The Reliability and Validity of Magnetic Resonance Imaging in Patients with Hand Osteoarthritis

Thesis by

Ida Kristin Haugen

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Diakonhjemmet Hospital

Department of Rheumatology

Oslo, Norway

University of Oslo

Faculty of Medicine

Oslo, Norway

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Abbreviations

2D = two-dimensional

3D = three-dimensional

ACR = American College of Rheumatology

AIMS-2 = Arthritis Impact Measurement Scales-2

Anti-CCP = Anti-Cyclic Citrullinated Peptide

AUSCAN = Australian Canadian hand index

AvmICC = Average measure Intraclass Correlation Coefficient

B0 = external magnetic field

BLOKS = Boston Leeds Osteoarthritis Knee Score

BML = Bone Marrow Lesion

CMC= Carpometacarpal

CR = Conventional Radiography

CT = Computed Tomography

dGEMRIC = delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage

DIP = Distal Interphalangeal

DMOAD = Disease-Modifying Osteoarthritis Drug

EULAR = European League Against Rheumatism

FIHOA = Functional Index of Hand Osteoarthritis

FOV = Field of View

Gd = Gadolinium

GEE = Generalised Estimating Equations

GRE = Gradient Echo

HAQ = Health Assessment Questionnaire

HOAMS = Hip Osteoarthritis Magnetic resonance imaging Scoring system

hrMRI = high-resolution Magnetic Resonance Imaging

ICC = Intraclass Correlation Coefficient

ICF = International Classification of Functioning, disability and health

JSN = Joint Space Narrowing

κ = Kappa

KL = Kellgren-Lawrence

KOSS = Knee Osteoarthritis Scoring System

MCP = Metacarpophalangeal

MOAKS = Magnetic resonance imaging Osteoarthritis Knee Score

MRI = Magnetic Resonance Imaging

NSAIDs = Nonsteroidal Antiinflammatory Drugs

OA = Osteoarthritis

OARSI = Osteoarthritis Research Society International

OMERACT = Outcome Measures in Rheumatoid Arthritis Clinical Trials (Outcome Measures in Rheumatology)

OR = Odds Ratio

PACS = Picture Archiving and Communication System

PASS = Patient Acceptable Symptom State

PCA = Percentage Close Agreement

PD = Proton Density

PEA = Percentage Exact Agreement

PIP = Proximal Interphalangeal

PsA = Psoriatic Arthritis

PsAMRIS = Psoriatic Arthritis Magnetic Resonance Imaging Score

RA = Rheumatoid Arthritis

RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Score

RF = Radiofrequency

SACRAH = Score for Assessment and quantification of Chronic Rheumatoid Affections of the Hands

SDD = Smallest Detectable Difference

SE = Spin Echo

SEM = Standard Error of Measurement

SF-36 = Short Form-36

SmICC = Single measure Intraclass Correlation Coefficient

STIR = Short Tau Inversion Recovery

TE = Echo Time

TI = Inversion Time (tau)

TR = Repetition Time

US = Ultrasonography

WORMS = Whole Organ Magnetic resonance imaging Scoring system

List of papers

I. Hand osteoarthritis and MRI: Development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score.

Haugen IK, Lillegraven S, Slatkowsky-Christensen B, Haavardsholm EA, Sesseng S, Kvien TK, van der Heijde D, Bøyesen P. Ann Rheum Dis 2011;70:1033-8

II. Comparison of features by MRI and radiographs of the interphalangeal finger joints in patients with hand osteoarthritis.

Haugen IK, Bøyesen P, Slatkowsky-Christensen B, Sesseng S, Bijsterbosch J, van der Heijde D, Kvien TK. Ann Rheum Dis 2011 Oct 11. [Epub ahead of print]

III. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis.

Haugen IK, Bøyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK. Ann Rheum Dis 2011 Nov 25. [Epub ahead of print]

1. Introduction and background

1.1. Clinical aspects of hand osteoarthritis (OA)

1.1.1 Definitions and classification criteria

Osteoarthritis (OA) is the most common musculoskeletal disease (1) and may have considerable impact on health-related quality of life (2). The hand, knee and hip joints are most frequently affected, and hand OA usually involves the distal interphalangeal (DIP), proximal interphalangeal (PIP) and thumb base joints (3). Hand OA is often co-occurring with OA in the larger joints and may represent a marker of a generalised OA susceptibility. Kellgren and Moore suggested the concept of generalised OA early in the 1950s (4), and numerous studies have later confirmed an association between hand and knee OA and to a lesser extent to hip and spine OA (5-7). However, there is still no consensus about the definition of generalised OA, i.e., the required number and location of affected joints (8).

OA was previously separated into primary and secondary OA based on the absence or presence of known prior events/diseases related to OA respectively (9). The distinction between these two phenotypes is currently not recommended (10).

The diagnosis of hand OA is based on a combination of medical history, clinical examination, radiographs and possibly laboratory tests (in order to exclude differential diagnoses) (11). The American College of Rheumatology (ACR) criteria for classification of hand OA are the most widely used hand OA criteria in clinical and epidemiological studies (Table 1) (12). The criteria include major clinical hand OA characteristics but do not involve the entire spectrum of disease manifestations. Radiography was considered of less value than clinical examination for the classification of symptomatic hand OA.

The most common method for radiographic definition of OA is the Kellgren-Lawrence (KL) grading scheme and atlas (13, 14). The definition of OA at a single joint (KL grade $\geq$ 2) is consistent across studies, but there are substantial variations in the required number of affected joints and/or the involvement of specific hand joints (15). Radiographic hand OA can further be separated into erosive and non-erosive OA, although the exact criteria for the definition of erosive hand OA are subject of debate (16). There is also no consensus whether erosive hand OA represents a different subset or a severe stage of hand OA (16, 17).

Table 1. The American College of Rheumatology classification criteria for clinical hand OA (traditional format).

Criterion:
1. Hand pain, aching or stiffness for most days of the prior month and 3 of 4 following features:
2. Hard tissue enlargement of 2 or more of 10 selected joints *
3. Hard tissue enlargement of 2 or more distal interphalangeal joints
4. Fewer than 3 swollen metacarpophalangeal joints *
5. Deformity of at least 1 of 10 selected joints *

* The 10 selected joints are the 2nd and 3rd distal interphalangeal, 2nd and 3rd proximal interphalangeal and the 1st carpometacarpal joints of both hands.

