimal technique has yet been determined.[2-4] Most popular are complete trapeziectomy with ligament reconstruction and tendon interposition (LRTI),[5] and other types of complete trapeziectomy. The complete removal of the trapezium can alleviate symptoms from both the CMC1 and the STT joint, but can also lead to proximal migration of the first metacarpal bone and lead to lower pinch strength.[6] Therefore, other surgical procedures are often performed to avoid migration and strength reduction such as hemitrapeziectomy, resection arthroplasty, CMC arthrodesis or joint prosthesis. Each of these techniques is associated with their own benefits and risks. For example, techniques in which most of the trapezium is spared, show less migration of the first metacarpal bone, but comparable other long-term results to complete trapeziectomy.[7-9] However, all these procedures have in common that the STT joint is not treated and it should therefore only be applied when this joint is not affected with OA.

Radiographical assessment is used to verify the presence of OA in the CMC1 and STT joint, and to rule out other diseases. However, evaluation of the STT joint can be difficult due to overprojection of the carpal bones. It has been reported that more than half of STT OA is missed on the radiograph,[10] which might lead to selecting an improper surgical procedure.

Detection of STT OA might be improved with CT (Computed Tomography) due to its better spatial resolution. In previous studies, CT was found to be more sensitive than radiography in the detection of osteophytes and cysts in knee OA,[11] and CT was better in determining the positions of bony structures and anomalies in hip OA.[12]

The purpose of this study was to compare CT with digital radiography for inter-reader reliability and detection rate of CMC1 and STT OA.

Material and Methods

Patient selection

In our centre patients who are clinically suspected for symptomatic OA of the CMC1 or STT joint and eligible for surgery are sometimes referred for CT examination of the wrist.

We searched in our PACS (Picture Archiving and Communication System) system for patients who had a CT-scan and radiograph of the wrist joint between January 2008 and March 2011. We selected only the patients who had been referred by the Department of Plastic, Reconstructive, and Hand Surgery for CT to assess possible CMC1 and/or STT OA, and who were 18 years or older without a history of hand trauma, congenital hand anomalies, or a known inflammatory disease. All patients needed to have a digital radiographic examination of the wrist within a 3–month period of the CT without relevant medical interventions within that period. The study was approved by the local medical ethics review committee.

Image evaluation

All CT scans and radiographs were scored for each feature that contributes to the radiographical classification system of Eaton and Glickel.[13] This system was designed to help treatment selection in symptomatic OA patients and assigns a grade between I and IV to the CMC1 joint, according to the severity of OA. Grades I-III describe isolated CMC1 OA in increasing severity, while the highest stage IV encompasses OA in both the CMC1 and STT joints. We chose to evaluate the differences between CT and radiography for each individual feature used in this system.

For the CMC1 joint, joint space narrowing (JSN) was assessed as the joint space between the first metacarpal bone and the trapezium and was compared with the joint space of the 2nd and 3rd CMC joints. JSN was scored as 0 = normal, 1 = 50% or more of the estimated original joint space left, 2 = less than 50%

of the estimated original joint space left, 3 = bony ankylosis. Osteophytes were defined as bony protrusions from the cortical shell and were scored for both the trapezium and the first metacarpal. Each bone was scored as: 0 = no osteophytes, 1 = one or more small osteophytes of less than 2 mm, 2 = one or more osteophytes larger than 2 mm. Subchondral sclerosis was defined as a visibly increased bone density in the subchondral bone, which appeared more radiopaque than normal. The 2nd and 3rd CMC joints were used for comparing the subchondral density. Bone cysts were defined as sharply sclerotic outlined radiolucent spots within the bone, and erosions were defined as a clear break within the cortical shell. If lesions looked like a typical cyst, but had a small break in the cortical shell, they were still considered cysts. Subchondral sclerosis, bone cysts and erosions were scored as 0 = absent, or 1= present for both the first metacarpal bone and the trapezium at the first CMC1 joint. Subluxation was calculated as a percentage of the base of the metacarpal bone that failed to cover the trapezium.

We used a reduced scoring system for the STT joint for feasibility. The STT joint was defined as the combination of the scaphotrapezial joint, the scaphotrapezoidal joint and the trapeziotrapezoidal joint. JSN, osteophytes, subchondral sclerosis, bone cysts and erosions were each scored over the whole STT joint as 0 = absent, 1 = doubtful or 2 = definite.

All images were scored by two musculoskeletal radiologists (GM and RO) with respectively 5 and 3 years of experience in evaluating hand radiographs and hand CT-scans. If both hands were imaged on both CT and radiograph, the hand in which the patient experienced the most pain was scored. The image evaluators were blinded to patient identity, clinical patient data and which CT corresponded to which radiograph. A training session to acquaint both radiologists with the scoring system was held before scoring the images.

CMC1 OA, STT OA, and Eaton and Glickel stages were derived from the scores provided. CMC1 OA was defined as the presence of JSN or an osteophyte. STT OA was defined as the presence of definite JSN or osteophyte, or as three or more STT features that were scored as doubtful. Eaton stage I was defined as no detectable CMC1 OA. Stage II was the presence of a JSN score of 1 and/or an osteophyte score of 1, without cysts or erosions in the CMC1 joint and without

STT OA. Stage III was a JSN score of 2, an osteophyte score of 2, or a JSN or osteophyte score of 1 with additional cysts or erosions, and no STT OA. Eaton stage IV was defined as all cases that had CMC1 and STT OA.

Statistics

Statistical data analysis was performed using SPSS version 19.0. Inter-rater reliability of radiography and CT was assessed using percentage agreement and intraclass correlation coefficients (ICC). The ICC was calculated as two-way random, single measures, absolute agreement.[14]

Results

The images of 30 patients were scored and analyzed. Twenty-one of these patients were female, the median age was 57 years (interquartile range 53-61), and 21 right and 9 left hands were assessed.

All radiographic examinations consisted of a minimum of two views, including a PA view of the wrist and a lateral and/or oblique view of the wrist. Some radiographic examinations included additional stress views. All CT examinations consisted of axial scanned wrists with slices of 0.4-0.75 mm, and reconstructions in the coronal and sagittal direction. In one CT examination the STT joint was not depicted on the coronal and sagittal reconstructions. This STT joint was excluded from all analyses that included STT joints.

The inter-reader reliability of CT for the detection of CMC1 OA (ICC 1.00) and STT OA (ICC 0.80) was higher than that of radiography (ICCs 0.15 and 0.45) (Table 1). On the CT images, both readers agreed that there were 28 cases with CMC1 OA and two cases without CMC1 OA. With radiography, however, both readers agreed that there were 23 cases with CMC1 OA and one without CMC1 OA. Disagreement in the six radiographical cases was caused three times by different judgements in osteophytes and three times by disagreement in both osteophytes and JSN. For the STT joint, both readers agreed on CT that there were 15 cases with STT OA and eleven cases without STT OA. The disagreement in the remaining three cases was caused once by a different judgment in osteophytes, once by a difference in cyst presence, and once by a difference in osteophytes and cyst. With radiography, both readers agreed that there

were five cases with STT OA and 17 cases without STT OA. The disagreement in the remaining seven cases was caused by different judgements of JSN in three cases, osteophyte presence in one case, cyst presence in one case, and a combination of these factors in two cases. Percentage agreement for CMC1 JSN was slightly lower with CT than with radiography. Interestingly, with radiography the disagreement between the readers was about the absence or presence of JSN, while on CT the readers mostly agreed that there was JSN, but disagreed about the severity of the JSN. Reliability of CT for the detection of erosions was lower than that of radiography. In almost all disconcordant erosions cases were cysts detected in the same joint by both readers.

Table 1. Inter-reader reliability on joint level for CT and CR.

		ICC CT	ICC CR	%Agreement CT	%Agreement CR
CMC1	presence of OA	1.00	0.15	100	80
	Joint space narrowing	0.76	0.70	67	70
	Osteophytes	0.87	0.66	90	67
	Subchondral sclerosis	*	0.67	80	83
	Bone Cyst	0.48	0.37	73	83
	Erosion	*	*	90	100
	Subluxation	0.65	0.62		
STT	presence of OA	0.80	0.45	90	76
	Joint space narrowing	0.81	0.41	76	69
	Osteophytes	0.69	0.53	72	76
	Subchondral sclerosis	*	0.70	38	79
	Bone cyst	0.77	0.52	82	90
	Erosion	0.24	*	62	93
Eaton Stage		0.86	0.63	86	55

CMC1 = first carpometacarpal joint, STT = scapho-trapezio-trapezoidal joint, CT = computed tomography, CR = conventional radiography, ICC = intraclass correlation coefficient, OA = osteoarthritis, * = incalculable

Each reader individually detected more OA in both joints with CT than with CR (Tables 2 and 3). Reader 1 detected three cases of CMC1 OA and 12 cases of STT OA with CT which he did not detect with radiography. Reader 2 detected three cases of CMC1 OA and five cases of STT OA which he did not detect with radiography. In only one case was STT OA detected with radiography and not with CT by one of the readers. In this case the JSN in the STT joint was scored as definite on radiography and doubtful on CT. Two examples of patients in whom STT OA was only detected with CT are shown in Figures 1 and 2.

Table 2. Presence and absence of detected CMC1 OA by modality for both readers.

CMC1 OA Reader 1	CT positive	CT negative	CMC1 OA Reader 2	CT positive	CT negative
CR positive	25	2	CR positive	25	0
CR negative	3	0	CR negative	3	2

CR = conventional radiography, CT = computed tomography

Table 3. Presence and absence of detected STT OA by modality for both readers.

STT OA Reader 1	CT positive	CT negative	STT OA Reader 2	CT positive	CT negative
CR positive	6	0	CR positive	10	1
CR negative	12	11	CR negative	5	13

CR = conventional radiography, CT = computed tomography

For the separate OA scores, more pathological features were detected with CT than with radiography (Table 4). This also resulted in higher Eaton stages with CT than with radiography. Compared with radiography, 59% of patients were staged higher on CT by reader 1 and 31% was staged higher by reader 2 (Table 5). Typical examples of patients with Eaton stagse I-IV on CT are shown in Fig 3.

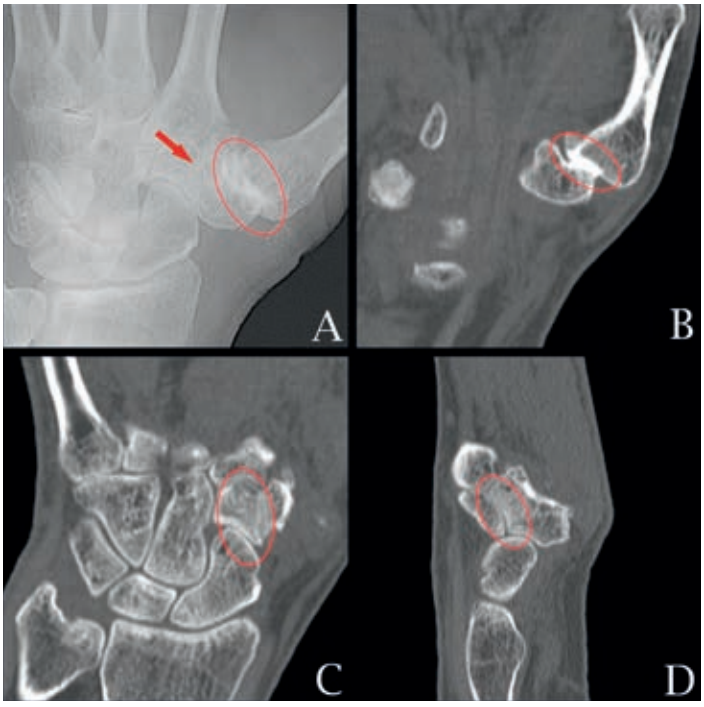

Fig. 1 Example of a patient with CMC1 OA in which STT OA was only detected with CT and not with radiography. A: The radiograph shows joint space narrowing, subchondral sclerosis and subluxation at the CMC1 joint (circle), but the trapezium-trapezoid joint is difficult to asses (arrow). B: These features in the CMC1 joint (circle) are also clearly visible on CT. C-D: Additionally, joint space narrowing is visible between the trapezium and the trapezoid (circles) on a coronal (C) and sagittal (D) image

Table 4. CT and radiography scores by both readers. The numbers indicate the number of patients with that score. A description of each score is provided in the materials & methods section.

	Reader 1								Reader 2							
	CT				CR				CT				CR			
score given by reader:	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
CMC1 (n=30)																
Joint space narrowing	6	7	17	0	14	9	7	0	4	14	9	3	8	13	9	0
Osteophytes	2	6	22		3	14	13		2	7	21		5	12	13	
Subchondral sclerosis	0	30			12	18			6	24			13	17		
Bone Cyst	17	13			27	3			13	17			24	6		
Erosion	27	3			30	0			30	0			30	0		
Subluxation (mean)		38%				23%				34%				22%		
STT (n=29)																
Joint space narrowing	16	3	10		23	3	3		12	5	12		19	1	9	
Osteophytes	16	5	8		23	6	0		13	7	9		21	4	4	
Subchondral sclerosis	11	9	9		20	5	4		29	0	0		20	1	8	
Bone Cysts	15	3	11		26	0	3		15	3	11		25	0	4	
Erosion	26	1	2		27	1	1		16	1	12		29	0	0	

CMC1 = first carpometacarpal joint, STT = scapho-trapezio-trapezoidal joint, CT = computed tomography,
CR = conventional radiography, ICC = intraclass correlation coefficient, OA = osteoarthritis

Table 5. Cross tabulation of the Eaton stage for each patient using CT and radiography for both readers.

Reader 1		**CT**				**Total**
		1	**2**	**3**	**4**	
CR	1	0	1	1	1	3
	2	2	1	3	6	12
	3	0	1	2	5	8
	4	0	0	0	6	6
Total		2	3	6	18	29

Reader 2		**CT**				**Total**
		1	**2**	**3**	**4**	
CR	1	2	1	1	1	5
	2	0	2	2	2	6
	3	0	0	5	2	7
	4	0	0	1	10	11
Total		2	3	9	15	29

CR = conventional radiography, CT = computed tomography

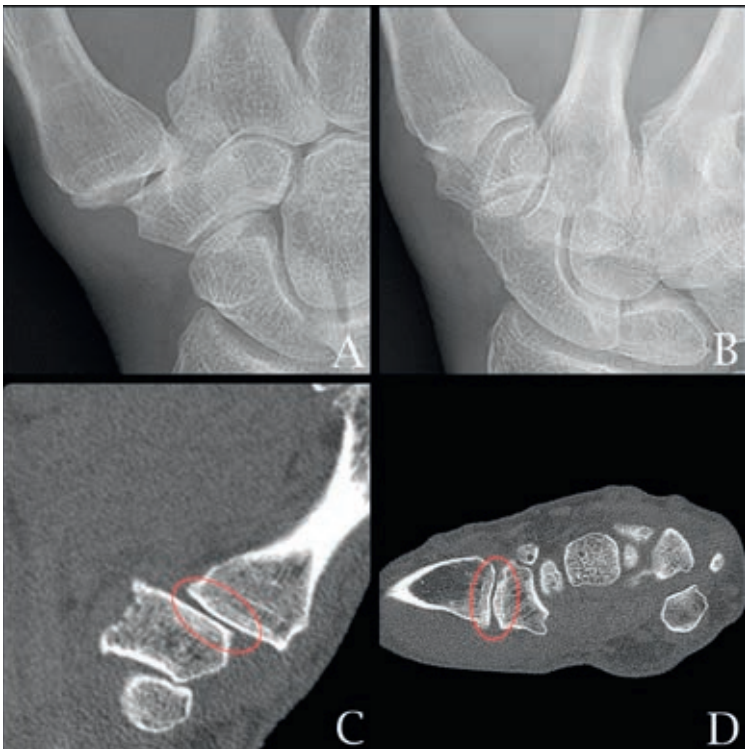

Fig. 2 Example of a patient in which both readers scored non-OA of the CMC1 joint with CR, but OA with CT. A-B: The CMC1 joint space show some subluxation, beginning osteophytes, but no JSN, so according to definition no OA. C-D: On the CT the subluxation is more prominent, and the focal joint space narrowing (circles) in the CMC1 joint is visible on the coronal (C) and saggital (D) images.

Discussion

Our data show that CT has a good inter-reader reliability in determining thumb base OA, and that CT detects more CMC1 and STT OA in patients with clinically suspected OA than radiography.

The inter-reader reliability of CT was high for CMC1 OA, STT OA and the Eaton stage. Reliability of radiography was, however, moderate. As the three-dimensional surfaces of the joint can be visualized more detailed with CT and its multi-planar reconstructions, it was expected that the reliability of CT would be higher than that of radiography.

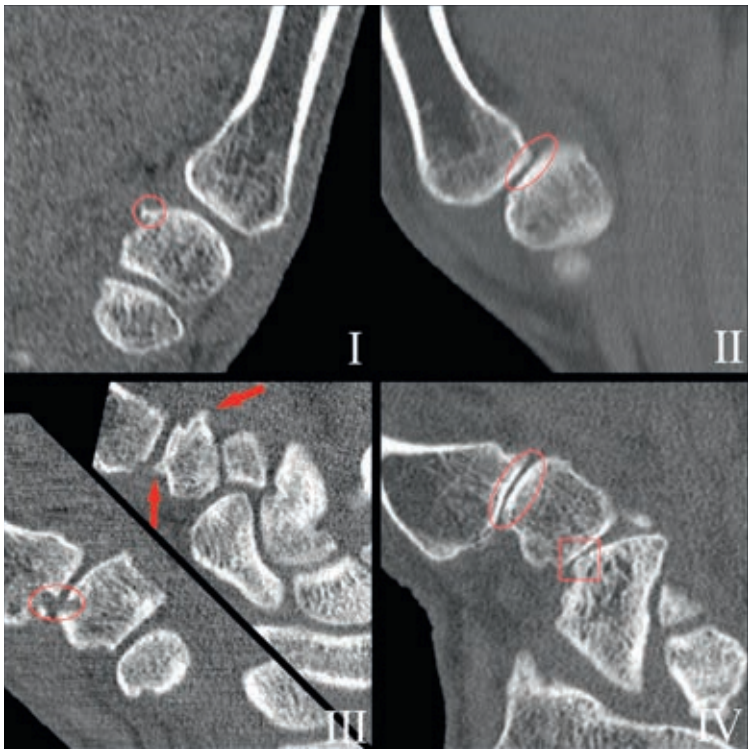

Fig. 3 Examples of Eaton stages on CT. Stage I: There is no joint space narrowing or subluxation, only a small osteophyte is visible (circle). Stage II: Focal joint space narrowing is present. Stage III: There are erosions (circle), osteophytes larger than 2 mm (arrows), and (limited) JSN. Note that the STT joint space is normal. Stage IV: There is evident JSN between trapezium and metacarpal bone (circle) and between the trapezium and scaphoid (square)

The reliability of the radiographical Eaton stage in our study is in agreement with those of previous studies,[15-17] but our reliability of CT Eaton stage was higher than that reported in a recent study (κ=0.02-0.038).[18] In that CT study, the authors report that their reliability was low because the complicated Eaton and Glickel system was scored by their readers without prior training or experience. Our reliability was probably higher because we defined and scored each separate feature of the scoring system, defined which features should lead to which score, and organized a training session.

We found that CT detected more patients with CMC1 and STT OA than radiography, and consequently higher Eaton stages were scored with CT. While reader 1 detected twelve additional STT OA patients with CT, reader 2 only detected five additional patients. The high reliability results from CT, however, suggests that there was no real difference in OA detection with CT, but that the readers missed these patients with radiography.

The decision to operate on a patient is mostly determined by clinical symptoms and the results of previous therapy. However, at present, selection of the surgical technique is strongly dependent on the personal preference of the surgeon. For example, most US hand surgeons (62%) would treat patients with Eaton stage III with a trapeziectomy with LRTI,[19] while the most preferred treatment in this situation by Dutch colleagues was hemitrapeziectomy.[16] CT can be beneficial for those clinicians who prefer to treat their patients with hemitrapeziectomy, CMC arthrodesis or joint replacement procedures, since it is often not possible to evaluate the STT joint surgically during these procedures. Therefore, it is important to have ruled out STT OA before the operation. The increased detection of STT OA with CT may improve treatment selection. In clinical practice CT could therefore be indicated for those patients who are eligible for thumb base surgery and who showed no radiographical OA in the STT joint.