1.1.2 Epidemiology

The prevalence and pattern of radiographic hand OA have been extensively studied (3, 18-22), whereas the incidence and longitudinal course of hand OA in the general population are less well described (3, 23-25). The estimates show large variation, which may be due to differences in types of populations, disease definitions and/or risk factors such as genetic background or environmental exposures (26). Studies of rural societies have shown higher estimates of hand OA than studies of more modern Caucasian societies (3, 18-21), while the estimates are lower among Chinese (22). The age-standardised prevalence of radiographic hand OA in the Framingham OA study was similar in women and men (44% vs. 38%), whereas symptomatic hand OA was twice as frequent in women (14% vs. 7%) (3). OA in the DIP, PIP and thumb base joints were more frequent in women than in men, whereas OA in the metacarpophalangeal (MCP) and wrist joints were more frequent in men (3).

Studies using clinical or self-reported OA criteria show lower prevalence estimates of hand OA than studies using radiographic definitions (27, 28). A Norwegian population-based study found that the prevalence of self-reported hand OA was 4% (28).

Few studies have described the epidemiology of erosive hand OA in the general population (3, 29, 30). The age-standardised prevalence of erosive hand OA was much higher in women than in men in the Framingham OA study (10% vs. 3%), and it was especially frequent in women 60 years of age or older (3).

1.1.3 Pathogenesis

OA was previously considered as a degenerative cartilage disease but is now recognised to involve the whole joint, including the subchondral bone, synovium, capsule, ligaments and menisci (if present) (31). We have limited knowledge about the pathogenesis of hand OA, and this section will therefore mainly present studies performed in knee OA.

OA in early stages is a dynamic process with catabolic and anabolic activities, and it is characterised by increased chondrocyte proliferation and an up-regulation of the synthetic activity in the extracellular matrix of the cartilage. Growth factors and bone morphogenetic proteins stimulate the repair of cartilage and the formation of osteophytes. The demand subsequently surpasses the capacity of repair. Abnormal mechanical loading and synovial inflammation contribute to dysregulation of the chondrocytes and an imbalance in favour of increased catabolic activity in the cartilage with gradual loss of proteoglycans and collagen type II. These changes are accompanied by fibrillation of the cartilage surface and localised production of fibrocartilage. Degradation will result in less ability to withstand normal biomechanical stresses, creating a vicious cycle of cartilage damage (32).

The periarticular bone plays an important role in the OA pathogenesis and can be separated into the subchondral bone plate (cortical bone), subchondral trabecular bone and bone at the joint margins. The bone alterations in OA reflect bone remodelling and repair processes. OA is characterised by increased thickness of the subchondral plate, modified architecture of the trabecular bone (thickening and increased number of trabeculae), development of subchondral cysts and osteophyte formation at the joint margins (33). Subchondral erosions in hand OA seem to be associated with biomechanical loading (reflected as cartilage loss) and may possibly be a result of the remodelling process (34). Similarly, the cysts may either represent intrusion of joint fluid into the bone by fissurated cartilage (35) and/or be consequences of repair of bone destruction (36, 37). Osteophytes are formed at the joint margins by proliferation of periosteal and synovial cells, which subsequently differentiate into chondrocytes that undergo hypertrophy and endochondral ossification (32, 38).

Synovitis in OA is assumed to be secondary to cartilage breakdown. Degradation products are released into the synovial fluid and get phagocytosed by the synovial cells, which produce catabolic and pro-inflammatory mediators. Hence, the production of proteins responsible for cartilage breakdown is enhanced, creating a positive feedback loop (39).

1.1.4 Risk factors

Hand OA is caused by a combination of systemic risk factors and local biomechanical factors (Figure 1).

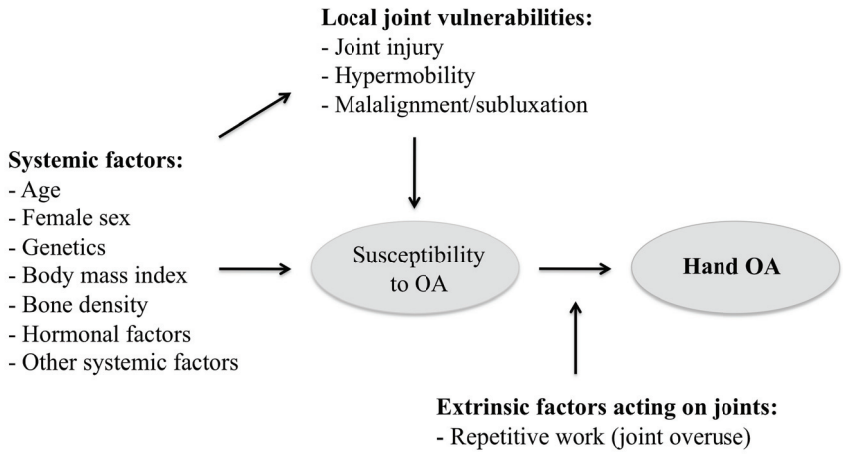

Figure 1. Risk factors for development of hand OA, modified from Hunter DJ (40).

The prevalence and incidence of hand OA increase with age (3), which is probably due to a cumulative exposure to various risk factors and biologic changes related to aging. Epidemiological studies have shown that hand OA is more common in women than in men after the age of menopause (3), but the relationship between sexual hormones and OA is controversial. Most evidence points in the direction of no relation between female hormonal aspects and OA in the hand, hip and knee joints, but the results are conflicting (41).

The genetic influence in hand OA has been estimated to be approximately 30-60% (42, 43). OA is genetically heterogeneous with multiple genes contributing to small increases in the overall risk of OA. Candidate gene studies and genome-wide association studies have revealed polymorphisms and mutations in genes in control of skeletal development, genes encoding extracellular matrix proteins and signal proteins related to inflammation (44-46).

Obesity has been discovered as a risk factor for hand OA, suggesting that the link between obesity and OA is not only mediated through biomechanical loading (47, 48). Recent studies have suggested that metabolic factors associated with obesity alter the systemic

levels of pro-inflammatory cytokines, which are also related to OA. However, clinical studies have shown inconsistent results regarding the association between metabolic factors related to obesity and hand OA (49-52). A link between hand OA and cardiovascular disease has recently been discovered (20, 53), but the mechanisms behind this association are not fully understood and need further investigation.

The association between bone mineral density (BMD) and hand OA varies across studies (54-56). Most clinical data suggest an inverse relationship between OA and osteoporosis, but low bone mass may also have a negative effect on the joint cartilage homeostasis (57).

Biomechanical factors are important in hand OA and not only knee and hip OA. However, it is more appropriate to consider the finger joints as load-bearing rather than weight-bearing. Most of the intra-articular force in the finger joints is due to contraction of muscles that traverse the joints rather than direct loading (58). The DIP joints sustain the highest pressure per area during precision grip with contraction of m. flexor profundus, whereas the more proximal joints such as the PIP and MCP joints experience the highest pressure during power grip when contraction of m. flexor superficialis plays a larger role (58). Manual occupation and extensive use of the hands have been associated with hand OA (59-62). Clinical studies have suggested that extensive use of precision grip may increase the risk of OA in the DIP joints, while extensive use of forceful gripping may lead to OA in the MCP joints (62-64). However, there are conflicting results regarding handedness and hand OA development (65-67), and the balance between use and overuse is not yet known.

Hypermobility and subluxation are proven risk factors for thumb base OA (68, 69), while hypermobility is shown to protect against OA in the PIP joints (70, 71).

1.1.5 Management

The European League Against Rheumatism (EULAR), ACR and Osteoarthritis Research Society International (OARSI) have published guidelines and recommendations for the management of OA (72-75). However, only EULAR has specific recommendations for hand OA (76). Both non-pharmacological and pharmacological treatment are required for optimal management of hand OA, and the treatment should be individualised according to the localisation of OA, presence of inflammation, levels of symptoms, comorbidities, comedication and the patients´ own preferences (76).

Non-pharmacological therapy

Non-pharmacological therapy including information, exercise and splints are recommended for all patients with hand OA according to the EULAR recommendations (76).

Pharmacological therapy

Disease-modifying osteoarthritis drugs (DMOADs) are currently not available (77), and pharmacotherapy therefore aims to relieve pain and improve function.

Local treatments are according to the EULAR recommendations preferred over systemic treatments, especially for mild/moderate pain and when few joints are affected (76). Paracetamol (acetaminophen) is recommended as first line therapy due to efficacy and safety reasons, whereas nonsteroidal antiinflammatory drugs (NSAIDs) should be used if inadequate response of paracetamol or if clinical signs of inflammation are present (76). Patients who do not respond to oral analgesics may receive intra-articular injections of corticosteroids, which is most relevant for the 1st carpometacarpal (CMC) joint (76). Opioids and narcotics are indicated only when all other pharmacological options have been considered (76).

Oral glucosamine, chondroitin sulphate, diacerhein, avocado soybean unsaponifiables and intra-articular hyaluronan may have a symptomatic benefit (76), but there are few studies performed in hand OA. The effect of chondroitin sulphate on structural progression and clinical symptoms has been studies in hand OA with limited or conflicting results (78-82). A systematic review similarly concluded with minimal effect of chondroitin sulphate in knee and hip OA (83). The evidence concerning the effect of intra-articular hyaluronan on OA in the 1st CMC joint is sparse, and most studies have been small and not placebo-controlled (84-87). One controlled study showed no significant differences in pain and physical function compared to placebo (88). Anti-inflammatory treatment with a synergistic drug of dipyridamole and prednisolone showed a better effect on pain than placebo in hand OA (89, 90). Hydroxychloroquine, clodronate (bisphosponate) and monoclonal antibodies against interleukin-1 and tumour necrosis factor-α have also been tested in erosive hand OA, but the results regarding the effect on structural progression and clinical symptoms are limited and conflicting (91-96). Treatment with Vitamin K showed no structural effect (97).

To date, no trials have studied the effect of oral glucosamine, diacerhein, avocado soybean unsaponifiables, calcitonin or tetracycline in hand OA. Studies have mainly been performed in knee OA, and none have so far been approved as a DMOAD due to limited/conflicting results or small effect sizes (77). Several trials on the effect of other potential DMOADs are ongoing (98), but these studies will not be discussed in this thesis.

Surgery

Surgery (trapezioectomy alone or with synthetic/biologic interpositions, osteotomy, arthrodesis, total joint replacement) is effective in severe thumb base OA and should be considered in patients with severe symptoms when conservative treatments have failed (76).

1.2 The OMERACT filter for outcome measures in Rheumatology

OMERACT was originally an acronym for "Outcome Measures in Rheumatoid Arthritis Clinical Trials" but was later broadened to stand for "Outcome Measures in Rheumatology". It has been an international meeting for professionals interested in outcome measures in rheumatology since 1992. The aim of OMERACT is to improve outcome measures in rheumatology through a data-driven, iterative consensus process, and the guidelines are forever "preliminary" based on the assumption that future data will lead to further refinement and modification of the guidelines. The selection of valid domains follows the guidelines formulated by Bombardier and Tugwell (99-102) and re-formulated into the "OMERACT filter" (103). The filter can be summarised into three domains, of which each represents a question to be answered of the outcome measure (Table 2). An outcome measure is valid for use if it can answer all three questions.

The OMERACT process inspired the work in this thesis. We have focused on aspects from the first and second domains; the construct validity and reliability of MRI in hand OA.

Table 2. The OMERACT filter (103).

Domain	Question	Content
Truth	Is the measure truthful, unbiased and does it measure what is intended?	This concept captures issues of face, content, construct and criterion validity.
Discrimination	Does the measure discriminate between situations of interest?	This concept captures issues of reliability and sensitivity to change, either for states at one time (for classification/prognosis) or states at different times (to measure change).
Feasibility	Can the measure be applied easily, given constraints of time, money and interpretability?	This concept captures the practical extent to which an outcome measure can be applied successfully.

Validity of MRI includes different aspects concerning whether MRI is measuring what it intends to measure (104, 105). Good face validity requires that the outcome measure is generally viewed as relevant and useful based on the current knowledge. Content validity refers to whether the outcome measure is covering all the areas of relevance (in this thesis: both relevant OA features and anatomical coverage), while construct validity refers to whether the outcome measure makes biological sense and whether it is consistent with other measures. Criterion validity is the degree to which the outcome measure truly reflects a gold standard. In this thesis, we focused on the construct validity of MRI against conventional radiography (CR) (paper II) and measures of pain and physical function (paper III).

Reliability refers to the consistency of the measurement, i.e., the degree to which an instrument measures the same at two separate times. In this thesis, both the same observer and different observers re-evaluated the MRI scans (blinded for the first measurement) in order to make repeated measurements, and the intra-observer and inter-observer reliability could be calculated respectively (paper I). Sensitivity to change was not examined due to only cross-sectional MRI data.

The 3rd aspect of the OMERACT filter, i.e., the feasibility of the proposed MRI scoring system in hand OA (paper I), will be briefly discussed.

1.3 Clinical assessment of hand OA

1.3.1 Clinical joint examination

Physical examination is needed to confirm and characterise joint involvement and to exclude differential diagnoses such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Clinical joint examination includes assessment of bony enlargement, soft tissue swelling, tenderness and limited motion.

Heberden's and Bouchard's nodes are firm swellings over the lateral or dorsal aspects of the DIP and PIP joints respectively (106). These nodes are associated (but not synonymous) with underlying radiographic changes of OA and especially osteophytes (107, 108). Bony enlargement can be difficult to distinguish from joint effusion. It has been suggested that the lateral nodes are occurring in area with the least resistance in the capsule, such as between the extensor tendon and the collateral ligaments (106, 109, 110), while the dorsal nodes represent traction spurs. The lateral and dorsal nodes may also coexist and fuse (106).