Multiple systematic reviews examined the optimal surgical technique for CMC1 OA, and concluded that there is insufficient evidence to determine a superior operating technique in terms of patient outcome.[2-4] These reviews and almost all of the studies included, did not take into account the presence or absence of STT OA or the Eaton stage. As described by Eaton in 1987, patients with different Eaton stages will probably benefit from different types of surgery.[13] Wajon et al. therefore advised future studies to group patients into Eaton stages to determine the most appropriate procedure for each stage.[4] As CT imaging may be more precise in determining the Eaton stage than radiography, it could improve the detection of Eaton stage-specific treatment effects in future surgical trials.

This study has limitations. As this was a retrospective study, we could only collect limited data. For example, it would have been interesting to compare our results with intra-operative findings in patients who had surgery. However, the severity of osteoarthritis was mostly not documented in the surgical reports. Selection bias may be present, as we do not know the exact reason for referral for each patient. All the included patients however, were referred from our hand surgery outpatient clinic, and these patients are usually only referred when they are suspected of having severe symptomatic thumb base OA eligible for surgery. The results might have been different if more patients with less severe thumb base OA (Eaton stages I and II) had been included.

From our results, we do not know how many patients were false-positives or false-negatives on CT. In future studies, it may therefore be valuable to compare the two imaging modalities with a true reference standard, e.g., arthroscopy. While it is not a standard procedure, both the CMC1 and the STT joints are assessable by surgeons skilled in arthroscopy,[20-23] although the joint space between trapezium and trapezoid might be difficult to assess with arthroscopy.

In conclusion, CT had a higher inter-reader reliability and detection rate for both CMC1 and STT OA than radiography. As surgical treatment selection of thumb base OA depends on the presence of pathology in the CMC1 and STT joints, CT may improve treatment selection and surgical planning.

Acknowledgements
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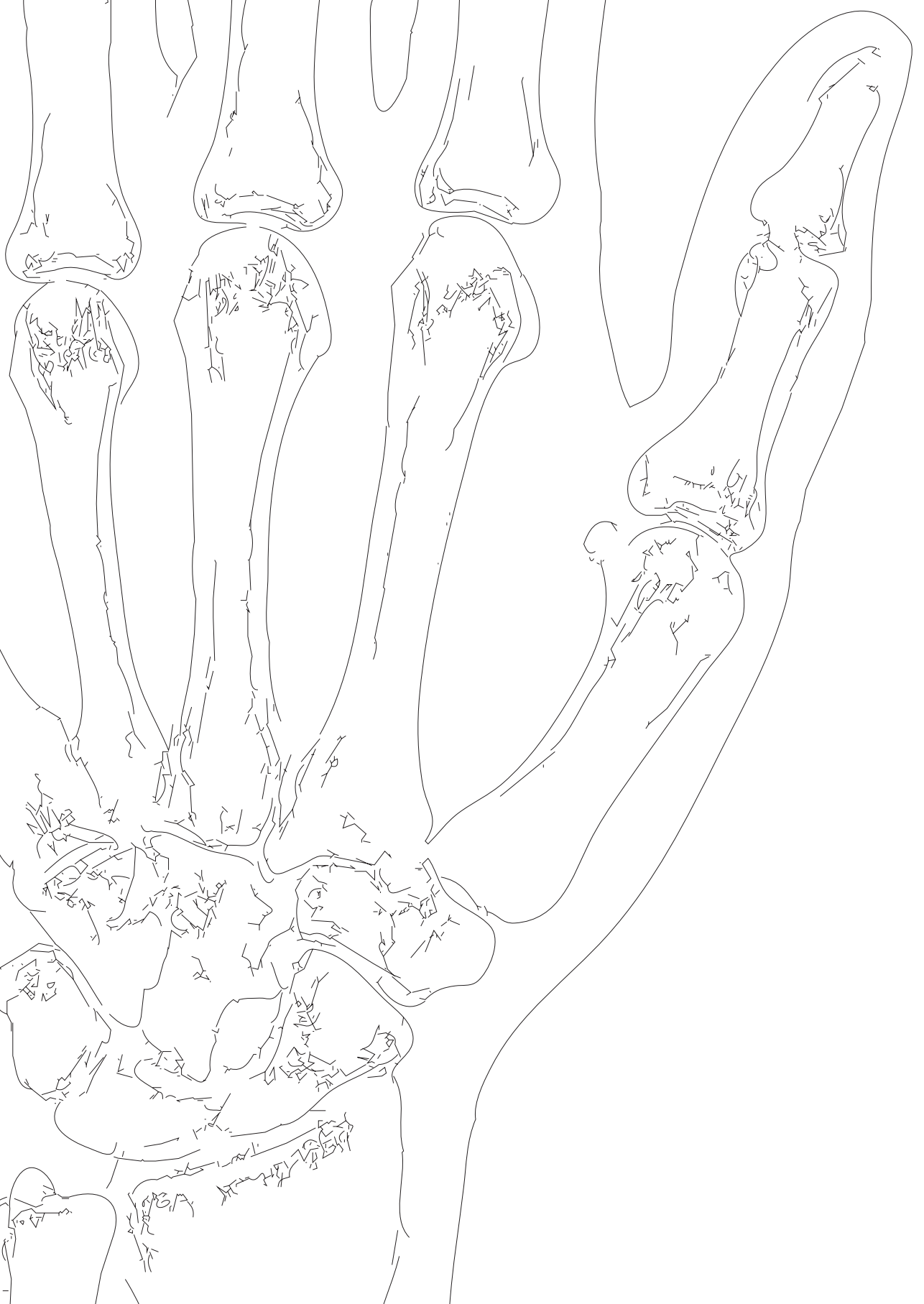

Chapter 4

Accuracy of MRI for cartilage loss in severe osteoarthritis of the first carpometacarpal joint: a comparison study with histology.

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Abstract

Background Magnetic resonance imaging (MRI) is increasingly used for research in hand osteoarthritis, but imaging the thin cartilage layers in the hand joints remains challenging. We therefore assessed the accuracy of MRI in detecting cartilage loss in patients with symptomatic osteoarthritis of the first carpometacarpal (CMC1) joint.

Methods Twelve patients scheduled for trapeziectomy to treat severe symptomatic osteoarthritis of the CMC1 joint underwent a preoperative high resolution 3D spoiled gradient (SPGR) MRI scan. Subsequently, the resected trapezium was evaluated histologically. The sections were scored for cartilage damage severity (Osteoarthritis Research Society International OARSI score), and extent of damage (percentage of surface area). Each MRI scan was scored for the area of normal cartilage, partial cartilage loss and full cartilage loss. The percentages of the total surface area with any cartilage loss and full-thickness cartilage loss were calculated for both MRI and histology.

Results MRI and histology both identified large areas of overall cartilage loss. The median (IQR) surface area of any cartilage loss on MRI was 98% (82%-100%), and on histological assessment 96% (87%-98%). However, MRI underestimated the extent of full-thickness cartilage loss. The median (IQR) surface area of full-thickness cartilage loss on MRI was 43% (22%-70%), and on histology 79% (67%-85%). The difference was caused by a thin layer of high signal on the articulating surface which was interpreted as damaged cartilage on MRI but which was not identified on histology.

Conclusions 3D SPGR MRI of the CMC1 joint visualizes overall cartilage damage, but underestimates full-thickness cartilage loss in patients with advanced osteoarthritis.

Introduction

Osteoarthritis (OA) of the hand is the most prevalent disease of the hand joint, which can lead to pain and functional impairment. The disease is characterised by cartilage loss, subchondral bone changes and inflammation of the synovium. Despite the fact that only changes of bone are directly visible on conventional radiography (CR), and that joint damage on CR is only weakly associated with symptoms,[1] it is the most widely used imaging method for assessing structural changes in hand OA in both clinical practice and clinical trials.[2, 3] Magnetic resonance imaging (MRI) is gaining popularity in hand OA studies[4, 5] as it depicts bone, cartilage, and soft tissue changes, and images the complete joint in multiple planes. As a result, MRI has given us new insights into hand OA such as the involvement of collateral ligaments,[6, 7] the high prevalence of synovitis,[8] and significant associations of joint pain with bone marrow lesions (BML) and synovitis. [9, 10]

MRI of cartilage in hand OA has yet been less well-explored, yet accurate cartilage assessment would be a valuable addition to other pathological change detected by MRI in the assessment and follow-up of the whole joint in hand OA. In studies of knee OA, quantification of cartilage using MRI is often an outcome measure in clinical trials, but cartilage imaging in the small joints of the hand is more challenging, as smaller voxel sizes are needed to depict the thin cartilage layer. Previous studies have reported that reliable quantitative evaluation of the cartilage layer in the small joints of the hand can be performed using conventional MRI and small dedicated coils.[11, 12] While in-vivo cartilage quantification with MRI in knee OA correlates well with histological findings,[13, 14] to our knowledge, there are no reports in the literature of a comparison between in-vivo MRI cartilage assessment of hand joints and histology. As surgery in hand OA is only regularly performed for treatment of thumb base OA, comparison between MRI and histology is only feasible in patients with symptomatic thumb base OA.

The aim of this study was therefore to quantitatively compare MRI-detected cartilage loss in patients with OA in the first carpometacarpal (CMC1) joint with histology.

Methods

Patients

We recruited 20 symptomatic patients who had been scheduled for trapeziectomy or hemitrapeziectomy to treat OA in the CMC1 joint. From April 2010 until October 2011 consecutive eligible patients at a University hospital and two teaching hospitals in the Netherlands were invited to participate in the study. The indication for surgery was based on severe pain and/or loss of function. Prior to surgery, patients underwent MRI and functional assessment of the thumb. Patients with previous surgery to the thumb base, or patients with contra-indications to MRI scanning were excluded. Patients were operated by their own treating hand surgeon. Additionally two healthy controls were included for comparison of MRI images only. This study was approved by the local ethics committees of the participating hospitals. All patients provided written informed consent prior to the investigation.

MRI acquisition

MR images were obtained using 3.0T scanners (GE HD and GE Discovery MR750, GE healthcare, Milwaukee, Wisconsin). Patients were placed in the prone position with the arm extended above the head, the hand placed in the center of the magnet, and the thumb fully extended on a custom-made platform to stabilize and immobilize the hand. A custom-made 4.0 mm loop coil was placed on the dorsal side of the CMC1 joint and taped to the hand. Sagittal 3D fast spoiled gradient (SPGR) sequences with fat saturation (FS) were obtained with a spatial resolution of 0.1 by 0.2 mm (echo time (TE) minimal; field of view (FOV) 3-4 cm; frequency 256-320; phase 128-224; slice thickness 0.7 mm; bandwidth 15.6 kHz; two signals acquired). Proton density weighted fast recovery fast spin echo (FRFSE) sequences were acquired in the coronal and sagittal plane (repetition time (TR) 2400; TE 30; echo train length (ETL) 6; FOV 3-4 cm; frequency 256-320; phase 128-160; slice thickness 1.0 mm; bandwidth 15.6 kHz; three signals acquired). T2 weighted FRFSE sequences with fat saturation were obtained in coronal direction (TR 3000; TE 68; ETL 6; FOV 4 cm; frequency 192; phase 128; slice thickness 2.0 mm; bandwidth 15.6 kHz; four signals acquired). The scanning acquisition time was 25 minutes.

MRI evaluation

Reading exercises were performed on the MR images from patients of whom histology was not possible. In the first exercise we tested a scoring method for cartilage assessment similar to the MRI osteoarthritis knee score (MOAKS).[15] However, we decided not to use this scoring method as the tested cases all received the highest score possible, even though clear differences in cartilage damage were visible on the images. In the second exercise we tested the currently used scoring method, which uses the same definitions as MOAKS for identification of partial-thickness cartilage loss and full-thickness cartilage loss, but the extent of the cartilage damage is not scored on an ordinal scale from 0-3, but on a ratio scale from 0-100%. After the second exercise we decided to score a thin layer of one or two voxels of high signal intensity (comparable to cartilage) on the bony surface area as partial-thickness loss and not as full-thickness loss. All images were evaluated by two musculoskeletal radiologists and a hand surgeon (GM, EO and HC) together in consensus. The readers were blinded to patient data, clinical data, histological findings and other imaging results. The anonymized images were read using the open source software ClearCanvas Workstation (ClearCanvas Inc., Toronto, Canada). Using all available sequences, the articular surface of the trapezium was evaluated for grade of cartilage loss as normal cartilage thickness, partial-thickness loss of cartilage, or full-thickness loss of cartilage. On each 0.7 mm SPGR FS slice the readers indicated the surface corresponding to each grade. Measurements from all slices per patient were summed to compute the total articular surface, total area of normal thickness, total area of partial-thickness loss, total area of full-thickness loss, and total area of any thickness loss (full and partial thickness loss combined). Percentages of these were calculated for comparison with histological findings. The image quality of the SPGR images was scored as either low, sufficient for evaluation, or good. Low means that there is a reasonable chance that error was introduced because of low image quality.

The CMC1 joints were scored for presence or absence of osteophytes, erosions/cysts and subluxation. Osteophytes were defined as abnormal bone formation in the peri-articular region on the SPGR and PD images. Erosions/cysts were considered as a single feature and were defined as sharply marginated bone lesions with increased signal intensity on SPGR images, and intermediate signal on PD images, which were visible in two planes. The joint was considered to be

subluxated when 33% or more of the metacarpal surface area was not aligned with the trapezial surface area in the coronal or sagittal plane. Synovitis was not scored as we did not use a contrast agent.

Tissue preparation

During surgery the trapezium bone was extracted as a whole or in multiple parts. If the trapezium was not extracted in one piece, care was taken that the articular area of the trapezium facing the 1st metacarpal bone was kept intact by splitting the trapezium horizontally leaving at least 5 mm of the distal trapezium intact. The resected trapezium was fixed in neutral buffered 10% formalin in the operating room. Trapezium bones were decalcified in formic acid. Large decalcified specimens were cut in half, and all samples were embedded in paraffin. Each millimeter, a five µm thick sections was cut in the sagittal direction of the bone, mounted and stained with thionin.[16]

Histology

All histological sections were scored for cartilage damage by a trained researcher (MS). To determine the reproducibility of these scores, 10 patients were also scored by GvO, an experienced cartilage researcher. The scorers were blinded to the results of the MRI evaluation. All available sections were scored for severity and extent of cartilage damage. Severity of cartilage damage was scored according to the semi-quantitative grading and staging system devised by the Osteoarthritis Research Society International (OARSI) working group.[17] Grade, defined by depth of cartilage damage, and stage, defined by the horizontal extent of cartilage damage were assessed. The OARSI grading system consists of six grades that describe increasing depth of cartilage damage. Grades 1-4 are subsequently described as: grade 1, edema or cell changes with an intact surface; grade 2, small surface discontinuities; grade 3, vertical fissures; and grade 4, delamination of the superficial zone. For comparison with MRI we defined grades 1-4 together as "cartilage with (near) normal thickness". Grade 4.5 is described as mid-zone excavation, and was defined by us as "partial thickness loss of cartilage" for comparison with MRI. Grades 5 and 6 are described as: grade 5, complete erosion of hyaline cartilage to the level of mineralized bone; and grade 6, deformation and change in the contour of the articular surface. For comparison with MRI we defined grades 5 and 6 together as "full-thickness cartilage loss" (see Fig. 1 for examples).

Each histological section was scored for the amount of the articular surface that corresponded to each grade in decimals of percentage (i.e. 0%, 10%, 20% etc). The sum of the scores for each section had to be 100%. If there was no identifiable articular surface in a section, then no score was assigned to that section. Finally, all section scores per patient were averaged to calculate the total percentage area of (near) normal cartilage thickness, partial-thickness cartilage loss, and full-thickness cartilage loss.

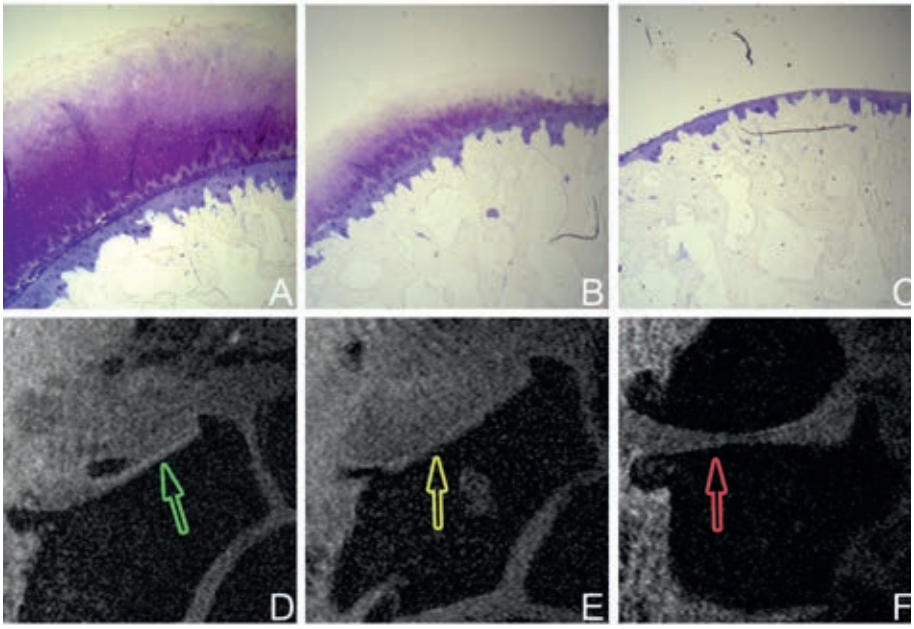

Figure 1. Example images of histological grading (A-C) and MRI scoring (D-F), all in one patient. The arrows in D-F point to the locations shown in A-C. A,D: Cartilage of (near) normal thickness. B,E: Partial thickness loss of cartilage. C,F: Full thickness loss of cartilage. Due to subluxation in the joint, the metacarpal base is not seen in D and E. Image quality of the MR images was rated as good.

Statistical analysis

Descriptive statistics were used to describe the results of MRI and histological evaulation. Inter-reader reliability of the histology scores was calculated using the intraclass correlation coefficient (ICC). The ICC values were calculated as two-way random, single measures, absolute agreement.[18]

Results

Patients

Twenty patients and two healthy controls were included in the study. In five patients, the trapezium was very deformed and could not be extracted without severely damaging the distal articular surface. We were therefore unable to obtain histological specimens from these patients. During histological analysis of the 15 specimens, we noticed that a considerable part of the articular surface was missing in the specimens of three patients. These patients were excluded from further analysis. The MRI scans of the excluded patients were used for training and calibration of the MRI score.

The final patient group therefore consisted of 12 patients; two were male and 10 were female, with an average age of 60 (range 46-77) years. The median number of days between MRI and surgery was 8 (range 1-39). Mean grip strength (SD) was 23 (11) kg, and mean pinch strength (SD) was 3.8 (0.9) kg. Self-reported pain assessed by visual analog score (possible range 0-100) varied widely between patients. The median (IQR) pain score at rest was 19 (5-31), and the median pain score during thumb activity was 57 (37-67)

MRI

The image quality in eight out of our twelve patients was adequate or higher, but was low in the other four patients. All patients had one or more osteophytes at the trapezium. All but one patient had cysts and/or erosions on the trapezium, and seven out of twelve CMC1 joints were malaligned or subluxated. Overall cartilage damage was severe (table 1). All patients had at least one small area with full-thickness cartilage loss. Five out of twelve patients did not have any remaining area of cartilage of normal thickness. The median (IQR) surface area of trapezial cartilage damage was 98% (82%-100%). The percentage area with full-thickness cartilage loss was 43% (22%-70%). The image quality in both healthy controls was good, and they both had normal cartilage layers, without any damage.