1.3.2 Patient-reported outcomes

Patients with hand OA suffer from joint pain, swelling, stiffness, limited motion and deformity, resulting in poorer health-related quality of life (2). They describe problems within many domains of activity and participation, and tasks requiring considerable grip strength combined with twisting of the hands represent the most frequently described hand related problems (111). The International Classification of Functioning, Disability and Health (ICF) by the World Health Organisation offers a comprehensive understanding of functioning, which is described as a complex interplay between body functions and structures, activities, participation and contextual factors (112).

The OMERACT initiative has recommended pain, physical function and patient global assessment as the three core domains in hand OA (113). However, there is no consensus about the preferred instrument (114). Several disease-specific instruments have been designed for hand OA, such as the Australian Canadian (AUSCAN) hand index (115), the Score for Assessment and quantification of Chronic Rheumatoid Affections of the Hands (SACRAH) (116), the Cochin Hand Functional Disability Scale (117) and the Functional Index of Hand OA (FIHOA) (118). The AUSCAN and SACRAH comprise pain, stiffness

and physical function, while the FIHOA and Cochin comprise physical function only. The Arthritis Impact Measurement Scales-2 (AIMS-2), which is an arthritis-specific instrument, has also a subscale of hand and finger function (119). The instruments have been translated, and the Norwegian versions of AUSCAN, FIHOA and AIMS-2 have shown satisfactory psychometric properties (120-123). Levels of "Patient-Acceptable Symptom State" (PASS) for AUSCAN pain (below 8.2 on a 0-20 scale) and AUSCAN physical function (below 16.1 on a 0-36 scale) have been proposed (124).

Joint pain can also be measured on visual analogue scales (0-100 mm).

1.3.3 Objective measures of physical function

Measurement of grip strength is a surrogate marker of impairment in hand OA and can be measured by a hand dynamometer (e.g., JAMAR) (125).

The fine motor dexterity of the hand can be measured with Moberg Pick-up test. The patients are instructed to pick up twelve items one at a time and place them into a container as fast as possible, and the performance is timed with a stop watch (126).

1.4 Magnetic resonance imaging (MRI) in OA

1.4.1 Principles of MRI

A detailed description of the theoretical basis of MRI physics is beyond the scope of this thesis. The following sections will give a brief introduction of the principles and technical aspects of MRI (127, 128).

MRI is based on the electromagnetic properties of the atomic nuclei. The hydrogen nuclei (1 proton, 0 neutron) are most often used in clinical MRI due to the abundance in the human body. The hydrogen nuclei spin around their own axis, inducing a magnetic field around each nucleus. The magnetic moments have a size and a direction (i.e., a vector), but they will be randomly orientated in the absence of an external magnetic field (B0). When the nuclei are exposed to B0, the magnetic moments of the nuclei will align with B0 in parallel or anti-parallel direction, creating a net magnetisation vector. B0 also causes the nuclei to

spin around the axis of B0, which is called precession. The hydrogen nuclei have a precessional frequency that is different from other MRI active nuclei, and this allows specific imaging of hydrogen nuclei in the body.

The hydrogen nuclei gain energy from resonance, which is the phenomenon that occurs when the nuclei are exposed to an oscillation that is close to their natural precessional frequency. Application of a radiofrequency (RF) pulse leads to excitation of the hydrogen nuclei in parallel position to B0 into anti-parallel position or into the transversal plane by a certain angle (i.e., flip angle). The hydrogen nuclei also move into the same phase. This coherent moving of magnetisation in the transverse plane produces magnetic field fluctuations and an electrical voltage in the receiver coil. This electrical voltage constitutes the MRI signal.

When the RF pulse is switched off, the net magnetisation vector will again be influenced by B0 and will try to align with it. The nuclei must lose the energy that was previously gained by the RF pulse in a process called relaxation. Recovery is the regain of magnetisation in the longitudinal plane, while decay is the loss of magnetisation in the transversal plane.

1.4.2 Technical aspects of MRI

The MRI unit

The main components of an MRI unit are the following (127, 128):

1. The main magnet, which produces B0. The strength of B0 is important for image quality (higher strength increases signal-to-noise ratio and gives higher resolution) and feasibility (higher strength gives less scanning time).

2. The gradient coils, which provide the exact location and amplitude of the signal. Gradients are alterations to the magnetic field that are generated by coils of wire located within the bore of the magnet along the longitudinal, vertical and horizontal axes.

3. The RF transmission system, which provides excitation of the hydrogen nuclei. It consists of a radiofrequency sender and receiver.

4. The data processing system for image acquisition. The raw imaging data is stored in the MRI system and must be transformed to obtain the final images.

MR pulse sequences

Spin echo (SE) and gradient echo (GRE) sequences represent two fundamental types of MRI pulse sequences (128). The pulse sequences can also be either two-dimensional (2D) with one plane acquired at a time or three-dimensional (3D) with imaging of an entire volume in one acquisition. The 3D images can be manipulated to look at the anatomy in any plane and at any angle of obliquity.

In SE sequences, an initial RF pulse directs the net magnetisation vector into the transverse plane (i.e., the flip angle is always 90 degrees). A second RF pulse with a flip angle of 180 degrees is then applied to rephase the spinning nuclei. In this thesis, we used a 2D Short Tau Inversion Recovery (STIR) sequence, which is a SE sequence variant with a 180 degrees preparatory pulse in order to null the signal from fat (128).

In GRE sequences, the flip angle is variable (15-75 degrees) and the net magnetisation vector will partly be flipped into the transverse plane. Gradients instead of RF pulses are used to dephase and rephase the transverse magnetisation. In this thesis, we used a 3D Dixon technique.

The STIR and Dixon techniques are described in more detail in the next sections.

Image quality

The image quality is mainly dependent of contrasts, resolution and noise/artefacts (127, 128):

1. Contrast

Contrast refers to the difference in signal intensities between two regions of an MRI scan. Factors that affect image contrasts are usually divided into intrinsic and extrinsic contrast parameters.

Intrinsic contrast parameters are inherent to the body's tissue and cannot be changed. Images obtain contrast mainly through mechanisms of T1 recovery, T2 decay, T2* (T2 star) decay and proton density (PD). During T1 recovery ("spin-lattice"), the nuclei are getting realigned with B0 due to release of energy from the spinning nuclei to the environment. Time 1 (T1) is the time in milliseconds required for 63% of the nuclei to realign with B0.

During T2 decay (“spin-spin”) and T2* decay, the nuclei are dephased due to interaction between the spinning nuclei and magnetic field inhomogeneities respectively. Time 2 (T2) is the time in milliseconds when the magnetisation in the transverse plane has lost 63% of its original value. PD is a measure of proton concentration, i.e., the number of atomic nuclei per given volume. Water and fat represents two extremes of MRI contrast with different T1 and T2 times.

The inherent T1, T2 and PD mechanisms occur simultaneously in any image, but one process can be made dominant by external contrast parameters. The most important parameters are repetition time (TR), echo time (TE) and flip angle, which all can be selected at the operator console. The TR time is time interval between the beginnings of two successive series of RF pulses, and it controls the extent of T1 recovery before a new serie of RF pulses is applied. The TE time is the interval between the centre of the RF pulse and the centre of the recorded echo, and it controls the amount of T2 decay before the signal is received.

In T1-weighted images, the T1 contrast is accentuated by a short TR interval. Tissue with long T1 (e.g., water) will not be able to recover and align with B0. Water has less longitudinal magnetisation than fat before the next RF pulse and therefore less transverse magnetisation after the RF pulse. Hence, water will appear dark compared to tissues with short T1 (e.g., fat). TE is short in order to limit the T2-weighting.

In T2-weighted images, a long TE interval is used to accentuate the inherent differences in T2 between different tissues. Tissues with long T2 (e.g., water) will take longer to decay and will have greater signal and appear brighter than signal with short T2 (e.g., fat). TR value is long in order to limit the T1-weighting.

With PD-weighting, the numbers of protons per unit volume is the main determinant for image contrast. The effects of T1 and T2 contrast must be diminished by long TR and short TE values to achieve PD-weighting.

The fat signal will occur bright in many important clinical imaging sequences and can obscure underlying pathology such as inflammation and oedema (129). Hence, in many situations it is useful to null the signal from fat. This can be done by several methods such as chemical shift selective saturation, out-of-phase imaging (Dixon technique) and STIR

sequences. We will here briefly explain the mechanisms of fat saturation by the Dixon technique and the STIR sequence, which were used in the current thesis.

The Dixon technique is used in GRE sequences to null the signal from voxels (i.e., pixel volumes) in which fat and water coexist. Fat and water have different precessional frequencies and can therefore be imaged when they are in the same phase at certain time points and when they are at different phases at other time points. By adding and subtracting the "in-phase" and "out-of-phase" images, water and fat images can be separated (130, 131). The technique allows fast acquisition of T1-weighted images (131).

STIR is an inversion recovery pulse that uses the inversion time (TI, tau), which is the time it takes for fat to recover from full inversion (180 degrees) to the transverse plane (90 degrees) so that there is no longitudinal magnetisation of fat (null point). The conventional 90 degrees RF pulse will flip the fat vector back to 180 degrees inversion, so there is no transverse component of fat after excitation. Hence, no signal will be produced from fat whereas water will still produce signal. Several 180 degrees pulses can then be applied in order to amplify the signal from water. Practically STIR is only used with fast SE or SE techniques. T2 and T1 differences contribute additively to the contrast in STIR sequences, and the contrast is therefore very good and tissues with long T1 and long T2 appear very bright (127, 129).

2. Resolution

The spatial resolution is the ability to distinguish between two points as separate and distinct. The resolution is controlled by the voxel size, which is a volume of tissue within the patient determined by the pixel area and slice thickness. The pixel area is determined by the size of the field of view (FOV) and the number of pixels in the FOV (i.e., matrix). The spatial resolution is higher when the voxels are small. However, small voxels contain less nuclei that contribute to the signal and will therefore have lower signal-to-noise ratio (127).

3. Noise and artefacts

Signal-to-noise ratio is defined as the ratio between a signal (i.e., meaningful information) and the background noise (i.e., unwanted signal generated by the patient in the magnet and the background electrical noise of the system). It should be as high as possible and is

achieved by a coarse (not fine) matrix, thick slices and high field strength as well as specialised coils.

Artefacts represent undesired image distortions, which can lead to misinterpretations of MRI data. Pitfalls in scoring of MRI scans of the wrist and MCP joints in RA have been described (132), and many of the same considerations are applicable in hand OA. The following sections will describe the artefacts that are most relevant in the current thesis:

Partial volume artefacts occur when a structure is only partly contained within the voxel, and they are most marked in regions where tissues of different signal intensity adjoin (e.g., the interface between inflamed synovial membrane and bone). Inhomogeneity of fat suppression may occur when the area being imaged lies within a part of B0 that is not completely uniform. Both partial volume artefacts and inhomogeneous fat suppression may result in an appearance mimicking bone marrow lesions (BMLs).

Susceptibility artefacts can occur when adjacent tissues have different susceptibilities, which is the degree of magnetisation by B0. A wide range of precessional frequencies can appear within a voxel, which can cancel each other out. Metal artefact is an example of a severe susceptibility artefact.

The “magic-angle” phenomenon refers to the increase in signal intensity that occurs when collagen fibres are oriented at 55 degrees relative to B0. Collagen fibres restrict the mobility of water protons and promote interactions between the nuclei, contributing to T2 decay and low signal intensity. The extent of the “spin-spin” interactions varies according to the angle of the fibres in relation to the axis of B0 and is minimal at an angle of 55° (i.e., maximal T2 time). Hence, the signal intensity of the collagen fibres with this specific angle in relation to B0 will be increased. This artefact affects any collagen-containing structures, including articular cartilage, menisci and ligaments (of which the latter is relevant in this thesis), and it can mimic tissue damage or reduce contrast towards adjacent structures (133).

Other artefacts include chemical shift artefacts, truncation artefacts, wrap-around artefacts, movement artefacts and pulsation artefacts, which will not be explained in further detail (132).

1.4.3 Advantages and limitations of MRI

MRI allows the joint to be visualised as a whole organ and provides much more detailed picture of the OA changes than any other imaging modality without any radiation. MRI has unlimited image contrast possibilities, and contrast-enhanced imaging provides additional information about synovitis (134).

Disadvantages of MRI include the high price compared with CR, long acquisition time and contraindications to the procedure. MRI is contraindicated in patients with aneurysm clips, pacemakers, cochlear implant and metallic splinters in the eye. The MRI equipment is expensive to purchase, maintain and operate. Experts are needed for input on the selection of sequences and correct utilisation, and the readers must be aware of artefacts during the interpretation of images (134, 135).

Gadolinium (Gd) contrast may lead to nephrogenic systemic fibrosis and should not be administrated to persons with reduced kidney function (136). It typically manifests with skin tightening, tethering and hyperpigmentation, and systemic fibrosis of internal organs has been identified due to deposition of free Gd in the tissues (136).

1.4.4 Assessment of OA pathologies with MRI

Cartilage morphology and composition

MRI of the cartilage can be classified into morphological (structural) and compositional assessment (137).