Table 1. Histological and MRI scoring results for each individual patient. For both methods the percentages of the articular surface are shown that were normal, had partial cartilage thickness loss, or had full cartilage thickness loss, as well as the MRI image quality.

Patient	Histology			MRI			
	Normal	Partial thickness loss	Full thickness loss	Normal	Partial thickness loss	Full thickness loss	Image Quality
1	0	0	100	28	45	27	adequate
2	6	9	85	0	44	56	low
3	0	25	75	0	77	23	adequate
4	2	10	88	17	68	15	adequate
5	22	30	48	37	54	9	good
6	0	15	85	14	15	71	adequate
7	4	17	79	2	31	68	adequate
8	25	22	53	35	22	43	good
9	10	31	59	19	61	20	adequate
10	1	18	82	0	74	26	low
11	3	11	86	0	26	74	low
12	16	10	74	0	7	93	low

Histology

The mean number of histological sections acquired from each trapezium containing articular surface was 10 (range 9-14). Ten patients were scored independently by both readers. The inter-reader reliability for the detection of any cartilage loss over all scored sections containing articular surface (n=100) was ICC=0.70 (95%CI= 0.53-0.81), and the inter-reader reliability over all sections for full cartilage loss was ICC=0.84 (95% CI= 0.76-0.90). Overall cartilage quality was poor (table 1). No patient had any normal healthy cartilage remaining. The best cartilage observed had a histological grade of 3, with vertical fissures into the mid zone and depletion of matrix staining in the upper half of the cartilage. In eleven out of twelve patients there was complete erosion of the cartilage on more than half of the articulating surface. The median (IQR) surface area of trapezial cartilage damage was 96% (87%-98%). The percentage area with full-thickness cartilage loss was 79% (67%-85%). After analysis, the largest differences between histological scores were in areas near osteophytes, which were sometimes partly covered with cartilage (fig2). For scoring purposes osteophytes were excluded from the articular surface, and the cartilage formed on top of osteophytes was ignored. The lack of a clear anatomical landmark

between the original articular surface and osteophytes was the main cause of variations in scoring, as it was inconsistently scored where the articular surface stopped and the osteophyte began.

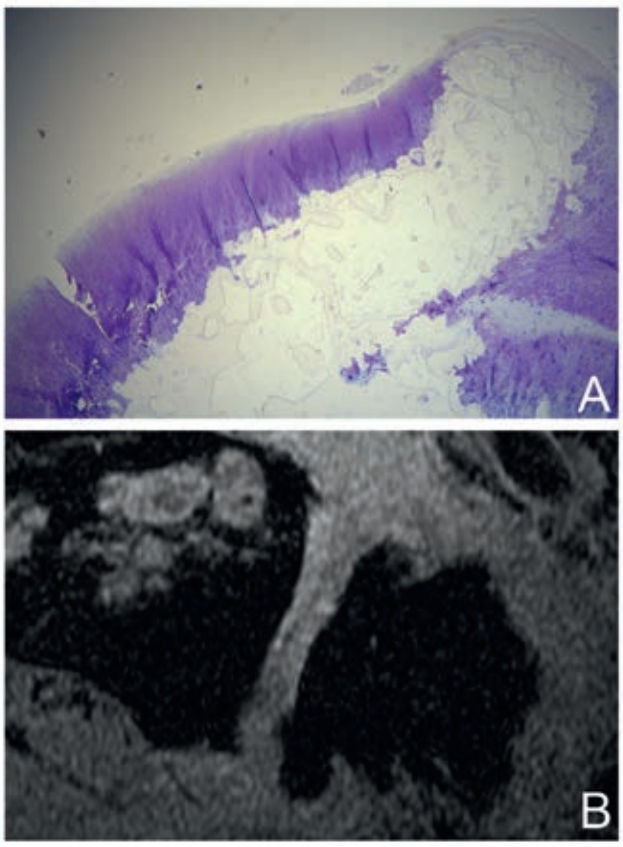

Figure 2. A: Part of a histological section of patient 9. On the right side is an osteophyte visible. The remaining cartilage continues partly on to the articulating surfaces of the osteophyte. B: SPGR image of the same patient, where the same osteophyte is on the upper side of the trapezium. Cartilage is visible in the centre of the articulating surface of the trapezium and continuing partly on the osteophyte, comparable with the histological image.

MRI vs histology

Both MRI and histology identified large areas of cartilage loss, with histology identifying slightly larger areas compared with MRI. The individual scores for each patient obtained by the two modalities are represented in Figure 3. Histology identified substantially larger areas with full-thickness cartilage

loss than MRI (figure 4). Retrospective direct comparison of SPGR images and histological sections showed that the difference between MRI and histology in scoring any cartilage loss could in most cases be attributed to a thin layer of high signal intensity on the bony surface, which was scored as cartilage on MRI, but was not identified as cartilage on histological sections. (Figure 5)

MRI image quality was scored as low in 4 out of 12 patients due to motion artefacts and inability to place the surface coil in the optimal position because of disfigurement of the joint. However we did not find a relationship between image quality and discrepancies between MRI and histological evolution.

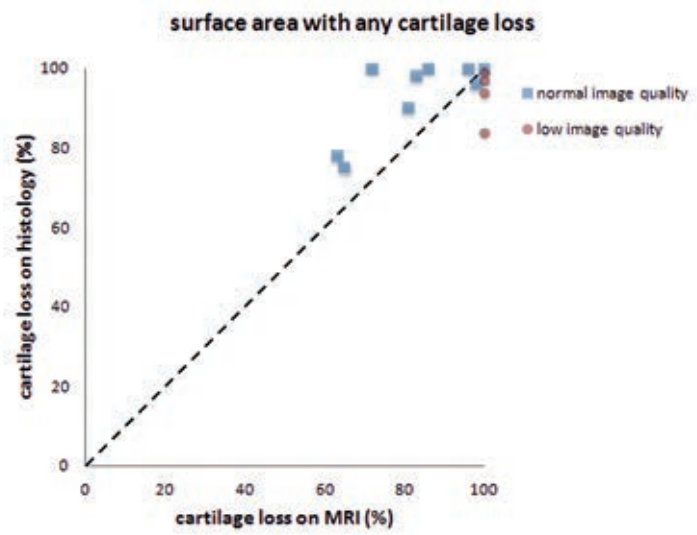

Figure 3. Scatterplot of the relative area of the trapezial articular surface with any cartilage loss. Each dot represents one patient measured by MRI and histology. Perfect agreement would result in all dots on the diagonal line.

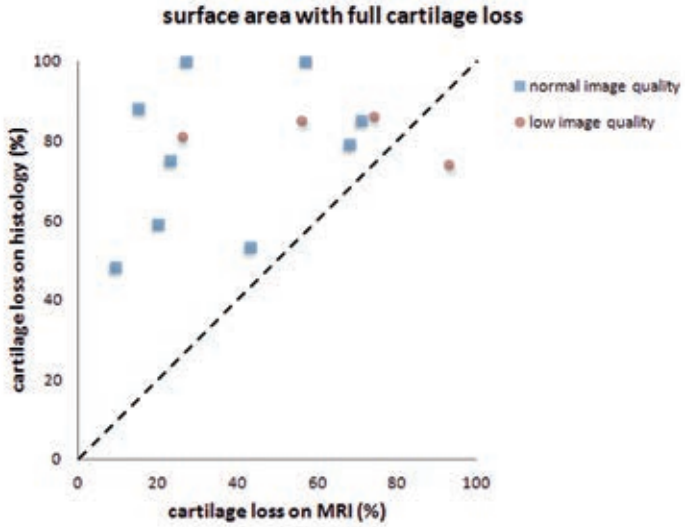

Figure 4. Scatterplot of the relative area of the trapezial articular surface with full-thickness cartilage loss. Each dot represents one patient measured by MRI and histology. Perfect agreement would result in all dots on the diagonal line.

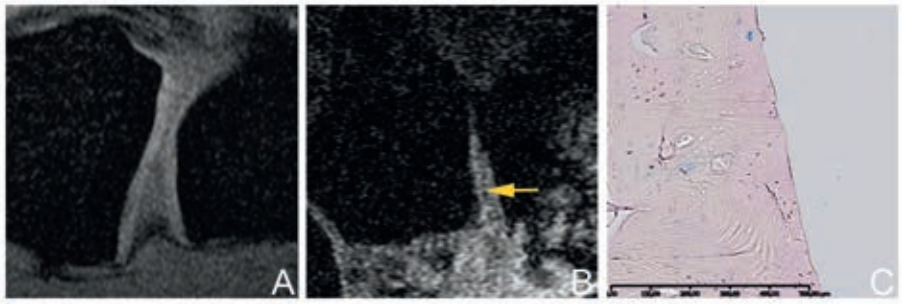

Figure 5. A: Zoomed in SPGR image with fat saturation of the CMC1 joint of a healthy volunteer, showing a thick cartilage layer with high signal intensity. B: Image of the CMC1 joint of patient 1. The arrow points to a thin band of high signal intensity which was scored as partial thickness loss (some cartilage still seems remaining). The image quality was rated as adequate. C: Magnification view of a histological section of patient 1, each tick on the scale bar representing 50 micrometer. The whole articular surface area of this patient looked like this, showing nothing but bare bone.

Discussion

Our study showed that the overall extent of cartilage loss in small hand joints could be detected with 3D SPGR MRI images. However, MRI underestimated the area of full-thickness cartilage loss.

Previous studies have shown that the SPGR sequence is an accurate sequence to image knee joint cartilage.[19, 20] While it has been shown that SPGR may overestimate cartilage damage in early OA due to magnetic field inhomogeneity artefacts, a considerable underestimation of cartilage damage has not been reported. In previous studies assessing the accuracy of detection of cartilage defects and/or cartilage volume in the knee using MRI, the patient group either consisted of patients with relatively little damage,[19, 21-23] or the areas with severe cartilage damage were not analyzed.[14, 24] In the studies of patients with knee OA and relatively little cartilage damage, SPGR MRI had high sensitivity and specificity for detecting cartilage lesions in comparison with arthroscopy[19, 23] and very good correlation with cartilage thickness on histology.[22]

The underestimation of full cartilage loss with MRI was caused by thin layers of high signal on the articular surface that were visible on SPGR MRI, which were interpreted as thin layers of damaged cartilage. On retrospective comparison of the acquired SPGR and PD images and histology, the thin layers of high signal intensity on SPGR images were not identifiable on the PD images, and histological examination showed bare bone at the corresponding locations. These thin lines of high signal intensity adjacent to subchondral bone have previously received little attention in knee OA, as the line is very thin compared to the thicker knee cartilage, and has been counted as full-thickness cartilage loss in MRI knee OA studies.[25] The same kind of thin lines were previously described by Yoshioka et al.[26] in healthy volunteers on the posterior region of the femoral condyle within normal cartilage. The origin of this line is unclear. In our study it may have been caused by an artefact, but we cannot exclude the possibility that it represents a real anatomical substrate such as a loose-lying layer of thin soft tissue, which may be lost during histological preparation.

We recognize that our study has limitations. First, the study design required patients to be scheduled for trapeziectomy, limiting the spectrum of disease severity. However, this is the only feasible method for acquiring in vivo histological specimens of cartilage from the small joints of the hand. To maximize the variation in cartilage status between our subjects, we included all patients undergoing trapeziectomy for treatment of pain and functional impairment, irrelevant of the severity of radiographical osteoarthritis. While we expected to also include some patients with mild cartilage damage, all our patients had severe cartilage damage on histology. Patients with milder OA or pre-clinical OA

will have less damaged cartilage, but as mild thinning of the cartilage was also detectable in the less damaged areas of the joints in our patients, we expect that the imaging method can be used in patients with less severe OA.

The second limitation concerns image quality. Four out of twelve of our MRI examinations were of low image quality, which may have impacted the MRI results of these four patients. Our coil was a loop coil with a diameter of 40 mm, which was optimal for imaging the CMC1 joint in healthy volunteers. However, in our patients with CMC1 OA, the distance between the coil and the center of the joint was larger because of the presence of osteophytes and subluxation, and the inability of patients to hold the thumb in full extension for optimal coil placement, reducing signal-to-noise ratio. Motion artefacts also had a big impact on image quality. Improvements in either patient/coil positioning or the coil itself should be able to increase overall image quality.

The third limitation concerns the chosen MRI pulse sequence. We chose to assess cartilage with a 3D SPGR fat-suppressed pulse sequence for its high in-plane resolution with thin 0.7 mm slices, to be able to detect small cartilage lesions. This pulse sequence has previously shown promising results in finger joints. [11, 27] In healthy volunteers this sequence clearly delineated high signal cartilage layers. In our study population of patients with advanced OA only and with histologically proven abnormal cartilage, the signal intensity of cartilage was lower than expected based on the MRI in healthy volunteers. Our MRI readers therefore sometimes had trouble delineating the cartilage from the joint fluid, which is a known disadvantage of this pulse sequence. [28, 29] While this will have introduced some error in the results, this was often resolved after crosschecking with the PD and T2 FSE sequences to make the distinction between fluid and cartilage. In this study we did not detect any small focal areas of cartilage loss, raising the question whether such thin slices are required to evaluate cartilage damage in advanced OA. Other pulse sequences such as Duel Echo Steady State (DESS), SPGR with iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL), and true fast imaging with steady state precession (TrueFISP) were found to have better cartilage to fluid contrast in the knee joints in healthy volunteers.[28, 29] If these sequences can be adequately optimized for the small FOV and high resolution, they may improve accuracy for detecting cartilage damage in the small joints of the hand.

Our MRI scoring method worked for a low number of patients, but is too time consuming for larger studies. We chose this method to be as accurate as possible, but would not advice it for use in larger studies; instead, either automated segmentation for detailed detection of cartilage damage or a semi-quantitative score would probably be better.

Conclusion

3D SPGR MRI of the carpometacarpal joint of the thumb is able to detect the overall extent of cartilage damage. However, in severe cartilage damage, a layer of high signal intensity on the bone can be seen on 3D SPGR MRI, which does not always correspond to cartilage on histology, and could therefore lead to overestimation of the remaining cartilage.

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Author contributions

MS contributed to the design, collected the MRI data, scored the histology, performed the analysis and drafted the manuscript. HC contributed to the design, provided part of the patients, scored MRI data, and revised the manuscript. RS, JvN and JL obtained the funding, conceived the study, helped with design, and revised the manuscript. JJ provided most of the patients and revised the manuscript. GvO contributed to design, scored the histology, and critically revised the manuscript. EO scored MRI data, and critically revised the manuscript. GM contributed to design, scored MRI data, helped with interpretation of data and helped draft the manuscript. All authors read and approved the final manuscript.

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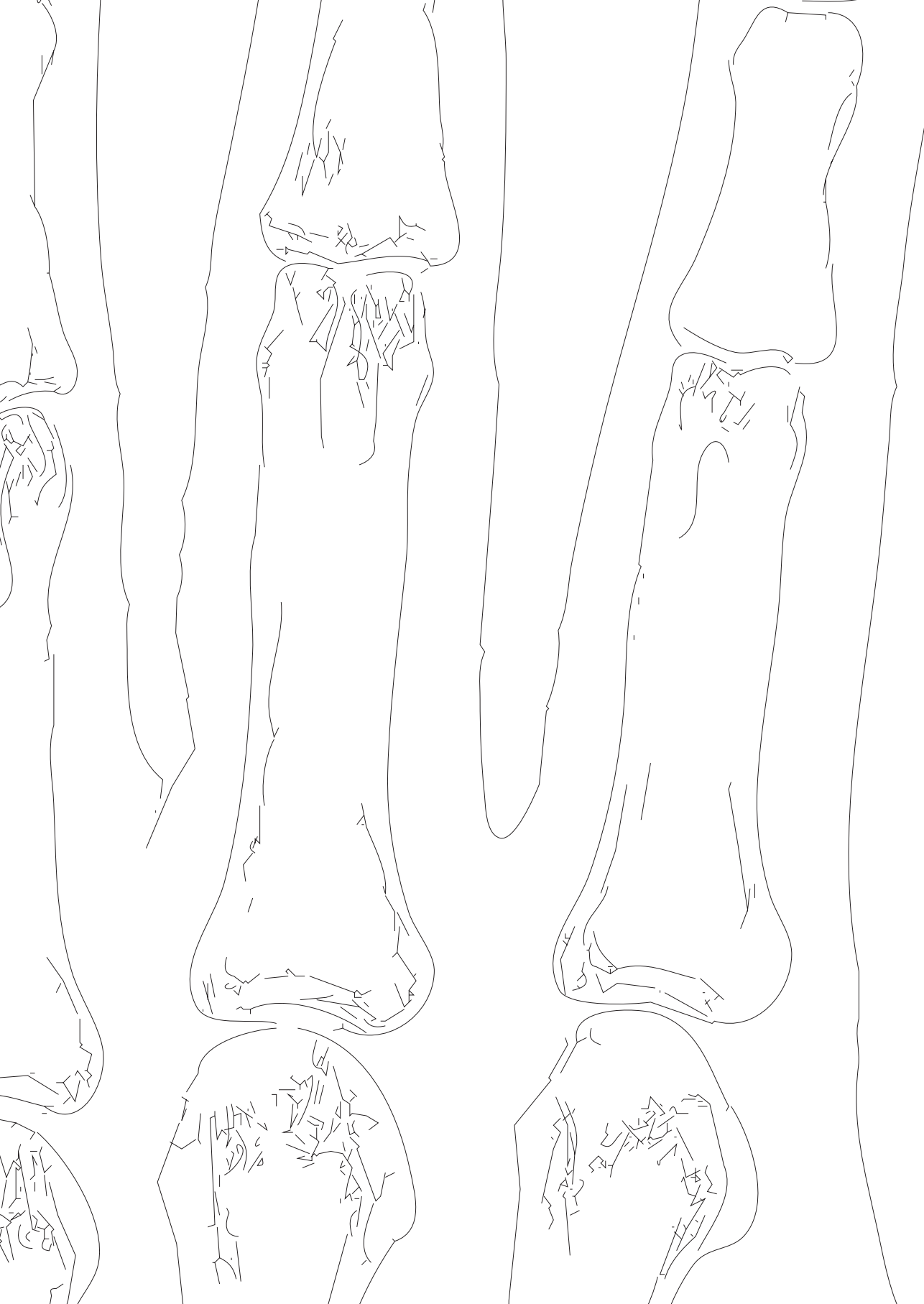


Chapter 5

Cartilage evaluation in finger joints in healthy controls and early hand osteoarthritis patients using high-resolution MRI

Michael S. Saltzherr, Galied S.R. Muradin, Ida K. Haugen, Ruud W. Selles, Johan W. van Neck, J. Henk Coert, J. Mieke W. Hazes, Jolanda J. Luime

Abstract

Objective: To compare direct evaluation of cartilage with high resolution MRI (hrMRI) to indirect cartilage evaluation using MRI inter-bone distance in hand OA patients and healthy controls.

Design: 41 hand OA patients and 18 healthy controls underwent hrMRI of the 2nd and 3rd metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. The images were read by two independent readers using OMERACT hand OA MRI inter-bone distance score (0-3 scale) and a new hrMRI cartilage score with direct evaluation of the cartilage (0-3 scale). Inter-reader and intra-reader reliability was calculated using exact and close agreement and kappa values. The prevalence of abnormal scores and agreement between methods was assessed in both hand OA patients and healthy controls.

Results: The intra- and inter-reader reliability of both scores was comparable, with exact agreement in 73-83% and close agreement in 95-100%. In hand OA patients 27% of 161 joints had both cartilage damage and loss of inter-bone distance, cartilage damage by hrMRI only was present in 20% of joints and reduced inter-bone distance only in 4% of joints. In the healthy controls, 1 of 71 joints were scored as abnormal by both hrMRI and inter bone distance scoring, 1 joint was scored as abnormal using the hrMRI cartilage score only, whereas 15% of joints had only reduced inter bone distance.

Conclusions: Direct cartilage evaluation of MCP and PIP joints using hrMRI is reliable. The higher prevalence of hrMRI cartilage damage in hand OA patients and the lower prevalence in healthy controls in comparison to evaluation of inter-bone distance suggests a better validity.