The cartilage morphology can be evaluated by semi-quantitative or quantitative methods. Focal cartilage defects are best visualised by either direct MRI arthrography (intra-articular contrast) or indirect arthrography (intravenous contrast with delayed imaging so the contrast can diffuse into the synovial fluid). Other good alternatives are fluid-sensitive sequences (fat-saturated PD-weighted and T2-weighted fast SE sequences), which give an arthrographic effect of the cartilage (low signal intensity) against the synovial fluid (high signal intensity). Conventional T1-weighted SE images offer poor contrast between cartilage and fluid. GRE imaging with fat-saturation, which was used in the current thesis, provides the highest contrast between cartilage (high signal intensity) and bone (low signal intensity) but less contrast between the cartilage and the adjacent synovial fluid. GRE

sequences are therefore less suitable for assessment of focal cartilage defects, but they are frequently used in knee OA for quantitative assessment of cartilage volume and thickness due to the high spatial resolution (134).

Compositional assessment of cartilage includes techniques such as T2 mapping, T1rho, delayed Gd-enhanced MRI of Cartilage (dGEMRIC), sodium imaging and diffusion-weighted imaging (137). These techniques allow biochemical or molecular imaging of the cartilage and may detect "pre-morphological" cartilage changes (138-140). These techniques are not part of the current thesis and will not be further explained.

Synovitis

MRI can visualise synovitis, either with or without the use of Gd contrast. Gd contrast has been recommended for optimal assessment of synovitis in knee OA and RA (141, 142). Use of contrast promotes the distinction between synovial effusion and synovial tissue, but diffusion of contrast from the synovial membrane to the synovial fluid obscures the boundary between these two components.

Synovitis is usually evaluated by semi-quantitative scoring methods (as described later), but quantification of synovitis can also be performed by semi-automated volume analyses (143) or dynamic contrast-enhanced MRI (144, 145).

Bone morphology

Cysts are seen as well-defined areas with fluid-like signal intensity on unenhanced MRI scans. Most subchondral cysts show post-Gd enhancement, which may be due to entering of synovial fluid or tissue through chondral fissures and/or diffusion of contrast into the cysts from surrounding areas with bone remodelling (37).

OA-related BMLs are seen as hyperintense areas often with diffuse borders. Optimal assessment can be achieved by either a fat-saturated T2-weighted, PD-weighted or a STIR sequence (134). Histological studies in knee OA have shown that BMLs mainly contain necrosis, fibrosis, remodelled trabeculae and only minimal oedema (146). The mineral content in these lesions is reduced due to remodelling with high bone turn-over (147).

Bone attrition in the knee is seen as flattening or depression of the joint plate (148), which is probably caused by bone remodelling (149). Erosions in the finger joints may have a similar

appearance with typical “seagull wing” configuration, but the erosions can also be located at the joint margins (150).

Cortical bone produces a signal void on MRI. The imaging of osteophytes is therefore dependent on good contrast towards the adjacent tissues.

Ligaments and tendons

Foci of high signal intensity due to the “magic angle” phenomenon on MRI scans may mimic inflammation and tear (133).

1.4.5 MRI scoring systems in knee and hip OA

To date, four semi-quantitative MRI scoring systems for knee OA have been published: The Whole Organ MRI scoring system (WORMS), Knee Osteoarthritis Scoring System (KOSS), Boston Leeds Osteoarthritis Knee Score (BLOKS) and MRI Osteoarthritis Knee Score (MOAKS) (151-154). They include a variety of OA features that are believed to be relevant to pain and functional integrity of the joint and/or the pathophysiological processes. The details of the different scoring systems will not be explained in detail in this thesis. The WORMS is most commonly used and includes the following features: Cartilage, BMLs, cysts, osteophytes, attrition, meniscal status, combined effusion/synovitis, collateral/cruciate ligaments and periarticular features (151). KOSS and BLOKS cover mostly the same features but differ with respect to the grading and the use of a lesion-orientated approach rather than a strict subregional approach (152, 153). The process behind the development of the scoring system was only described for the BLOKS (153). Excellent reliability data has been published for WORMS, KOSS and BLOKS (155). However, limitations of the scoring systems have been revealed, and the MOAKS was therefore just recently evolved (154). Furthermore, a separate scoring system for assessment of contrast-enhanced synovitis in knee OA was recently proposed, showing good reliability and validity against patient-reported pain (156).

The Hip OA MRI scoring system (HOAMS) was recently presented (157). The scoring system is extensive and includes features such as cartilage, BMLs, subchondral cysts, osteophytes, labral lesions, synovitis, effusion, loose bodies, attrition, dysplasia, greater trochanter tendonitis/bursitis, labral hypertrophy, paralabral cysts and herniation pits. Good reliability was found for most features. The authors did not describe the process behind the

development of the scoring system but emphasised that the current study was only the initial step in the development of an MRI scoring system for hip OA. Further validation, assessment of responsiveness and refinement of the scoring system are needed (157).

1.4.6 MRI scoring systems in inflammatory arthritic diseases

The OMERACT RA MRI score (RAMRIS) and PsA MRI score (PsAMRIS) have facilitated the use of MRI for assessment of pathology in RA and PsA respectively. The scoring systems were developed by similar processes by a group of experts (mainly radiologists and rheumatologists) under the umbrella of OMERACT. The processes have included agreement upon definitions, scoring exercises and eventual possible modifications of the scoring systems.

The RAMRIS consists of a core set of MRI sequences as well as definitions and a semi-quantitative scoring system for erosions, bone marrow oedema and synovitis located in the wrist and MCP joints. The core set of sequences should include MRI scans in 2 planes with T1-weighted images pre- and post-Gd for assessment of synovitis (grade 0-3) and erosions (grade 0-10) in addition to a T2-weighted fat-saturated sequence or a STIR sequence for assessment of bone marrow oedema (grade 0-3) (158). Furthermore, the OMERACT group has in collaboration with EULAR developed an atlas with reference images in RA joints (159, 160). Several exercises have been performed with good intra- and inter-reader reliability for both cross-sectional and longitudinal readings (104, 161).

The PsAMRIS similarly consists of a core set of MRI sequences as well as definitions and a semi-quantitative scoring system for erosions (grade 0-10), bone marrow oedema (grade 0-3), synovitis (grade 0-3), flexor tenosynovitis (grade 0-3), periarticular inflammation (grade 0-1) and bone proliferation (grade 0-1) located in the MCP, PIP and DIP joints (162). The core set of MRI sequences was the same as reported for RAMRIS. The definitions of the features are presented in table 3. Bone oedema, erosions and bone proliferations were assessed in the distal and proximal part of the joint separately, and the assessed area extended from the surface to the middle of the phalanx. The scoring system has shown good intra- and inter-reader reliability for both cross-sectional and longitudinal readings (163).

Table 3. The definitions of features in PsAMRIS (162).