Introduction

Hand osteoarthritis (OA) is a common disease, leading to pain and functional impairment in daily activities.[1, 2] Current standard treatment options aim at symptom relief using pain medication or splinting both with limited effect. Disease modifying drugs to stop progression of hand OA are not yet available, but interest in researching these drugs for OA is increasing, and sensitive measures of structural joint damage are needed to evaluate of the effect of these drugs.

Traditionally conventional radiography has been used for the assessment of hand OA structural features, and is currently the only imaging method approved by the regulatory agencies for detecting disease modifying effects despite not being able to visualize cartilage directly.[3] Magnetic resonance imaging (MRI) has the advantage that it can depict cartilage directly and is increasingly being used as a structural outcome measure in clinical trials in knee OA.[4, 5] While MRI has contributed to increasing knowledge about the underlying mechanisms in hand OA,[6, 7] it is difficult to assess the thin cartilage layer in small hand joints using standard clinical MRI coils.

Recently, a hand OA MRI scoring system (HOAMRIS) was developed by the OMERACT MRI task force group, for which good reliability was demonstrated in both cross-sectional and longitudinal settings. [8, 9] The system is used to rate bone damage, synovial inflammation, and loss of joint space, but does not include a direct cartilage damage score, as the thin cartilage layer in small hand joints could not be accurately assessed on the MRI images used for the creation and evaluation of the OMERACT HOAMRIS.[10] However, it has been shown that with higher resolution images using dedicated MRI coils the cartilage of MCP joints can be measured reliably, [11] and it is to be expected that direct evaluation of cartilage is more accurate than indirect measurement of inter bone distance.

Hence, the aim of this study was to compare direct cartilage evaluation using high resolution MRI (hrMRI) with indirect cartilage evaluation of MRI inter-bone distance, by evaluating their reliability, and prevalence and agreement of cartilage damage in hand OA patients and healthy controls.

Methods

Participants

We included 50 patients with hand OA, of whom 19 had previously participated in the Rotterdam Early Arthritis Cohort (REACH) [12] and an additional 31 new patients from our rheumatology outpatient clinic. A flowchart is provided in Fig 1. All patients were clinically diagnosed with hand OA by a rheumatologist and were excluded if they had a clinical suspicion or diagnosis of any other rheumatic disease. To establish this diagnosis, all patients underwent at least a clinical examination and multidirectional radiographs of both hands. Patients with isolated thumb base OA without signs of OA in MCP, PIP or DIP joints were also excluded. Additionally, 20 healthy female volunteers between the age of 18 and 35 were invited. Healthy volunteers were excluded if they had any symptoms of pain, swelling or stiffness in the hand joints or if they had a previous history of hand surgery or trauma. They did not undergo clinical examination or radiography.

Patients and healthy controls were excluded from participation if they had a contraindication for MRI (e.g., pacemaker, metallic fragments in orbita), or for gadolinium contrast. Recruitment started in January 2011 and lasted until December 2012. All patients and volunteers provided written informed consent prior to the investigation. The study was approved by the local ethics committee.

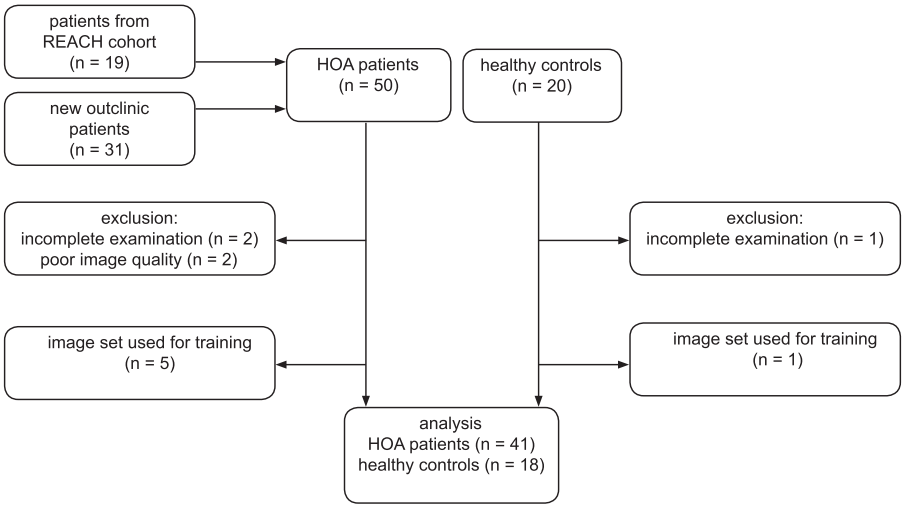
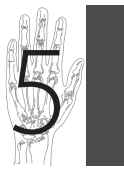


Figure 1. Flow chart of patient recruitment and inclusion.

MRI acquisition

Prior to this study, a custom-built multichannel receive coil for high-resolution finger joint imaging was created in collaboration with Machnet BV (Roden, The Netherlands). This coil was designed specifically for imaging of finger joints affected by rheumatic diseases and allowed us to scan two adjacent metacarpophalangeal (MCP) and the two corresponding proximal interphalangeal (PIP) joints in one session with high resolution on a clinical 3T MRI scanner (Discovery MR 750, GE Healthcare, Milwaukee, WI). Hand OA patients and healthy volunteers were scanned using this coil in a prone superman position. Patients were positioned comfortably using torso, head and arm supports to minimize motion artefacts. The second and third MCP and PIP joints were scanned. The entire scanning protocol consisted of a coronal proton density (PD) and sagittal fat-suppressed spoiled gradient echo (SPGR) images of each joint separately. Additional performed sequences were not further used in this study. The PD sequence was a Fast recovery Fast Spin Echo sequence with parameters: repetition time (TR) 1500; echo time (TE) 30; echo train length (ETL) 4; Field of view (FOV) 8x8 cm; matrix size 320x320; slice thickness (ST) 2mm with a 0.1 mm gap; bandwidth 41; number of excitations (NEX) 2; with no phase wrap (NPW) and tailored radiofrequency pulse (TRF) options enabled; scan time was 4 min and 28s.The SPGR was a 3D fast SPGR with parameters: minimum TR and TE; flip angle of 30; FOV 3x2.4 cm for the PIP joints and 4x3.2 cm for the MCP joints; ST 0.8mm; matrix 320x224; bandwith 16; NEX 2; with fat suppression and zero filling interpolation processing options on. Scan time per joint was 3m and 28s.



MRI scoring systems

A face-to-face meeting and following online discussions were organized to demonstrate HOAMRIS[9] to the MRI readers, modify the definitions of cartilage scoring specifically for our hrMRIs, and test the reliability. Prior to the meeting, JL identified five patients and one healthy control with different amounts of MRI pathology. MSS (radiology resident with training in reading musculoskeletal MRI), GSRM (musculoskeletal radiologist with previous RAMRIS experience) and IKH (co-developer of HOAMRIS) independently read all images. The images were read in two rounds of 3 patients each and after each round, the results were discussed to improve reliability.

Inter-bone distance was scored according to the HOAMRIS without any modification of the definition using the coronal PD images. It is scaled as: 0 = normal; 1 = loss of cartilage space without bone-to-bone contact; 2 = focal complete loss of cartilage space with bone-bone contact; 3 = cartilage space loss and bone-bone contact affecting > 50% of the articulating joint area. The hrMRI cartilage score was defined in line with the MRI Osteoarthritis Knee Score (MOAKS),[13] scoring both the size of any cartilage thickness loss and the size of full-thickness cartilage loss. A single cartilage score (0-3) was created based on these two items: 0 = no cartilage damage, 0.5 = Single focal cartilage defect <10% of surface area with abrupt edges, 1 = thinning of the cartilage layer > 10% of the surface area, without complete thickness loss, 2 = Global thinning of the cartilage layers with areas with (near) complete thickness loss, without direct bone-bone contact, 3 = Severe cartilage thickness loss with areas of direct bone-bone contact. The 0.5 grade has been removed from the tables in the results, as it was never scored. The cartilage was assessed on the high-resolution SPGR images. The MRI examinations for final analysis were independently read by both MS and GM. To determine intra-reader reliability, MS re-evaluated 10 randomly selected MRI examinations 4 months after the initial reading. A separate reader also measured the cartilage thickness and inter bone distance of all joints using a ruler tool. The measures were performed in the middle of the joint using the sagittal SPGR images.

Statistics

We present the mean values of both readers. Inter-reader and intra-reader reliability were calculated using percentage exact agreement (PEA), percentage close agreement (PCA), and a linear weighted kappa (κ_w). PEA was calculated as the percentage of joints with the exact same value by both readers. PCA was calculated as the percentage of joints with a difference of ≤ 1 between readers. Weighted kappa was interpreted as 0-0.20: poor; 0.21-0.40: fair; 0.41-0.60: moderate; 0.61-0.80: good; 0.81-1.00: very good agreement.[14] The number of joints with cartilage damage and reduced inter-bone distance was calculated, and the agreement between the two features assessed in a table.

Results

We acquired 19 MRI image sets of the dominant hand of healthy controls and 48 MRI Image sets of patients diagnosed with hand OA. The images of 5 hand OA patients and 1 healthy control were used for training and calibration. Two image sets of hand OA patients were excluded because of poor image quality. In the remaining image sets of 18 healthy controls and 41 patients, 3 joints could not be rated on the PD images and 1 joint on the SPGR images because of artefacts. Details of patient characteristics can be found in Table 1.

Table 1. Characteristics of participants in final reading

	Hand OA patients (n=41)	Healthy controls (n=18)
Female, n (%)	36 (85)	18 (100)
Age, mean (range) yrs	59 (40-80)	25 (18-31)
Right hand scanned, n (%)	32 (78)	12 (67)
ACR criteria hand OA, n (%)	31 (76)	0 (0)
AUSCAN pain, mean (SD) [0-500]	201(114)	.
AUSCAN physical, mean (SD) [0-900]	419(222)	.
Hand grip strength of scanned hand, mean (SD) kg	22.9(8.0)	.

ACR, American College of Rheumatology; AUSCAN, Australian/Canadian Hand Index

The inter-reader and intra-reader PEA and PCA values of both scores were comparable (Table 2). The inter-reader reliability kappa score of the hrMRI cartilage score was significantly higher than for inter-bone distance. The intra-reader reliability was similar for both features. Readers agreed in 170/233 joints on the inter bone distance scale. They agreed on normal inter-bone distance in 142 joints, reduced inter-bone distance grade 1 in 25 joints and grade 2 in 3 joints. Most discrepancies in the inter-bone distance score were between grade 0 (normal) and grade 1 (narrowing without bone-bone contact) (50 out of the 63 discrepant joints). In these instances reader 2 scored higher in 38/50 discrepant joints. 24 of these discrepancies were in healthy controls. Readers agreed in 176/234 joints on the hrMRI cartilage score. They agreed on normal cartilage in 137 joints, cartilage damage grade 1 in 21 joints, grade 2 in 16 joint and grade 3 in 2 joints. The observers disagreed the most on grade 0 (normal) versus grade 1 (thinning of cartilage >10% of surface) and grade 1 versus grade 2 (thinning with complete cartilage loss without bone-bone contact) in 23 joint and 22 joints, respectively. Reader 1 scored higher in 42/45 discrepancies.

Table 2. Reliability of cartilage scores

	PEA (%)	PCA (%)	κ_w (95% CI)
Inter-reader reliability			
Inter bone distance (n=233)	73	97	0.39 (0.27-0.51)
High-res cartilage score (n=234)	75	95	0.59 (0.53-0.66)
Intra-reader reliability			
Inter bone distance (n=36)	83	97	0.59 (0.32-0.86)
High-res cartilage score (n=39)	77	100	0.62 (0.42-0.82)

n = number of assessed joints; PEA, percentage exact agreement; PCA, percentage close agreement; $\kappa_{w,}$ linearly weighted kappa; CI, Confidence interval

According to the hrMRI cartilage score 64/81 PIP and 21/81MCP joints had cartilage damage, including 27 PIP and 5 MCP joints with areas of full-thickness loss. Compared to the inter bone distance score, with hrMRI an additional 33 joints were scored as abnormal in OA patients, and 8 less joints in healthy controls were scored as abnormal (Table 3).

Table 3. Reclassification table of inter bone distance to the high-resolution cartilage score

	No cartilage damage	Thinning of cartilage layer >10% of surface area, without complete loss	Thinning of cartilage with areas with complete cartilage loss Without bone-bone contact	Severe cartilage loss including areas with direct bone-bone contact
Joints of hand OA patients (n=161)				
Normal inter bone distance	77	19	14	0
Loss of cartilage space without bone-bone contact	7	19	15	2
Focal complete loss with bone-bone contact	0	1	4	2
Bone-bone contact >50%	0	0	0	0
Joints of healthy controls (n=71)				
Normal inter bone distance	59	1	0	0
Loss of cartilage space without bone-bone contact	9	1	0	0
Focal complete loss with bone-bone contact	1	0	0	0
Bone-bone contact >50%	0	0	0	0

n= number of assessed joints. Presented values are means of the two readers (rounded down).

In the hand OA patients, normal inter-bone distance was found in 110/161 (68%) joints (41 PIP and 69 MCP joints). In these joints, 33 (24 PIP and 9 MCP) showed thinning of the cartilage layer on the SPGR images of which 14 (12 PIP and 2 MCP) showed areas with full thickness cartilage loss (see Table 4 and Figure 2 for an example). In total seven (3 PIP and 4 MCP) joints in the hand OA patients showed no cartilage damage on SPGR images, but they were scored as abnormal using the inter bone distance with the coronal PD images. In the healthy controls, reduced inter-bone distance was found in 11 (10 PIP and 1 MCP) joints, of which 9 did not show cartilage loss on the SPGR images. Using the hrMRI cartilage score, the readers scored 2 PIP joints in healthy controls as abnormal.

Table 4. Number of joints with cartilage damage split by joint type (n=232)

	joints in HOA patients			joints in healthy controls		
	PIP joints n=81	MCP joints n=80	Total pat. n=41	PIP joints n=36	MCP joints n=35	Total hc n=18
Inter bone distance >0	38	12	23	10	1	7
hrMRI cartilage score >0	60	17	34	2	0	2
Full thickness cartilage loss on hrMRI	31	6	22	0	0	0

hrMRI = high resolution MRI; hc = healthy controls; MCP = metacarpal phalangeal joint; DIP = distal interphalangeal joint. Presented values are means of the two readers (rounded down).

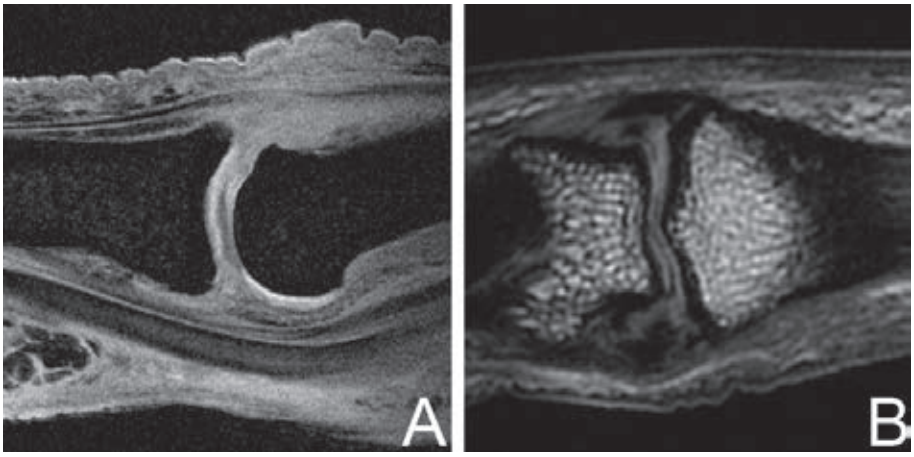


Figure 2. Cartilage thinning, only detected with direct cartilage imaging. A: Sagittal SPGR image of the PIP joint of a hand OA patient. There is loss of cartilage on the head of the proximal phalanx. B: Coronal PD image of the same joint at the level of the cartilage defect, which was scored by both readers as a joint without loss of inter bone distance.

Cartilage thickness showed large variation in healthy controls (Figure 3). In the MCP joints the thickness varied between 0.3 and 0.9 mm with a mean of 0.6 mm (sd 0.1) mm, and in the PIP joints thickness varied between 0.2 and 0.7 mm with a mean of 0.4 mm (sd 0.1). These values showed a very large overlap with the hand OA patients. In the hand OA patients the mean cartilage thickness for MCP joints varied between 0.0 and 1.0 mm with a mean of 0.5 mm (sd 0.2) and values for PIP joints varied between 0.0 and 0.9mm with a mean of 0.4 mm (sd 0.1).

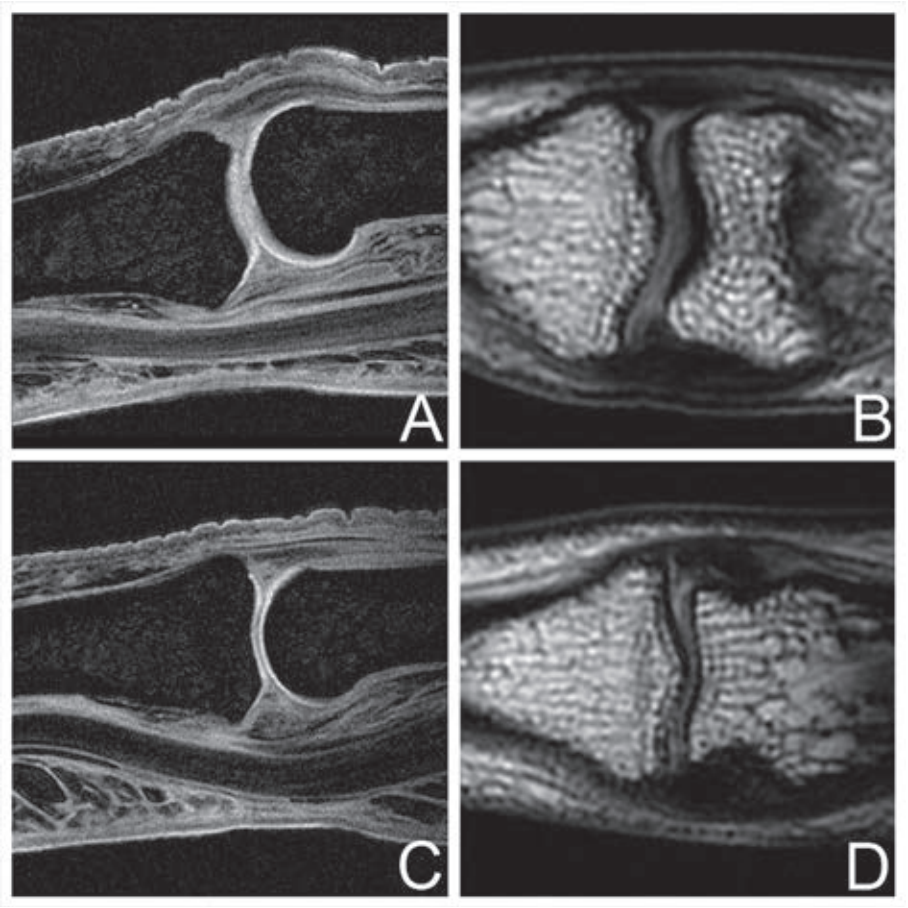


Figure 3. Variation of cartilage thickness in healthy controls. A+C: Sagittal SPGR images with fat suppression. B+D: Coronal FSE proton density image. A and B depict the same PIP joint in a healthy control with thick cartilage layers. C and D depict a PIP joint in a healthy control with thin cartilage layers.

Discussion

Using the high resolution MRI (hrMRI) cartilage score the readers identified more joints with cartilage damage in comparison with inter bone distance loss in the OA group, and less joints with cartilage damage in the healthy control group. Reliability of both scores were comparable.

Large variations of cartilage thickness and shape were present in both OA patients and the controls. The shape and thickness of the healthy cartilage layer showed considerable differences. For example, some healthy controls had considerably thinner cartilage centrally on the metacarpal head than on the rest of the metacarpal head. These variations make it challenging to distinguish normal vs. minor cartilage loss in cross sectional imaging studies in early hand OA, especially without a reference for the individual patient. This also occurs when inter bone distance scoring is used on thick slices, as thick slices have more partial volume averaging. Scoring on these thick slices is therefore more prone to underestimate cartilage damage in asymmetric damaged cartilage layers and may overestimate narrowing in patients with normal relatively thin cartilage layers, in comparison with direct cartilage imaging. Our results therefore suggest that direct evaluation of cartilage with hrMRI is more accurate for cartilage assessment.

The observed pattern of cartilage loss in our patients was overall diffuse loss of cartilage thickness over large areas of the joint. Small focal cartilage lesions with abrupt edges which have been observed in the knee[17, 18] were not detected in our study. The lowest grade of cartilage damage in our proposed scoring system (single abrupt focal cartilage damage lesion <10% of surface area) was included in analogy to the MOAKS scoring system in the knee [13], but not scored. Our results may suggest that either the normal pattern of cartilage loss in hand OA consists of more gradual and continual cartilage loss, or we are unable to see small focal lesions, even with our hrMRI images. Future studies using this or a similar hrMRI cartilage score should therefore consider removing this grade from the score.

This study adds to the available knowledge on hrMRI of small finger joints. We used a 3T MRI machine in combination with a special MRI coil as a normal

wrist coil will not be able to acquire comparable high resolution scans of finger joints. Our coil was designed to image 4 joints within one image session, without the need to adjust coil placement between image acquisitions. Single small loop coils, which are standard available from most MRI vendors could be used, but they need to be repositioned between series acquisition when more than a single joint is scanned. We used relatively long scan times to test the imaging possibilities, and future studies should explore whether it is possible to reduce the scan time. The PD sequence that was used for scoring the inter-bone distance on all 4 joints was acquired in 4:30 min (excluding pre-scans, set up time, etc), and this scan time can be reduced to make lower resolution, but still adequate coronal images. For the hrMRI cartilage images, each joint was scanned separately resulting in very thin 0.4mm slices without a gap and a total scan time of 14min for 4 joints. The size of the imaged 3D area for the PIP joints was in hindsight quite large, and further reducing the FOV in the IP joints, can decrease this scan time. Furthermore, faster and newer pulse sequences might also be used, if they can be adjusted to the small field of view.

A limitation of our study is the absence of a true gold standard. Comparison with histology is hard to obtain in our study population of healthy persons and patients with hand OA. In a previous study we found that in pre-operative obtained MRI of the CMC 1 joint in patients scheduled for trapeziectomy comparable hrMRI could detect cartilage damage with high sensitivity in comparison with histology, but might underestimate the amount of full-thickness loss when present[19].The systematical difference between MRI and histology in that study was identified and only present in area's with severe cartilage loss. As no patients with severe cartilage loss were present in our study, we expect our currents results of the MCP joints and PIP joints to be comparable with real cartilage loss. Another limitation is the inclusion of the second and third MCP and PIP joints only, as the used MRI coil was built specifically for imaging 2 MCP and 2 PIP joints. The second and third digits were chosen as these are the most affected in hand OA. However, hand OA is more often occurring in the DIP joints, than in PIP and MCP joints. We expect hrMRI to also be better than joint space narrowing detection in DIP joints, despite the smaller size of these joints.

In conclusion, we have demonstrated that cartilage can be detected directly with good reliability using hrMRI. As compared to evaluation of inter-bone distance, which is the current standard, direct evaluation of the cartilage using hrMRI identified more joints with pathology in OA patients and less joints with pathology in healthy controls, suggesting better sensitivity and specificity.

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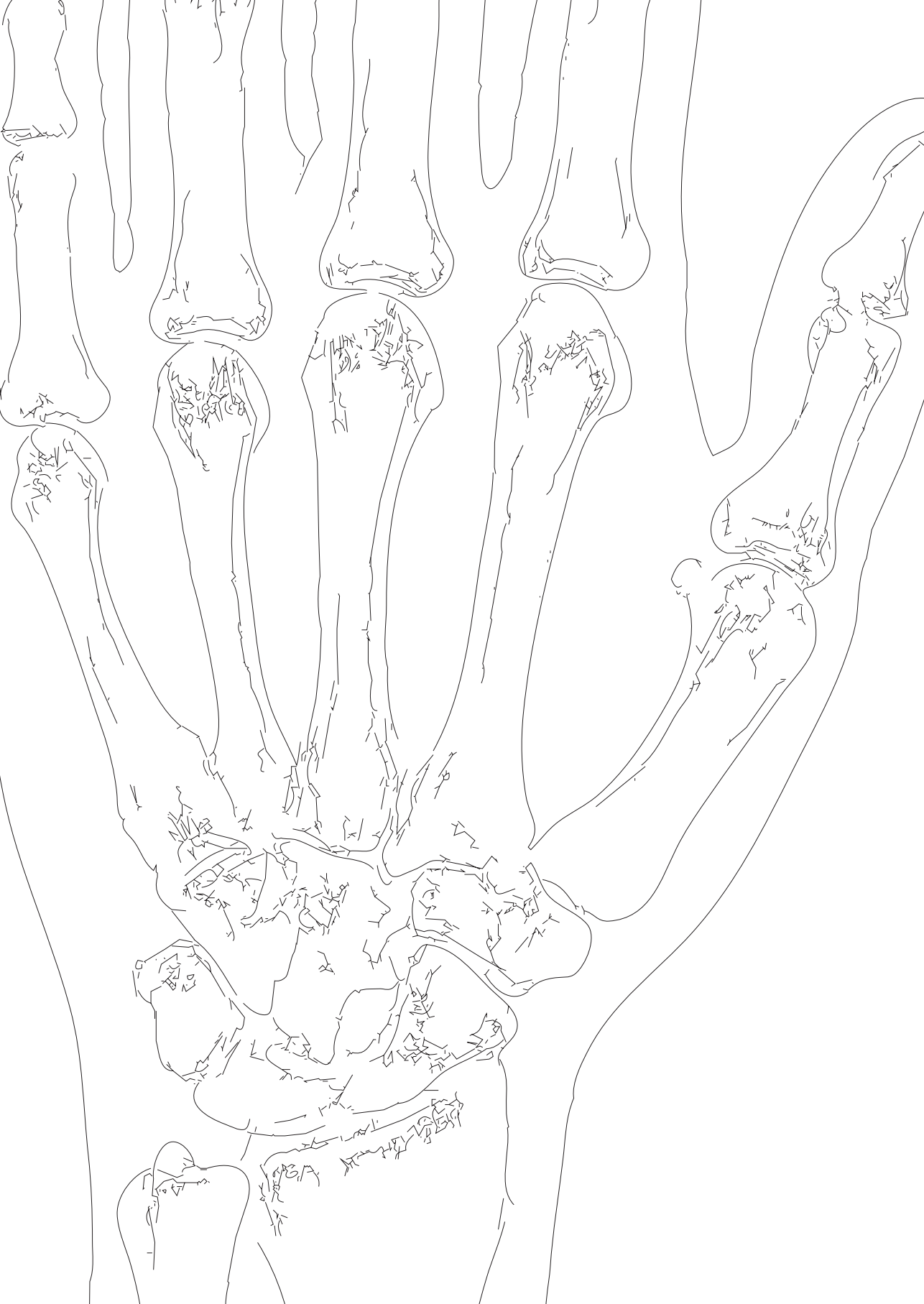

Chapter 6

Low field MRI for identification of inflammatory changes in hand arthralgia and early arthritis - a comparison with high field MRI and ultrasound

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Abstract

Objective: To evaluate 0.2T extremity MRI for detecting synovitis, bone erosions, and bone marrow oedema (BME) in patients with early inflammatory hand arthralgia, by comparison with 1.5T conventional MRI and ultrasound.

Methods: 40 patients with arthralgia or early arthritis in wrist or hand had contrast-enhanced MRI of wrist and MCP joints on 0.2T extremity MRI and 1.5T conventional MRI. The MRI examinations were evaluated for synovitis, erosions and BME using RAMRIS. 26 of those patients also had two ultrasound (US) examinations, once by using standardized views and once with free viewing. Both ultrasound examinations evaluated the MCP joints for synovitis and erosions and the wrist for synovitis.

Results: Agreement between the MRI scanners for detection of synovitis was good (κ=0.65), erosions moderate (κ=0.48), and BME poor (κ=0.19). 0.2T MRI detected less erosions than 1.5T MRI (82 vs 96) and less BME (8 vs 42). There was poor agreement between the different US scoring methods for synovitis (κ=0.13) and between the US and MRI method (κ=0.24-0.32). The standardized US method identified less joints with synovitis than 0.2T MRI (23 vs 46) but was very specific (93%). Almost no (6 and 0) erosions were found with the two different US methods.

Conclusions: In patients with hand arthralgia and early arthritis, contrast enhanced 0.2T MRI is good in detecting synovitis, slightly less sensitive for erosion detection than 1.5T, and more sensitive than US for both synovitis and erosions. However, most BME lesions were missed with 0.2T MRI, suggesting that higher field-strength scanners should be used for BME detection.

Introduction

Magnetic Resonance Imaging (MRI) is a valuable tool in the detection of patients with peripheral inflammatory joint diseases. It is more sensitive than radiography for detecting bone erosions,[1-3] it is very sensitive in the detection of synovitis,[4-7] and it is the only imaging technique which can detect bone marrow oedema (BME), which is often seen in inflammatory joint disease and is a predictor of progression of Rheumatoid Arthritis (RA).[8-10]

A variety of MRI hardware is used to detect these pathologies associated with inflammatory arthritis. Used magnetic field strengths vary from 0.2 to 3 Tesla (T); with 1.5T MRI currently being the most widely available. Higher field strength MRI scanners provide a better image quality, but low field extremity MRI scanners are less expensive and more comfortable for patients.[11, 12] Previous studies have shown that low field MRI, despite its lower image quality, is equally effective as high field MRI in the detection of synovitis and erosions in patients with established RA, but low field MRI seemed less accurate in the detection of bone marrow oedema and tenosynovitis as high field MRI.[13, 14]

Ultrasound is another imaging method to detect synovitis and is more affordable and better available than both MRI techniques. While ultrasound seems not as good as MRI to detect erosions [15], and cannot detect BME, ultrasound with power Doppler seems as good as low field and high field MRI to detect active synovitis in hand and MTP joints in patients with diagnosed RA [16, 17]

Most imaging studies have been performed on patients with diagnosed RA. However, patients with early inflammatory unclassified arthritis or arthralgia who may be at risk for developing RA or other inflammatory arthritis could benefit from early detection of inflammatory arthritis with MRI or ultrasound. Earlier detection of joint disease means earlier treatment, and possible prevention of permanent joint damage. For patients with arthralgia it is unknown how accurate low field MRI is in comparison with high field MRI and ultrasound.

We therefore investigated the utility of 0.2T extremity MRI for detecting synovitis, bone erosions, and bone marrow oedema in patients presenting

with early inflammatory hand pain, by comparison with 1.5T conventional MRI and ultrasound. As a secondary objective we compared 0.2T MRI with US in the same patients for detection of synovitis in wrist and MCP joints and erosions in MCP joints.

Patients and Methods

Patients

We recruited consecutive patients with swollen or painful wrist or hand joints who entered the Rotterdam Early Arthritis CoHort (REACH).[18] REACH is an inception cohort of patients with inflammatory joint disease in which patients enter from the general practitioner or from a rheumatology outpatient clinic at first consultation. Patients were included in REACH if they had one or more swollen joints or if they had two or more joints with pain with at least two of the following criteria suggestive of inflammatory arthritis: morning stiffness for more than 1 hour; 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; a family history of RA; or unexplained fatigue for less than 1 year. Patients were excluded from REACH if the joint complaints existed for more than twelve months, if the joint complaints were due to trauma or mechanical problems or if they were under 16 years of age.

Patients were excluded for this study if they already started a treatment with disease modifying antirheumatic drugs (DMARDs) or if they had a contra-indication to undergo contrast-enhanced MRI (e.g. pacemaker, metallic fragments in orbita, low kidney function). Patients were recruited in three hospitals situated in Rotterdam the Netherlands. Recruitment started in February 2010 at Erasmus MC, March 2011 at Maasstad hospital and April 2011 at Sint Fransiscus Gasthuis, and lasted until July 2011. The study was approved by the local ethics committee. All patients provided written informed consent prior to the investigation.

Clinical examination

In all patients joint swelling and joint tenderness was assessed by a trained research nurse. Additionally, C-reactive protein, erythrocyte sedimentation

rate, IgM rheumatoid factor (RF), antibodies against cyclic citrullinated peptides (anti-CCP) and conventional radiographs of hand and feet were obtained. Diagnosis was determined according to predefined definitions by the treating rheumatologists.[18]

Magnetic resonance imaging

Each patient underwent two MRI examinations of the wrist and 2nd-5th MCP joints of the most symptomatic hand: One on a 0.2T extremity MRI (C-Scan; Esaote, Genoa, Italy) and another on a 1.5T full body MRI (Discovery MR450; GE healthcare, Milwaukee, Wisconsin). Both MRI examinations were performed before and after intravenous administration of the gadolinium agent gadobutrol (Gadovist; Schering, Berlin, Germany), which was administered at a dose of 0.1 mmol/kg body weight. The examinations were performed on two separate days within one week, to allow for clearance of the contrast agent, and to minimize the time for biological variation. The exact imaging protocols were chosen for best image quality within a reasonable time frame after testing sessions with multiple volunteers and patients for both systems. Those protocols were in accordance with the guidelines of the MRI in rheumatoid arthritis study group of the Outcome Measures in Rheumatology (OMERACT) initiative.[19] The acquisition time was 20 minutes for the 1.5T MRI and 21 minutes for the low field extremity MRI. The complete examinations lasted between 40 and 60 minutes, including patient setup and contrast injection.

Low field extremity MRI

Patients were seated in a semi-sitting position with the arm abducted and the hand placed in the magnet. The hand was tightened with soft cushion pads within the centre of a dual phased array coil to minimise involuntary patient movement. A Coronal Short T1 Inversion Recovery (STIR) sequence was obtained (repetition time/echo time/inversion time, 1100/24/85 ms; matrix 192x60; slice thickness/slice gap, 3.0/0.3 mm; Field of view (FOV) 20x20 cm; 2 acquisitions) after which a T1 weighted 3D-gradient echo sequence before and after contrast injection was obtained (repetition time/echo time, 30/12 ms; flip angle 65°; matrix 192x60x80; slice thickness/slice gap, 1.0/0.0 mm; Field of view 14x14x8 cm; 1 acquisition). The gradient echo sequences were reconstructed in the coronal and axial planes.

High field MRI

Patients were placed in the prone position with the arm extended above the head and the hand placed in an 8-channel phased array wrist coil (Invivo Corp, Gainesville, Florida), within the centre of the magnet. The following sequences were obtained: a T2 weighted coronal Fast Recovery Fast Spin Echo (FRFSE) with fat suppression obtained (repetition time/echo time, automatic/68 ms; matrix 512x256; slice thickness/slice gap, 2.5/0.3 mm; Field of view 15x11.25 cm; 1 acquisitions, 19 slices), and T1 weighted coronal Spin Echo (SE) and Axial Fast Spin Echo (FSE) before and after contrast injection (repetition time/echo time, 500/15 ms; slice thickness/slice gap, 2.0/0.2 mm; 1 acquisitions; For coronal SE: matrix 512x512; Field of view 15x11.25 cm; for axial FSE: Echo train length 2; matrix 512x256; Field of view 12x6 cm).

MR Image evaluation

All images were evaluated by an experienced musculoskeletal radiologist (GSRM), after a training session. The reader was blinded to patient data, clinical data, and other imaging results. The anonymized images were read using the open source software ClearCanvas Workstation (ClearCanvas Inc., Toronto, Canada).

Images were scored according to the OMERACT RA MRI Score (RAMRIS) for synovitis, bone erosions and bone marrow oedema in MCP joints two through five and the wrist.[20-22], Images from the RAMRIS atlas were used as a guideline for scoring.[21, 22] Synovitis was scored in each MCP joint, the intercarpal-carpometacarpal area, the radiocarpal joint, and the distal radioulnar joint. Synovitis was scored according to RAMRIS as the presumed maximum volume of enhancing tissue in the synovial compartment (a score of 0: normal, 1: 0%– 33%, 2:34%–66%, and 3: 67%–100%), and a joint with a RAMRIS synovitis score ≥2 was defined as having synovitis, because grade 1 synovitis are often present in healthy controls.[23, 24] BME and erosions were scored for all carpal bones, all metacarpal bases and the distal radius and distal ulna. For the long bones, only the area from the articular surface to a depth of 1 cm was assessed. BME was present with a RAMRIS score >0. Erosions were scored, according to the percentage of eroded bone (a score of 0: no erosion, 1: 1%–10%, 2: 11%– 20%, etc). Wrist bones were defined as having an erosion with a RAMRIS erosion score ≥2, because RAMRIS grade 1 wrist erosions are often present in healthy controls.[23, 25]

Ultrasound

Each patient was also invited for two ultrasound examinations of the same hand imaged with MRI at the same day as one of the MRI examinations. One ultrasound examination ("standardized US") was performed by a trained researcher (DFTC) using a previously described standardized scanning protocol with fixed probe positions for evaluation in specific imaging planes, [26] based on EULAR guidelines and advice from OMERACT US working group concerning patient and probe positions.[27, 28] The second ultrasound examinations ("clinical US") were performed by an experienced musculoskeletal radiologist (GSRM) using the same standardized scoring form, but without restrictions for probe positions. Both examiners scanned the MCP joints, intercarpal joint area, radiocarpal joint and DRU-joint with grayscale and power Doppler for synovitis and erosions were only assessed in the MCP joints. Both examiners used the following definitions: Synovitis was defined as synovial thickening with bulging above the periarticular bones and/or visible Doppler flow within the synovium. Erosions were defined as a cortex defect, visible in two planes.

Statistical analysis

No formal sample size calculation was performed as we did not know the frequency of pathology that would be present in patients with inflammatory hand complaints on MRI. Based on the patient-flow in the REACH we expected that half of our 40 consecutive patients would have clinically observable arthritis allowing for a sufficient amount of pathology to detect with MRI. Simple descriptive techniques and calculation of agreement using Kohen's Kappa were used to compare the imaging methods.

Results

Patients

Out of 150 consecutive patients of the REACH cohort, 104 fulfilled our inclusion criteria, and were invited to participate (Figure 1). Forty-four patients entered the study. Two of those patients could not be scanned with the extremity MRI due to technical problems with the machine, two other patients did not want to complete the study after having the first MRI. Forty patients were analysed with MRI, of which 26 patients also had two ultrasound examinations. 2 patients did

not want additional US examinations, and for 12 patients it was logistically not possible to combine the ultrasound examinations with the MRI examinations, mostly because of unavailability of one or both of the US examiners. The baseline characteristics of the patients and their diagnosis after one year are shown in Table 1. The median number of days between all MRI and ultrasound examinations was 1 (IQR 1-2). Patients did not yet have a diagnosis at the time of the imaging visits. However, after one year 15 out of the 40 patients were diagnosed with RA, 14 with another form of arthritis (Table 1), and 9 patients with arthralgia that did not show clinical signs of arthritis. Two patients were lost to follow up. Their diagnoses at their last visit were osteoarthritis and arthralgia without arthritis.

Table 1. Patient characteristics.