Feature	Definition
Synovitis	An area in the synovial compartment that shows post-Gd enhancement of a thickness greater than the width of normal synovium.
Flexor tenosynovitis	Signal characteristics consistent with increased water content (i.e., high signal intensity on T2-weighted fat-saturated and STIR images, and low signal on T1-weighted images) or abnormal post-Gd enhancement adjacent to a tendon in an area with a tendon sheath.
Periarticular inflammation	Signal characteristics consistent with increased water content (i.e., high signal on T2-weighted fat-saturated and STIR images) or abnormal post-Gd enhancement at extra-articular sites including the periosteum and the entheses but not the tendon sheaths.
Bone marrow oedema	A lesion within the trabecular bone with signal characteristics consistent with increased water content (i.e., high signal intensity on T2-weighted fat-saturated or STIR images, low signal intensity on T1-weighted images) and often with ill-defined margins.
Bone erosion	A sharply marginated bone lesion with typical signal characteristics (i.e., loss of normal low signal intensity of cortical bone and normal high signal intensity of marrow fat on T1-weighted images), which are visible in two planes with a cortical break seen in at least one plane.
Bone proliferation	Abnormal bone formation in the periarticular region, such as at the entheses and across the joints.

Gd = gadolinium, STIR = Short Tau Inversion Recovery.

1.5 Conventional radiography (CR) in OA

1.5.1 Principles of CR

Radiography is the use of X-rays, which is a form of electromagnetic radiation with a wave-length in the range of 0.01 to 10 nanometres. The basic principles and interpretation of CR have remained essentially the same since the first discovery by Röntgen in 1895. An X-ray tube consists of two principle elements; a cathode and an anode. The cathode terminal is a tungsten alloy filament, which is heated to produce a stream of electrons. When high voltage is applied across the two terminals, the electrons are attracted towards the anode. X-rays are produced when they hit the tungsten target.

Due to the short wavelength, X-rays can penetrate materials that do not transmit visible light. The X-rays are projected towards an object, which will absorb a variable proportion of the X-rays depending on its density and composition. A detector (either analogue films sensitive to X-rays or digital detectors) captures the X-rays that pass through the object, leading to a 2D presentation of all the structures superimposed on each other. Dense structures that block the passage of the X-ray beam through the body, such as bones, appear white. Softer body tissues such as the skin and muscles allow the X-rays to pass through and appear darker (164, 165).

1.5.2 Technical aspects of CR

The X-ray generating system has three major components; the operating console, the X-ray tube (where X-rays are produced) and the generator (where electricity is transformed and rectified) (165).

X-rays cause blackening of the emulsion of a photographic film (165). Norwegian hospitals have the recent years converted from film-based to digital radiography, which consist of a digital detector instead of the analogue films and cassettes. The detector absorbs the energy carried by the X-rays, which is then transformed into electrical charges that are digitised and in a proportional manner quantified into a grey-scale image (166). The advantages of digital imaging include elimination of chemical processing of films, reduced space requirements for storage, adjustment using dedicated computer software to optimise image quality and rapid transmission of images to other locations.

Projections are described by the direction of the X-ray beam. The posteroanterior view (i.e., beam in dorsal to palmar direction) of the hands is always provided in both research and clinical settings. However, oblique and/or lateral views may provide additional information. Accurate interpretation of the radiographs depends on appropriate positioning of the hands (the hands should be opened, pronated and placed flat against the cassette) and appropriate film exposure. The exposure is determined by the ability of the beam to penetrate an object (controlled by voltage adjustment) and the number of X-rays photons (“light particles”) in the beam (milliampere per second) (165).

1.5.3 Advantages and limitations of CR

Plain radiography is the "gold standard" for imaging of OA joints. The method is inexpensive, fast, easily available and provides a good picture of bony changes such as osteophytes (located on the medial and lateral side of the joint), sclerosis, osteoporosis and soft tissue calcifications.

CR is limited by radiation exposure, but the dose of radiation for hand radiography is minimal (0.001 millisievert, which corresponds to only 3 hours of natural background radiation). The main limitation of radiography is its inability to directly visualise cartilage, synovitis, other non-osseous structures and BMLs. Reproducibility of positioning and joint alignment may be problematic for CR of the knees, but is less controversial for hand radiography (134, 135).

1.5.4 Assessment of OA pathologies with CR

CR provides a 2D picture of bony changes, such as osteophytes, erosions, cysts and sclerosis. Cartilage, synovium, synovial fluid and capsule have the same radiodensity as the surrounding soft tissues, and these structures cannot be visualised directly (165). Hence, radiographic joint space narrowing (JSN) is only an indirect measure of cartilage loss.

Osteophytes are seen as bony protrusions at the joint margins of the finger joints. The "true" intra-articular osteophytes are best visualised on CR with posteroanterior view. Traction spurs that develop at the dorsal side of the DIP and PIP joints as a physiological response at the insertion site of the extensor tendon can easily be seen on CR with lateral or oblique view (167). In this thesis, only the posteroanterior images were assessed.

Erosive hand OA is characterised by bone damage in the central part of the DIP and PIP joints and less frequently the thumb base (3, 29). They typically have "seagull wing" or "saw-tooth" patterns. Erosions located at the joint margins are less commonly seen on CR (150). Dorsal or plantar erosions can be recognised when they are seen in profile, but can be confused with cysts on frontal images. Subchondral cysts are seen as well-defined areas with loss of the trabecular bone structure. Sclerosis is seen as increased brightness of the subchondral bone on CR and represents increased thickness of the subchondral cortical plate and the subjacent horizontal trabeculae (168).

Radiographic JSN is still the only structural endpoint that is accepted by regulatory bodies in the United States (Food and Drug Administration) and Europe (European Medicines Agency) to prove efficacy of DMOADs in phase III clinical trials (169). JSN in hand OA can be measured on semi-quantitative scales or quantitatively with use of automated or semi-automated methods (170-173).

1.5.5 Radiographic scoring systems in hand OA

Several scoring systems for assessment of radiographic hand OA have been developed (174), and the most widely used systems will be presented in the following sections. The scales differ in assessed joints and whether they provide a global estimation of OA or evaluate individual OA features. Currently, there is no consensus on the preferred scale.

The Kellgren and Lawrence (KL) scale from 1957 was the first proposed radiographic scoring system (13) and is still most widely used (15). KL is a global scale, which grades OA on a 0-4 scale (of which grade ≥ 2 represents definite OA) based on the presence/severity of osteophytes/ossicles, JSN, sclerosis, pseudocystic areas and altered shape of bone ends (13). The World Health Organisation adopted the scale in 1961 as the "gold standard" for assessment of OA, and in 1963 the authors published an atlas with radiographic example images and legends describing the features in each particular film (14). The written definitions of the grades vary across joint groups, and these descriptions also differ from later written descriptions by Lawrence in 1977 (175). These different descriptions across publications have caused confusion in how to interpret the different grades. Further, the KL scale has been criticised for too much emphasis on osteophytes (176), as narrowed/sclerotic joints cannot be classified as having OA unless osteophytes are present. Thus, several studies have used modified KL scales to overcome these limitations.