Characteristic	n=40		n=26	
	median or count	(IQR) (%)	median or count	(IQR) (%)
Age (years)	47	(35-59)	52	(38-62)
Female gender	26	65%	16	62%
Disease duration (months)	4	(2-6)	4	(2-7)
Swollen joints (0-44)	2	(0-5)	2	(0-3)
Tender joints (0-44)	5	(3-12)	6	(4-12)
ESR (mm/h)	15	(5-15)	16	(5-28)
CRP (mg/l)	3	(1-3)	3	(2-8)
IgM RF positive (>12 IE/ml)	15	37.5%	11	42%
Anti-CCP positive (>10 U/ml)	11	27.5%	9	35%
Patients with swollen hand joints	24	60%	16	62%
Patients with erosions on hand x-ray (SvdH)	0	0%	0	0%
Diagnosis after one year:				
rheumatoid arthritis	15	37.5%	9	35%
unspecified arthritis	8	20%	6	23%
arthralgia without arthritis	7	17.5%	5	19%
osteoarthritis	4	10%	1	4%
psoriatic arthritis	2	5%	1	4%
fibromyalgia	2	5%	2	8%
undifferentiated spondylarthropathy	1	2.5%	0	0%
unknown	2	5%	0	0%

Median (IQR) for continuous variables, number % for counts. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; Anti-CCP, antibody to cyclic citrullinated protein.

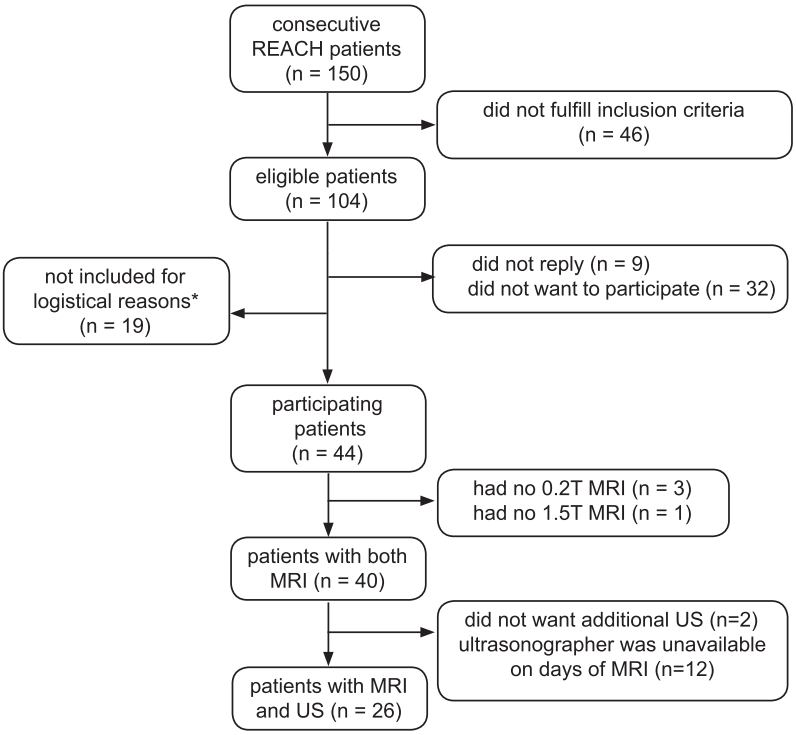

Figure 1. Patient flowchart

*= Patients that could not be included for logistical reasons were patients who wanted to participate, but for who it was not possible to plan both MRI examinations before starting therapy.

Low field versus high field MRI

With 1.5T MRI, 19 out of 40 patients had one or more joints with synovitis, 19 had erosions, 17 had BME. Table 2 displays the amount of detected pathology for both MRI methods, and their agreement in cases. There was good agreement between both MRI methods for synovitis detection (κ=0.65). In most cases where the MRI results did not match, contrast enhancement was visible on both image sets, but synovitis was scored 2 on one image set and 1 on the other. An example of this is shown in Fig 2. On patient level, 17 patients had synovitis with both methods, 2 patients were identified with 1.5T MRI only and 5 patients with 0.2T MRI only. Synovitis was detected the most in the second MCP joint and the radiocarpal joint.

There was moderate agreement for erosion detection (κ=0.48) between MRI methods. While 1.5T MRI detected 18 more erosions in total, this did not result in more patients having erosions with 1.5T MRI, as 19 patients had erosions with both methods, 1 patient had erosions with 1.5T MRI only, and 2 patients had erosions with 0.2T MRI only. Most erosions in the MCP joints were present in the heads of the second and third metacarpal bone, and most erosions in the wrist were present in the scaphoid, lunate, triquetrum and capitate bone.

BME was uninterpretable on the 1.5T images in one patient, and therefore analysed in 39 patients. There was poor agreement (κ=0.19) for BME detection between the MRI methods, as only 8 bones showed BME on 0.2T. In all patients with BME, BME was present in a wrist bone, with the lunate bone being most affected (11 patients on 1.5T MRI). A typical example of BME not detected with 0.2T is shown in Fig 3.

On the 0.2T scanner, the proximal part of the wrist was partly outside the field of view (FOV) in seven patients. The distal radius (n=6), distal ulna (n=6), distal radioulnar joint (n=7), and lunate bone (n=1) were not analysed with both methods if they were outside the 0.2T FOV.

Low field MRI versus ultrasound

Table 3 displays the amount of detected pathology for both MRI and both ultrasound methods and their agreement in numbers in the ultrasound subset of 26 patients. The clinical ultrasound and MRI methods detected almost the same amount of joints with synovitis, but there was poor agreement between clinical ultrasound and 1.5T MRI (κ=0.26) and between clinical ultrasound and 0.2T MRI (κ=0.25). 9 patients were scored positive for one or more joints with synovitis with both 0.2T MRI and clinical ultrasound, 8 patients were scored positive for synovitis with 1.5T MRI, and 5 patients were scored positive with clinical ultrasound. Standardised US detected less joints with synovitis than the other methods (Table 3), resulting in 5 patients having synovitis. However, almost all joints with synovitis on standardised US also had synovitis on MRI (93% vs 1.5T). 6 erosions were detected with the clinical US method in two different patients. No erosions were detected with the standardized ultrasound method.

Table 2. Number of structures with pathology on both low field 0.2T extremity MRI and clinical 1.5T MRI scanner.

	Erosions (n=40)			**BME** (n=39)		
	1.5T	0.2T	agree	1.5T	0.2T	agree
mcp 2 distal	0	0	0	1	0	0
mcp 2 prox	17	10	7	1	2	0
mcp 3 distal	1	0	0	0	0	0
mcp 3 prox	12	11	8	1	0	0
mcp 4 distal	1	0	0	0	0	0
mcp 4 prox	4	3	0	2	0	0
mcp 5 dist	0	0	0	0	0	0
mcp 5 prox	9	4	4	0	0	0
base of MC1	4	3	2	3	2	1
base of MC2	4	8	1	0	0	0
base of MC3	0	3	0	0	0	0
base of MC4	1	4	1	0	0	0
base of MC5	1	2	0	0	0	0
trapezius	2	1	1	3	1	1
trapezoid	1	1	1	1	0	0
Capitate	8	8	5	4	0	0
Hamate	0	0	0	1	0	0
scaphoid	9	7	5	5	1	1
Lunate*	11	6	5	11	2	2
triquetrum	8	6	5	6	0	0
Pisiform	0	0	0	1	0	0
Radius**	1	0	0	1	0	0
Ulna**	2	1	1	1	0	0
Total (n=907/867)	96	78	46	42	8	5
	Synovitis					
	1.5T	0.2T	agree			
mcp 2	17	17	15			
mcp 3	12	14	11			
mcp 4	8	7	6			
mcp 5	7	4	3			
intercarpal	5	10	4			
radiocarpal	16	19	13			
DRU***	12	12	8			
Total (n=273)	77	83	60			

Agreement represents the amount that the pathological features was found in the same patient on both machines. * analysed in 39 patients for erosions and 38 for BME ** analysed in 34 patients for erosions and 33 for BME, ***analysed in 33 DRU-joints. MCP, metacarpal phalangeal joint; MC, metacarpal; BME, bone marrow edema; DRU, distal radio-ulnar joint

Table 3. Number of joints with synovitis or erosions per imaging method.

synovitis	MRI 1.5T	MRI 0.2T	US Clinical	US standardized	both MRI agree	1.5T - clinical US agree	1.5T - standardized US agree	Both US agree	0.2T - clinical US agree	0.2T - standardized US agree
mcp 2	11	10	12	3	9	6	3	3	6	3
mcp 3	6	7	7	2	5	1	2	0	1	2
mcp 4	4	4	4	0	3	1	0	0	1	0
mcp 5	4	2	6	2	2	2	1	1	2	1
ic	3	5	0	4	2	0	2	0	0	0
rc	11	11	12	9	8	6	5	4	7	5
dru	8	7	8	3	4	6	2	2	4	2
Total (n=182)	**47**	**46**	**49**	**23**	**33**	**22**	**13**	**10**	**21**	**15**

erosions	1.5T	0.2T	US clinical	US standardized	both MRI agree	1.5T - clinical US agree	0.2T - clinical US agree
mcp 2	11	8	2	0	5	2	2
mcp 3	8	9	2	0	6	2	2
mcp 4	2	2	2	0	0	1	0
mcp 5	6	3	0	0	3	0	0
Total (n=104)	**27**	**22**	**6**	**0**	**14**	**5**	**4**

Agreement represents the amount that synovitis was detected in the same joint for both methods. MCP, metacarpal joint; IC, intercarpal joint space; rc, radiocarpal joint; dru, distal radio-ulnar joint.

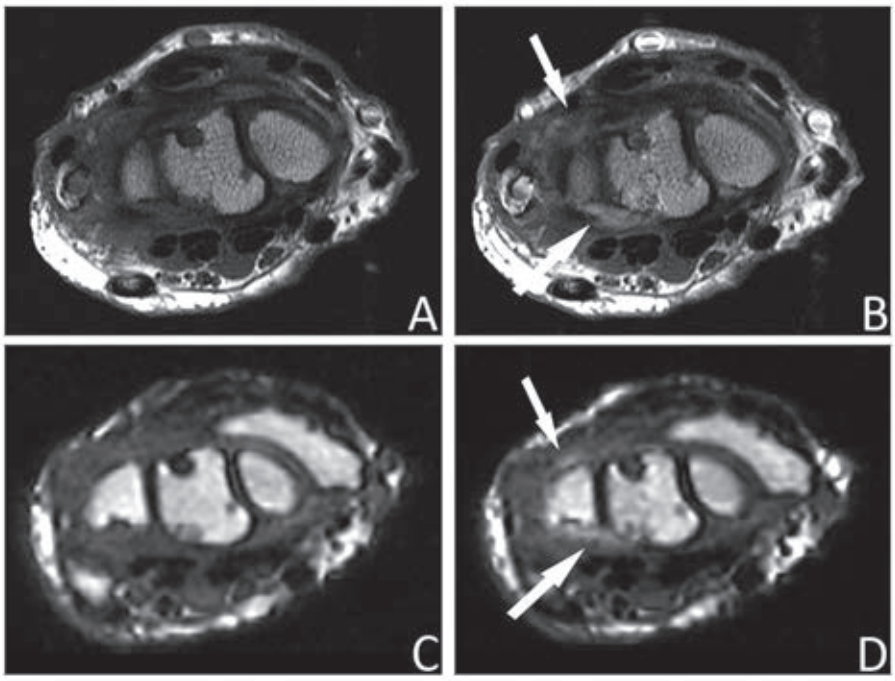

Figure 2. Example of synovitis that was scored differently at 0.2T and 1.5T in the radiocarpal joint. Axial T1-weighted images, (A) at 1.5T before contrast injection, (B) 1.5T after contrast injection, (C) 0.2T before contrast injection, and (D) 0.2T after contrast injection. Both MRIs show contrast enhancement (arrows), but this patient was scored RAMRIS synovitis grade 1 at 0.2T and RAMRIS synovitis grade 2 at 1.5T.

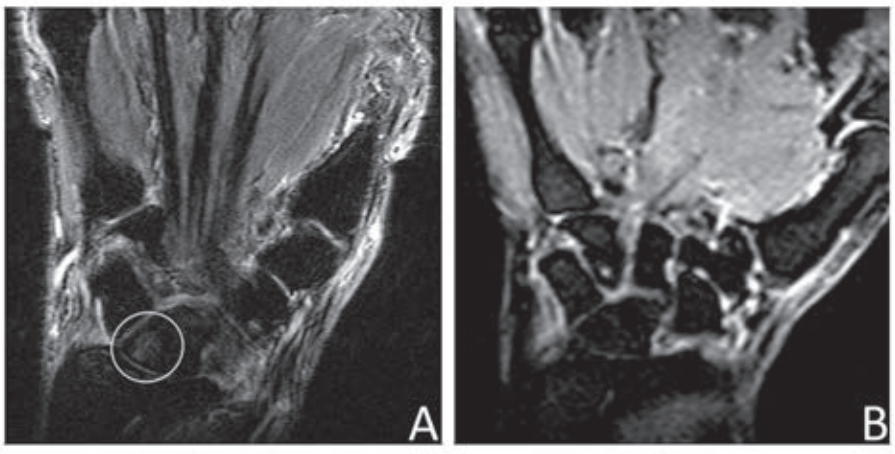

Figure 3. Example of BME that was detected at 1.5T but not at 0.2T. (A) 1.5T T2-weighted image with fat saturation. (B) 0.2T STIR image. An area with higher signal intensity can be seen in the lunate bone at 1.5T (A, circle), indicating BME. BME is not visualized in the lunate bone, possibly because the general signal intensity within the bones is higher, concealing the BME in the lunate.

Discussion

Contrast enhanced 0.2T MRI in patients with early arthritis or inflammatory hand arthralgia showed good agreement with 1.5T MRI for detection of synovitis, moderate agreement for detection of erosions and poor agreement for detection of BME. Ultrasound showed poor agreement with both 1.5T and 0.2T MRI for detection of synovitis and erosions. These results suggest that contrast enhanced 0.2T MRI is a good method for synovitis detection, better that ultrasound.

Our MRI synovitis results are in line with studies performed in cohorts of RA patients, in which there was an overall good agreement between low and high field MRI of κ 0.69-0.94, and ICC 0.40-0.96,[13, 14, 29]. The standardized US examination evaluating the joints in specific fixed imaging planes detected less joints with synovitis and identified less patients with synovitis compared to the US examination of the joint without fixed planes, and MRI. However, if synovitis was detected with standardized US, it was almost always also present on MRI. These ultrasound findings are in line with a recent systematic review in RA patients. This review identified 12 studies on US detection of synovitis in hand and wrist with MRI used as the reference standard [30]. The included US studies showed variable amounts of sensitivity, variable amounts of specificity in the wrist, and high specificity in almost all MCP and PIP studies. No information about scanning protocol or probe positions was further specified in this review, which may explain the large variation in results. The clinical US method without fixed planes detected more joints with synovitis than standardized US, but this method also had a low agreement with synovitis on MRI. Previously, it has also been shown that US without fixed planes give varying results in research,[31, 32] and this method therefore seems suboptimal. The lower sensitivity of fixed plane ultrasound in detection of synovitis may be explained due to the fact that there is often asymmetric or focal synovial thickening which may be only visible outside the standardized planes.

There was moderate agreement for erosions detection between 0.2T extremity MRI and 1.5T MRI. The agreement we found was lower than similar studies with diagnosed RA patients where high agreement was found in all wrist and MCP bones: κ 0.65-1,[14] ICC 0.76-0.99,[29] and ICC 0.94.[13] A possible explanation

for this difference is that the cortical defects in our patient group were overall smaller than in RA patients, and that these smaller defects are harder to detect with low field MRI. While 50% of our patients had an MRI detected erosion, almost no erosions were found with the US scoring methods, and zero erosions were found with radiography. This difference between imaging methods is in line with previous studies in RA patients, [2, 3, 15] were it has been shown that ultrasound is more sensitive for erosions than radiography and MRI is far more sensitive than the other two methods. CT studies show that these MRI detected erosions are true cortical breaks.[33] While radiographic erosions were once considered pathognomic for RA, these MRI detected cortical breaks are also found in healthy controls [23, 24, 34] and not specific for RA. Future studies should investigate the clinical relevance of these MRI detected cortical breaks for patients with possible inflammatory arthritis.

0.2T MRI showed poor diagnostic performance in detecting BME, as it only detected 8 bones with BME in contrast to 42 with 1.5T MRI. Other studies with the same low field MRI machine found that it is also not sensitive in detecting BME in RA patients (sensitivity 0.39 and varying agreement with high field MRI (ICC 0.05-0.94)).[13, 29] The proportion of undetected BME in our study was higher than previously reported for RA patients.[11]. Our arthralgia and early RA patients probably had less severe BME, and this less severe BME is missed more often with our low field MRI. A recent study with different field strength MRI units showed that BME detection is better with newer low field scanners, but also showed that reliability was lower for BME detection with a 0.23T MRI in comparison with 0.6T and higher field strength scanners [35], favouring scanners from 0.6T and higher.

This cross sectional analysis has several limitations and strengths, An advantage of extremity MRI is improved patient comfort.[12] Out of the 32 patients that declined participation in our study, 9 patients indicated that they did not want to undergo an MRI in a whole body scanner. An extremity MRI may therefore be a good alternative for detecting synovitis and erosions in patients with claustrophobia. Imaging examinations were mostly performed on subsequent days, but an interval of maximal 6 days was present. As no medical interventions were started before or during the interval, we do not expect a large biological variation between imaging examinations. However, nineteen patients were

unable to participate because of logistical problems. In most of these patients, this was because DMARD or steroid therapy needed to start before they were able to undergo two MRI-scans. Our patient sample will therefore probably have a low number of patients in which clinical findings were very suspect for RA. Another limitation of the study is that 14 patients did not have both ultrasound examinations, usually because one of the sonographers was unavailable on the MRI days, lowering the sample size of the comparison with ultrasound. A known limitation of the Artoscan 0.2 T unit specifically is that its maximum field of view is restricted to 12 cm. For 6 out of 40 patients the length of the complete wrist and MCP joints was larger than 12 cm, and the proximal part of the wrist was therefore not imaged. A total of 4 erosions were detected on the 1.5T MRI in the areas not imaged by the Artoscan. Newer low field scanners generally have a bigger FOV, and therefore may not have this problem.

In conclusion, in patients with arthralgia and early arthritis, low field extremity MRI is good in detecting synovitis, and more sensitive than US. It was less sensitive for detection of erosions than high field MRI. Most BME lesions were missed with low field MRI, suggesting that higher field-strength scanners should be used when one is interested in BME.

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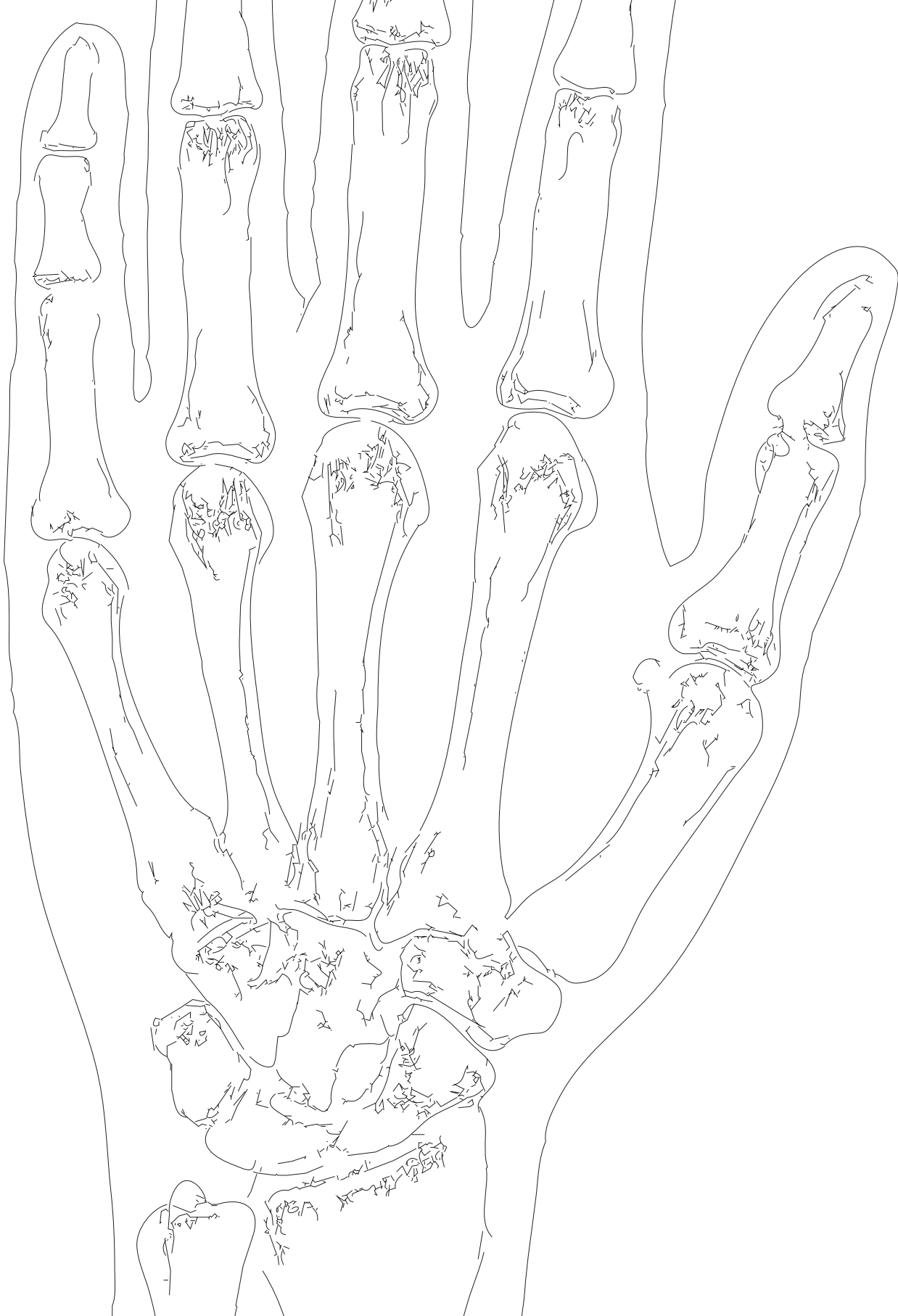

Chapter 7

General discussion

In this thesis we have used radiological imaging methods to image hand osteoarthritis (OA) and rheumatoid arthritis (RA) with the following aims:

- to assess construct validity and reliability of direct cartilage imaging with magnetic resonance imaging (MRI) in hand OA.
- to asses if computed tomography (CT) has better reliability and detection rate of thumb base OA than conventional radiography.
- to assess construct validity of low field extremity MRI in early arthritis patients.

MRI Direct cartilage imaging.

Direct cartilage imaging with high-resolution MRI (hrMRI) in hand joints is feasible, and more accurate than indirect scoring of joint space narrowing (JSN). In **chapter 4** we have shown that compared with histology, hrMRI accurately depicts the overall extent of cartilage damage. In **chapter 5** we have shown that direct scoring of cartilage defects using hrMRI is certainly as reliable as JSN scoring using normal MRI, and that with hrMRI more cartilage damage was detected in hand OA (HOA) patients, and less cartilage defects were scored in healthy controls. While this does not prove that hrMRI has better sensitivity and specificity, it indicates that direct cartilage imaging with MRI is more accurate.

All the advantages of direct cartilage imaging come at a cost, as with hrMRI only a few joints can be imaged in a single examination. Previously, direct cartilage imaging of a single hand joint with hrMRI has been studied to quantify cartilage volume [1], and was shown to be a promising technique. Technological developments since then allow us to scan a small hand joint with a similar MRI sequence in less than one third of the scanning time, and with 4 times smaller voxel sizes. However, as each joint needs to be scanned separately with hrMRI, the use of hrMRI should be based on the specific research question. If the research question focusses on other aspects of OA like synovitis, whole hand imaging with lower resolution might be more appropriate. However, for example, if the effects of disease-modifying osteoarthritis drugs (DMOADS) should be assessed on all joint structures including cartilage, then hrMRI is probably preferred. Currently, MRI for cartilage imaging in HOA is only

interesting for research purposes, as the presence or absence of cartilage damage does not have clinical implications.

MRI Cartilage evaluation in hand joints can be further improved by using quantitative cartilage measurements. In this thesis we mostly used semi-quantitative scoring systems to assess the imaged cartilage. Fully quantitative measurements have the advantage of being less dependent on reader experience [2] and may be able to pinpoint smaller changes, but are very time-consuming when performed manually. Semi-automated and fully automated quantification of cartilage thickness programs are available for the knee joint and should be translated for use in small hand joints, so quantitative cartilage measurements can be used in larger hand OA studies. However, software for (fully)-automated cartilage quantification requires sufficient quality of the images. The in-plane resolution of the acquired hrMRI images in our studies should be high enough for (semi)-automatic quantification. However, the contrast between cartilage and joint fluid was low in some patients, which may hinder automatic quantification. This low contrast may partly be caused by partial volume averaging in the slice direction. Future studies should therefore also focus on improving the images for automated cartilage volume measurements, which could be done by creating more isometric voxel sizes, or optimizing other often used MRI sequences for knee cartilage, for use in small hand joints, to acquire better contrast.

Other promising MRI features for cartilage evaluation are markers of cartilage composition. All previously mentioned measurements asses the morphology of the cartilage. The MRI acquired techniques delayed gadolinium enhanced MRI of cartilage (dGEMRIC), T2-mapping and T1ρ-mapping each depict different aspects of the composition of the cartilage, and can display degeneration of the cartilage before morphological cartilage changes are present [3]. These biomarkers are still under investigation in knee OA and show promising, but varying results. Of these techniques, dGEMRIC seems to be the most robust method [4], and the only method investigated so far in small hand joints. Future studies should further investigate the additional worth of compositional cartilage biomarkers in small hand joints.

CT versus CR in thumb base OA

CT seems a better imaging modality than CR for detection of thumb base OA. In **chapter 3** we have shown that CT has a higher reliability than radiography for detection of OA features in the thumb base, and detects more OA features than radiography in patients with severe thumb base OA. It is known that CR has low sensitivity, but high specificity for detection of scaphotrapeziotrapezoidal (STT) OA[5]. We detected with CT more OA features in the STT joint, and expect most of these findings to be accurate. We therefore assume that CT has a better sensitivity than CR. However, we have no indication on how the specificity of CT relates to CR and future studies could determine this and it's sensitivity by comparing pre-operative CT with arthroscopy.

CT is advised above CR only in certain pre-operative situations. In daily practice, the higher sensitivity of CT would not matter in most clinical settings, as in most cases it will not lead to a changes in clinical management, as there are limited therapeutical options. However, in severe thumb base OA surgical resection may be considered, and the presence or absence of OA on adjacent joint surfaces may influence the type of surgery. Some hand surgeons advocate the use of imaging in severe OA to pre-operatively determine the joint status and plan the type of surgery, while others rather determine the joint state peroperatively[6]. We realize that it is unknown if use of pre-operative CT leads to any improved patient outcome, and to prove this a large trial is needed, which is probably not feasible. However, for those surgeons preferring to know the joint state pre-operatively, we would advise to use CT above CR for detection of OA in the STT joint.

Low field MRI and ultrasound in early arthritis

Contrast-enhanced low field MRI is good method for detection of synovitis. As shown in **chapter 6** contrast-enhanced low field MRI is as good as contrast-enhanced high field MRI for detection of synovitis in arthralgia and early arthritis patients. Standardized ultrasound examination had a lower sensitivity than MRI, but in comparison with high field MRI, was highly specific. The field strength of the MRI machine does not matter in the diagnostic capability

for synovitis, as long as gadolinium contrast is used. While synovitis can be assessed without contrast by using T2 fat saturated or short tau inversion recovery (STIR) images, it has been shown that reliability is then lower, that low field MRI machines lose sensitivity, and that high field MRI machines become less specific[7]. Unfortunately low field MRI cannot be advised for detection of bone marrow edema (BME), as the detection rate was poor.

MRI erosions were scored in half of our patients, but it is unlikely that the majority was caused by erosive disease. Half of our patients with early arthritis and inflammatory arthralgia had erosions on MRI, while only 38% of patients developed RA after one year. While some of these erosion-like lesions will be beginning erosions caused by RA, others may be normal anatomy like vascular channels, anatomical variants, or erosion-like pathology caused by other disease or degenerative processes. It is currently unknown what the clinical implications of these MRI erosions are. Recently, in a high-resolution CT study, the definitions of erosions were adjusted to make them more specific for RA [8]. Future research should prove if these updates really make the definition more specific for RA, and if so they should also be used for MRI. Until then CT and MRI remain very good for follow-up of bone lesions in RA patients, and by this help in determining disease progression or healing.

Conventional radiography remains the first imaging step to detect erosions in daily practice. CR is widely available, relatively cheap, and has short imaging times for assessment of all hand joints. While ultrasound is less sensitive for detecting erosions than CT and MRI, it is more sensitive for detection of erosions in finger joints than CR. The sensitivity becomes higher if the joint is better accessible with ultrasound, and the joint can be examined from multiple angles. The best sensitivity in the hand is therefore attained in the second and fifth metacarpal head. As specificity of ultrasound-detected erosions is high in comparison with CT and MRI, there is definitely a place for assessment of erosions in MCP and PIP joints while assessing for synovitis as long as the entire joint is scanned.

In the clinical setting, ultrasound remains the first imaging method of choice for detection of synovitis as it is relatively cheap, readily available and has a high specificity for synovitis detection**.** In the diagnostic process of early

inflammatory arthralgia, establishing the presence of arthritis is important, as this may have immediate implications for diagnosis and treatment. If clinical examination remains unsure, imaging plays a role in detecting subclinical synovitis. Ultrasound remains the first choice, and only in cases with negative ultrasound and remaining clinical suspicion for arthritis, MRI may play a role because of its higher sensitivity and specificity, when clinically relevant. For research purposes, e.g. in clinical trials the higher sensitivity of high field MRI, including its higher sensitivity to detect erosions and ability to detect BME, is a good reason to prefer above US.

Limitations of performed studies

There are a few limitations of the performed studies which should be taken into consideration**.**

A first limitation is that selection bias may be present in some of our studies. Selection bias is an error which can occur if the studied sample was not a good random sample of the targeted population. In chapter 6, patients with arthritis were only eligible for participation if they did not yet start treatment. This probably has led to some selection bias, as some patients with severe symptoms, and therefore with more possible imaging findings on MRI and US, had to start treatment before both MRI scans could be performed. We will therefore have imaged a subpopulation of patients with overall lower disease activity. If we extrapolate our findings to the general population of patients with inflammatory hand complaints, the sensitivity of ultrasound and low field MRI may be higher. In our OA studies in chapter 4 and 5, we studied hrMRI of cartilage in two vastly different subpopulations of patients with hand OA. In chapter 4 patients with severe CMC1 OA were imaged, while in chapter 5, generally patients with mild to moderate finger OA were imaged. We expect the validity results of chapter 4 to be generalizable to chapter 5, but we cannot be certain.

As a second limitation, radiological imaging will always be subject to some information bias. Information bias occurs due to systematic errors in measurement, which may then lead to misclassification. In radiology this can

happen during acquisition of images, detection of abnormalities on the images, and interpretation of these abnormalities. In all studies presented from chapter 3-6 we tried to minimize this bias. Systematical difference in image acquisition was minimized in all studies by using standardized imaging protocols, except in chapter 3 which was a retrospective study. In this study, different views were available per examination. We did not have enough data to subdivide the data for the used radiological views, but one can expect that the difference in accuracy between CT and CR can diminish if more specialized views are used for depiction of the CMC1 and STT joint, like the Bett's view.

In chapter 6, ultrasound was used in which purposely the acquisition of images was standardized for only one of the readers. There was a significant difference between the results of those readers, but we cannot determine if this could also be partly because of systematical difference in detection and interpretation. To minimize errors in both detection and interpretation, we employed multiple readers to reduce variability in chapters 3-5, either by using a consensus result, or by using the averages of the readers. To minimize errors in interpretation, scoring systems were used in chapter 3-6 which are specifically created to increase consistency of results within and between studies. Overall, information bias will be least present in the chapters about direct cartilage imaging. Some information bias may be present, but we do not think that this would have a significant effect on our conclusions.

As a third limitation, validity of imaging methods is ideally tested against a golden standard. In hand joint research, the ideal reference standard would be histology, which is hard to obtain. In most chapters construct validity was assessed instead by comparison with other radiological imaging methods.

Future imaging methods in hand joints.

New imaging methods can be considered for future evaluation of hand joints in the future. The recently developed tomosynthesis is a new radiological imaging method, which has not been described in the previous chapters. The technique uses x-rays to acquire images from multiple angles in a limited arc. It does not fully rotate around the patient like CT. As a result, Image quality,

monetary costs and radiation dose all fall between conventional radiography and CT. Tomosynthesis is currently used in mammography and research for other applications is ongoing. Recently, the value of tomosynthesis has been evaluated for features of OA and RA in hand joints. When CT was used as the reference standard, the specificity of both tomosynthesis and CR was high, but the sensitivity of tomosynthesis for JSN, osteophytes and erosions was much higher than CR.[9-11]. One study even concluded that the diagnostical performance of tomosynthesis was comparable to MRI for detection of erosions.[12] These studies are very promising and tomosynthesis may therefore find it's place in future research and clinical work.

Nuclear imaging methods are beyond the scope of this thesis, but may also be very interesting for OA and RA research. They show pathophysiology instead of anatomical details, and can be used in combination with radiological imaging methods. 18-fluoride is a positron emission tomography (PET)-tracer which is sensitive for bone remodeling. It has shown to be present in bone of OA patients at the place of BMLs and adjacent to mild cartilage damage. Future studies may show that 18F is an early marker of OA and predict (sub)chondral bone damage. The upcoming advent of PET-MRI may more easily combine these studies with morphological MRI and MRI measures of cartilage composition.

Conclusions:

- Direct cartilage imaging with high resolution MRI in small hand joints has a higher accuracy than indirect cartilage imaging.
- CT has a better detection rate of OA features in the STT joint than conventional radiography, and may therefore be recommend pre-surgery if this influences the surgical plan.
- Contrast enhanced low field MRI has a high accuracy for detection of early synovitis in the hand, but shows poor diagnostic performance in detection of bone marrow edema.
- Ultrasound has a lower sensitivity than contrast enhanced MRI for detection of early synovitis, but is specific.

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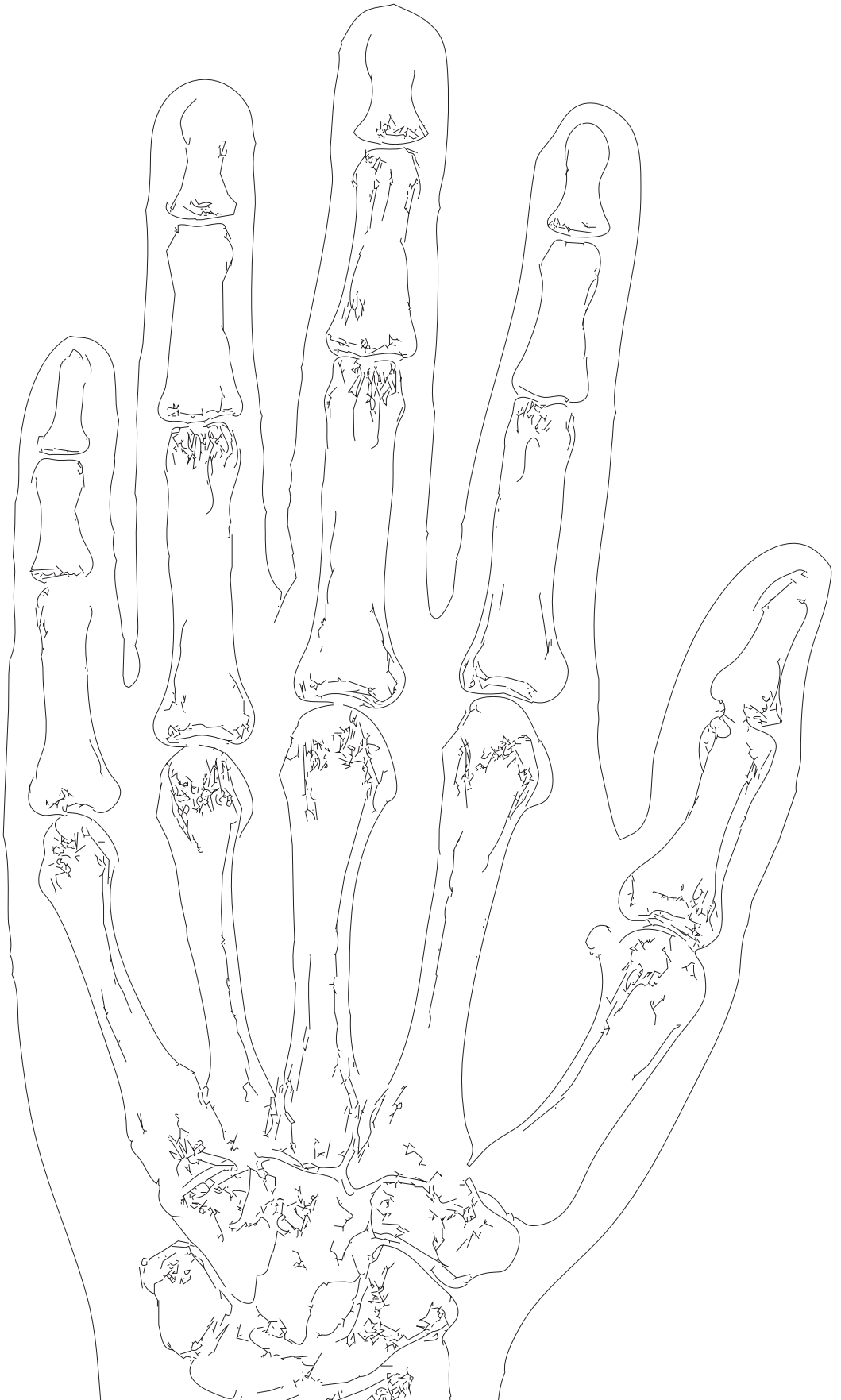


Summary
Nederlandse samenvatting

Summary

Osteoarthritis (OA) and rheumatoid arthritis (RA) are two prevalent joint disease of very different etiology, both affecting hand joints, and both a large cause of hand pain and hand disability in developed countries. The focus of this thesis lies on improving knowledge of radiological imaging techniques to detect features of OA and RA in hand joints.

In **chapter 1**, a general overview is given on osteoarthritis and rheumatoid arthritis, including the changes that happen in the joints on an anatomical level. The working mechanisms of the different radiological imaging methods are explained, as well as how these affect the imaging of hand joints with osteoarthritis and rheumatoid arthritis. The chapter ends with a discussion of the current role that imaging has in these diseases leading to the specific aims of this thesis: (I) To assess construct validity and reliability of direct cartilage imaging with MRI in hand OA; (II) to asses if CT has better reliability and detection rate of thumb base OA than conventional radiography; and (III) To assess construct validity of low-field extremity MRI in early arthritis patients.

Conventional radiography is the standard method to image hand OA. The available literature on imaging techniques other than conventional radiography for imaging hand OA was systematically reviewed in **Chapter 2.** Validity, reliability and responsiveness of these imaging methods were assessed. No CT studies measuring these properties for hand OA were found. The available MRI and US studies showed that they are promising candidates for early detection of hand OA and for future use in clinical trials. However, further research was still needed to improve US and MRI scoring methods, to further asses MRI reliability and to determine responsiveness of both US and MRI.

The presence of OA in the scaphotrapeziotrapezoidal (STT) joint affects the surgical procedure in patients with severe OA of the first carpometacarpal (CMC1) joint. In **chapter 3**, CT was compared with conventional radiography for the detection of OA of the CMC1 and STT joint. CT had a better inter-reader reliability and was more sensitive for detection of OA in the thumb base, especially in the STT joint. CT may therefore improve selection of treatment and planning of surgical procedures in patients with severe thumb base OA.

The validity of direct cartilage imaging in small hand joints with high resolution MRI (hrMRI) is assessed in **chapter 4**. Here patients with thumb base OA scheduled for trapeziectomy underwent hrMRI of the CMC1 joint before surgery. Afterwards histological sections of the removed trapezium were compared with MRI findings. Severe cartilage loss was present in these patients, and MRI accurately visualized the size of overall areas of cartilage damage. However, the depth of the cartilage loss was often underestimated by MRI. This was caused by thin lines of high signal intensity which were visible with MRI on the eroded articular which resembled remaining cartilage.

Chapter 5 continues the evaluation of direct cartilage imaging with hrMRI, by comparing it to indirect MRI cartilage evaluation using inter-bone distance in both hand OA patients and healthy controls. Reliability of the both methods was comparable. With direct cartilage imaging more joints with subtle cartilage damage were detected in hand OA patients, and less false positive joints were detected in healthy controls, suggesting better validity.

Finally, in **chapter 6**, a less expensive low field MRI was compared with normal high field MRI and ultrasound for the detection of synovitis, bone marrow edema, and erosions, in patients with hand arthralgia and early arthritis. Compared with high field MRI, low field MRI was as good in detecting synovitis, better than ultrasound; low field MRI had poor sensitivity for detecting bone marrow edema; and for erosions, low field MRI was better than ultrasound but less sensitive than high field MRI. **Chapter 7** is a general discussion about the acquired results, limitations of the performed research and future research opportunities concerning direct cartilage imaging with MRI; use of CT in the thumb base OA; and use of low field MRI and ultrasound in early arthritis. The main conclusions of this thesis were:

- Direct cartilage imaging with high resolution MRI in small hand joints has a higher accuracy than indirect cartilage imaging.
- CT has a better detection rate of OA features in the STT joint than conventional radiography, and may therefore be recommend pre-surgery if this influences the surgical plan.

- Contrast enhanced low field MRI has a high accuracy for detection of early synovitis in the hand, but shows poor diagnostic performance in detection of bone marrow edema.
- Ultrasound has a lower sensitivity than contrast enhanced MRI for detection of early synovitis, but is specific.

Nederlandse samenvatting

Artrose en reumatoïde artritis (RA) zijn twee verschillende gewrichtsziekten die veel voorkomen in de westerse wereld en vaak leiden tot pijn en functieverlies in onder andere de handen. Dit proefschrift richt zich op het verbeteren van de kennis over het detecteren van RA en artrose in handgewrichten met radiologische afbeeldingstechnieken.

Hoofdstuk 1 introduceert de ziekten artrose en reumatoide artritis en gaat in op de zichtbare veranderingen in het gewricht. Daarnaast worden de verschillende radiologische technieken beschreven, en de gewrichtsveranderingen van artrose en RA die hiermee gedetecteerd kunnen worden. Als laatste wordt de huidige rol van de radiologische beeldvorming bij deze ziekten beschreven, leidend tot de doelstellingen van dit proefschrift:

(I) Het bepalen van de constructvaliditeit en betrouwbaarheid van het direct afbeelden van kraakbeen met MRI in handartrose; (II) onderzoeken of CT meer en betrouwbaarder duimbasis artrose kan detecteren dan de standaard röntgenopname; (III) Het bepalen van de constructvaliditeit van lage veldsterkte MRI in patienten met vroege artritis.

De standaard en veel onderzochte methode om handartrose af te beelden is de normale röntgenfoto. In **hoofdstuk 2** is de beschikbare literatuur over het afbeelden van handartrose met andere beeldvormingstechnieken systematisch uiteengezet. Hierbij is voornamelijk gelet op de validiteit, betrouwbaarheid en responsiviteit van de beeldvormingstechnieken. Er bleken geen geschikte publicaties over CT te zijn. The beschikbare literatuur over MRI en echo liet zien dat beide methoden veelbelovend lijken voor zowel vroege detectie van handartrose als voor het gebruik in toekomstige klinische studies. Er is echter nog wel verder onderzoek nodig naar betere scoringsmethoden voor echo en MRI, meer onderzoek naar de betrouwbaarheid van MRI en meer onderzoek naar de responsiviteit van zowel MRI als echo.

De chirurgische techniek die gebruikt kan worden voor de behandeling van ernstige artrose van het eerste carpometacarpale (CMC1) gewricht wordt beïnvloed door de aan- of afwezigheid van artrose in het naastgelegen

scapho-trapezo-trapezoïdale (STT) gewricht. In **hoofdstuk 3** werden CT-onderzoeken vergeleken met röntgenfoto's om te zien hoe goed deze zijn in het detecteren van artrose van zowel het CMC1 als het STT gewricht. CT had een hogere betrouwbaarheid en CT was meer sensitief in het detecteren van duimbasisartrose, en dan voornamelijk voor het detecteren van STT artrose. CT kan daarvoor de selectie en planning verbeteren voor patiënten met duimbasis artrose.

De validiteit van het direct afbeelden van kraakbeen met hoge resolutie MRI (hrMRI) in kleine handgewrichten werd onderzocht in **hoofdstuk 4**. Patiënten met duimbasisartrose die gepland waren voor een trapeziëctomie kregen vlak voor de operatie een hrMRI scan van het CMC1 gewricht. Na de operatie werden histologische snede's gemaakt van het trapezium, en deze werden vergeleken met de bevindingen op MRI. Ernstig kraakbeenverlies was aanwezig in alle geopereerde patiënten. MRI kon accuraat de grootte van de kraakbeendefecten in beeld brengen, echter de diepte van de kraakbeendefecten werd met MRI vaak onderschat. Deze onderschatting werd veroorzaakt doordat op MRI een dunne lijn van hoge signaalintensiteit zichtbaar was op het al geërodeerde gewrichtsoppervlak, waardoor het leek dat er nog restkraakbeen aanwezig was.

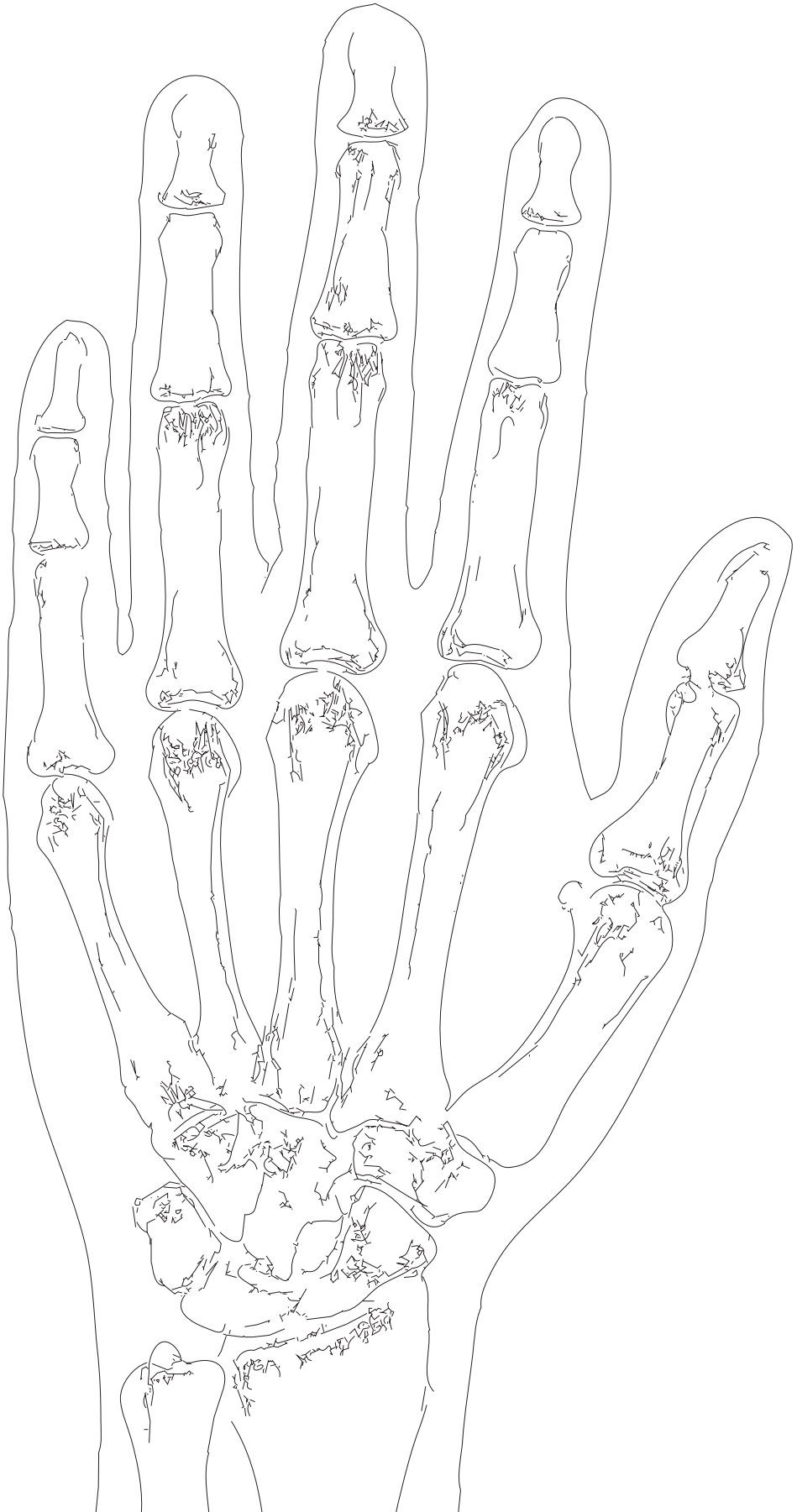
Hoofdstuk 5 gaat verder in op de evaluatie van het direct afbeelden van kraakbeen met hrMRI. Hier wordt hrMRI vergeleken met de meer gangbare MRI techniek om indirect kraakbeenschade te bepalen door het meten van de bot-bot afstand. Dit werd gedaan in zowel patiënten met handartose als gezonde controles. De betrouwbaarheid van beide MRI methoden was vergelijkbaar. Met het direct afbeelden van kraakbeen werden meer gewrichten met subtiele kraakbeenschade gevonden in de groep met handartose, en werden minder gewrichten met kraakbeenschade gedetecteerd in de groep van gezonde controles, passend bij een betere validiteit van het direct afbeelden van kraakbeen met hrMRI.

In **Hoofdstuk 6** wordt een geld besparende lage veldsterkte (0.2T) MRI scanner vergeleken met echografie en een normale hoge veldsterkte (1.5T) MRI voor het detecteren van synovitis, botoedeem en erosies bij patiënten met handpijn en/of vroege artritis. Vergeleken met 1.5T MRI, was 0.2T MRI goed in het detecteren van synovitis en beter dan echografie. 0.2T MRI had echter een

lage sensitiviteit voor het detecteren van botoedeem. Voor het detecteren van erosies was 0.2T MRI beter dan echografie, maar minder sensitief dan 1.5T MRI.

Hoofdstuk 7 betreft de algemene discussie over de gevonden resultaten, de limitaties van de studies en de toekomstige onderzoeksmogelijkheden betreffende direct kraakbeen visualisatie met MRI, het gebruik van CT in duimbasisartrose; en het gebruik van lage veldsterkte MRI en echo voor gebruik in voege artritis. De hoofdconclusies van dit proefschrift zijn:

- Direct afbeelden van kraakbeen met hoge resolutie MRI in handgewrichten heeft een hogere accuratesse dan indirect kraakbeen afbeelden.
- CT heeft een hogere detectie van artrose in het STT gewricht dan röntgenfoto's, en wordt daarom aangeraden in de pre-operatieve fase als dit de operatie kan beïnvloeden.
- Lage veldsterkte MRI met contrast heeft een goede accuratesse voor het detecteren van synovitis, maar is slecht in het detecteren van botoedeem.
- Echo heeft een lagere sensitiviteit dan MRI voor het detecteren van vroege synovitis, maar is wel specifiek.



Appendix

List of abbreviations

ACR	American college of rheumatology
anti-ccp	antibodies against cyclic citrullinated peptides
AUSCAN	Australian/Canadian hand index
BME	bone marrow edema
BML	bone marrow lesion
CMC	carpometacarpal joint
COSMIN	consensus-based standards for the selection of health status measurement instrument
CR	conventional radiology
CT	computed tomography
DIP	distal interphalangeal joint
DESS	duel echo steady state
dGEMRIC	delayed gadolinium-enhanced MRI of cartilage
DMARD	disease-modifying anti-rheumatic drug
DMOAD	disease-modifying osteoarthritis drug
ETL	echo train length
EULAR	European league against rheumatism
Fig	figure
FISP	fast imaging with steady state precession
FRFSE	fast recovery fast spin echo
FS	fat saturation
FSE	fast spin echo
FOV	field of view
HOA	hand osteoarthritis
HOAMRIS	hand osteoarthritis MRI scoring system
ICC	intraclass correlation coëfficient
IDEAL	iterative decomposition of water and fat with echo asymmetry and least-squares estimation
IQR	interquartile range
JSN	joint space narrowing
OA	osteoarthritis
OARSI	osteoarthritis research society international
LRTI	ligament reconstruction and tendon interposition
MCP	metacarpophalangeal

MOAKS	MRI osteoarthritis knee score
MRI	magnetic resonance imaging
MTP	metatarsophalangeal joint
NEX	number of excitations
OMERACT	outcome measures in rheumatoid arthritis clinical trials
PACS	picture archiving and communication system
PCA	percentage close agreement
PD	proton density
PEA	percentage exact agreement
PET	positron emission tomography
PIP	proximal interphalangeal joint
PsA	psoriatic arthritis
QAREL	quality appraisal of reliability studies
QUADAS	quality assessment of diagnostic accuracy studies
RA	rheumatoid arthritis
RAMRIS	rheumatoid arthritis MRI scoring system
REACH	Rotterdam early arthritis cohort
RF	rheumatoid factor
SD	standard deviation
SPECT	single photon emission computed tomography
SPGR	spoiled gradient
STIR	short tau inversion recovery
STT	scaphotrapeziotrapezoidal
TE	echo time
TR	repetition time
US	ultrasonography

List of publications

Saltzherr, M., Selles, R., Bierma-Zeinstra, S., Muradin, G., Coert, J., van Neck, J. and Luime, J. (2013). Metric properties of advanced imaging methods in osteoarthritis of the hand: a systematic review. *Annals of the Rheumatic Diseases*, 73(2), pp.365-375.

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Saltzherr, M., Muradin, G., Haugen, I., Selles, R., van Neck, J., Coert, J., Hazes, J., and Luime, J. Cartilage evaluation in finger joints in healthy controls and early hand osteoarthritis patients using high-resolution MRI. *Submitted*.

Saltzherr, M., Luime, J., Ten Cate, D., Østergaard, M., Conaghan, P., Ouwendijk, R., Weel, A., Hazes, J., Muradin, G. Low field MRI for identification of inflammatory changes in hand arthralgia and early arthritis - a comparison with high field MRI and ultrasound. *Submitted*.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: M.S. Saltzherr
Erasmus MC Department: Radiology and nuclear medicine, Rheumatology
Research School: NIHES
PhD period: 2009 until 2018
Promotors: prof. dr. J.M.W. Hazes, prof. dr. G.P. Krestin
co-promotors: dr. J.J. Luime, dr. R.W. Selles

1. PhD training	***Year***	***Workload (ECTS)***
General research skills		
- Biostatistics for clinicians	*2010*	*1.0*
- Diagnostic research	*2010*	*0.9*
- Regression analysis for clinicians	*2011*	*1.9*
- Courses for the quantitative researcher	*2011*	*1.4*
- Repeated measurements	*2011*	*1.4*
In depth-courses		
- Biomedical English Writing and Communication	*2010*	*4.0*
- Basiscursus Regelgeving en Organisatie van Klinische trials	*2010*	*1.0*
- Personal training in the Rheumatoid Arthritis MRI Scoring system, Hvidovre Hospital, Copenhagen	*2009*	*1.0*
Invited lectures		
"Modern imaging of osteoarthritis of the CMC1 joint" 19th Esser Course, Rotterdam, the Netherlands	2013	1.0

(Inter)national conferences with presentations

"Metric properties of imaging methods in hand OA: a systematic review" OARSI World Congress, San Diego, USA. Oral presentation	2011	2.0
"Metric properties of imaging methods in hand OA a systematic review" American Congress of Rheumatology. Poster presentation	2011	1.0
"Computed Tomography for the detection of thumb base osteoarthritis, comparison with digital radiography" European Congress of Radiology, Vienna, Austria. Poster presentation	2012	1.0
"Detection of synovitis, bone erosions, and bone marrow oedema in patients with inflammatory hand pain - a comparison of low field and high field MRI" EULAR Congress, Berlin, Germany. Poster presentation	2012	1.0
"Computed tomography for the detection of thumb base osteoarthritis comparison with digital radiography" Radiologendagen, 's-Hertogenbosch, the Netherlands. Oral presentation	*2012*	*2.0*
"Accuracy of MRI in evaluating cartilage loss in the CMC1 joint: a comparison with histology." European Congress of Radiology, Vienna, Austria. Poster presentation	*2013*	*1.0*
"Cartilage evaluation in finger joints in healthy controls and early hand osteoarthritis patients using high-resolution MRI" European society of musculoskeletal radiology annual congress, Amsterdam The Netherlands, Poster Presentation	2018	1.0

Other attended conferences		
Radiologendagen, 's-Hertogenbosch, the Netherlands	2013	1.0
Radiologendagen, Rotterdam, the Netherlands	2015	1.0
Radiologendagen, Rotterdam, the Netherlands	2018	1.0
Seminars and workshops		
Follow-up Workshop on Photoshop and illustrator, Rotterdam	2012	0.3
Follow-up Workshop on Indesign, Rotterdam	2012	0.15
18th Esser Course," Tendon Injuries of the Hand", Rotterdam	2012	0.2
Grants:		
EUR trustfonds travel grant	2009	
EUR trustfonds travel grant	2011	
Reumafonds travel grant	2011	
2. Teaching activities		
Supervising master's thesis		
- Supervising A. Hosseini, Medicine, Erasmus MC Rotterdam. Topic: Comparison of CT-scan and radiography for the detection of CMC1 osteoarthritis: implications for surgical intervention.	2011	3.0
Teaching practical anatomy and radiology to 1-4th year medical students, Erasmus MC	2013-2018	5.0
Lecturing anatomy and radiology to medical students during their radiology internships, Erasmus MC	2013-2018	5.0
Total:		39.1

Over de auteur

Michael Sean (roepnaam: Sjel) Saltzherr werd geboren op 22 Maart 1982 te Amersfoort. Het grootste deel van zijn jeugd woonde hij samen met zijn ouders en zijn zusje in Wijk bij Duurstede, en in 2000 behaalde hij zijn VWO diploma op het Revius Lyceum te Doorn. In datzelde jaar verhuisde hij naar Amsterdam om in 2001 zijn propedeuse Biomedische wetenschappen aan de Universiteit van Amsterdam te behalen. Hierna begon de start van de studie geneeskunde aan diezelfde universiteit op het AMC. De interesse in de radiologie werd gewekt tijdens het keuze co-schap radiologie in het AMC en niet lang daarna, in het voorjaar van 2008, behaalde hij zijn geneeskundediploma.

Na zijn studie werkte Sjel bijna een jaar in het geneeskundeonderwijs bij de afdeling huisartgseneeskunde in het VUMC, maar daarna was het tijd voor de definitieve overstap naar de radiologie. Hierboor begon Sjel aan de start van een promotietraject in het Erasmus, wat tot dit proefschrift heeft geleid. Dit promotietraject was een samenwerking tussen de afdelingen Reumatologie, Radiologie, Plastische, Reconstructieve- en Handchirurgie en de afdeling Revalidatiegeneeskunde. In 2013 begon Sjel daarnaast in het Erasmus MC aan de opleiding tot radioloog onder llopleider dr. Winnifred van Lankeren, welke hij begin december 2018 heeft afgerond. Sindsdien volgt hij een fellowship musculoskeletale radiologie, ook in het Erasmus MC, onder begeleiding van dr. Edwin Oei.

Sjel woont samen met Jenny Brouwer in Capelle aan den IJssel, en samen hebben ze twee zoons: Robin en Thomas.

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