Several scoring systems with more detailed assessment of individual hand OA features have been developed in order to address the deficiencies of the KL scale and optimise agreement (170, 177, 178). Among those, the OARSI atlas from 1995 (revision in 2007) is most frequently used (170, 178). With this atlas as reference, the presence/severity of individual features such as osteophytes, JSN, subchondral erosions (pseudowidening), cysts, subchondral sclerosis and malalignment are assessed on semi-quantitative scales.

Other global scales have been proposed with more emphasis on JSN in comparison to the KL scale (179, 180). However, none of these proposed indices have been extensively used.

Verbruggen *et al*. developed two numerical scoring systems for the progression and anatomic evolution of erosive and non-erosive hand OA (17, 181). The anatomical lesion progression system assesses changes of osteophytes, JSN and cysts (+/- 0.5 point for increase/decrease in size and +/- 1 point for appearance/disappearance) (181). The anatomical phase progression system is more frequently used and is based on an assumption of hand OA as a disease that undergoes predictable phases; S phase (the joint has classical hand OA features with osteophytes, JSN and/or subchondral bone changes), J phase (the joint space disappears), E phase (the subchondral plate becomes eroded) and lastly the R phase (repair or remodelling of the joint) (17). Recently, Verbruggen *et al.* also proposed a more complex scoring system; the Ghent University Scoring System, which is more sensitive for detection of progression during the destructive phases (182). With this scoring system, the proportions of normal subchondral bone, subchondral plate and joint space are assessed on 0-100 scales with 10 units increase.

2. General aims and specific research questions

2.1 General aims

The general aims of this thesis were to develop an MRI scoring system in hand OA and to study the reliability and validity of structural and inflammatory MRI features.

2.2 Specific research questions

- What is the intra-reader and inter-reader reliability for status scores of structural and inflammatory MRI features in hand OA (paper I)?
- How prevalent are structural and inflammatory MRI features in a cohort of hand OA patients (paper II-III)?
- What is the prevalence of structural and inflammatory MRI features across joints with different radiographic severity (paper II)?
- What is the agreement between MRI and CR in detection of structural OA features (paper II)?
- What is the sensitivity and specificity of MRI in detection of structural features in comparison to CR (paper II)?
- Are structural and inflammatory MRI features associated with tenderness in the same joint (paper III)?
- Is the amount of structural and inflammatory MRI features associated with patient-reported pain, functioning and measurement of grip strength (paper III)?

3. Material and methods

3.1 Study designs

The results in the current thesis are based on data from an observational study with cross-sectional study design.

In paper I, we presented an MRI scoring system for hand OA and applied a test-retest design in order to calculate the intra-reader and inter-reader reliability of the MRI readings. MRI scans of the DIP and PIP joints of the dominant hand from ten hand OA patients (one time point) were evaluated independently by three readers and the readings were repeated by the same readers after one week.

We validated the MRI features against radiographic features in paper II and against measures of pain and physical function in paper III (all examinations performed at approximately same time point).

3.2 Study population

3.2.1 The Oslo hand OA cohort

The initiative to the Oslo hand OA cohort started in 2000 with the intention to evaluate health-related quality of life in patients with hand OA and to study the prediction of long-term outcomes. Potential study participants were identified by using diagnostic codes in the hospital data system at Department of Rheumatology (Diakonhjemmet Hospital). Men and women between 50 and 70 years, who had been examined at the outpatient rheumatology clinic within the previous 2 years, were eligible for inclusion in the cohort if they had a diagnosis of hand OA and no other rheumatic diseases. In total 275 eligible patients with hand OA were identified after a thorough review of the patient records. The patients were contacted by postal mail, and 209 of 275 (76%) consented to participate in the data collection (questionnaires/interview, clinical examination and CR of both hands).

The 209 patients were again contacted by postal mail in 2008, and 128 of 209 (61%) met for a follow-up examination in the period 2008-2009. Reasons for non-participation at the

follow-up examination are shown in figure 2. In total 4 patients were diagnosed with or examined for RA or PsA during the period of follow-up, and they were therefore excluded from the cohort. The data collection included the same questionnaires and examinations (including CR) that were performed at baseline but also ultrasonography (US) of both hands and contrast-enhanced MRI of the dominant hand. MRI with T1-weighted pre-Gd and STIR images was performed in 107 patients, of whom 97 also had T1-weighted post-Gd images. Both CR and MRI were performed in 106 patients. MRI was optimally performed on the same day as the clinical examination, and 85 participants had an interval between MRI and clinical examination of 22 days or less. Prolonged interval between the examinations was mainly due to practical challenges at the Department of Radiology (Diakonhjemmet Hospital).

All patients described in this thesis had clinical and/or radiographic hand OA. The clinical ACR criteria were fulfilled by 100 of 107 patients (93%) (12), while 104 of 106 patients (98%) had radiographic hand OA defined as one or more joint(s) with KL grade $\geq$ 2 (13).

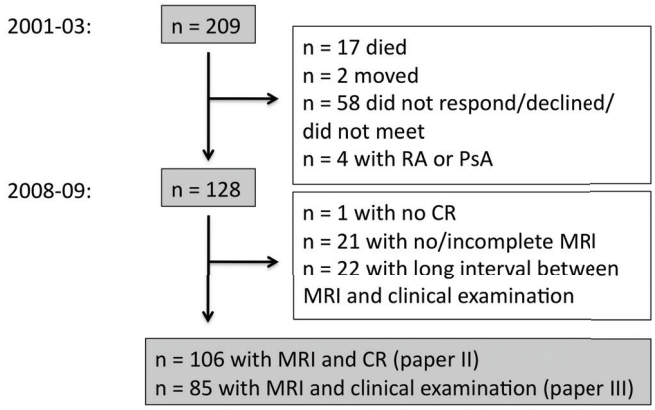

Figure 2. Flowchart of the patients in the Oslo hand OA cohort.

3.2.2 Selection of patients

The analyses in paper I-III were performed on data from the follow-up examination of the Oslo hand OA cohort in 2008-2009.

In paper I, we performed a reliability exercise using MRI scans from ten patients, who were randomly selected among 97 patients with pre-and post-Gd MRI scans. The selection of

patients was based on the severity of radiographic hand OA, i.e., the sum score of KL grades in the DIP and PIP joints in the hand that was imaged by MRI. We selected two patients with available T1-weighted pre- and post-Gd and STIR images from each quintile of the radiographic severity scores.

In paper II, we included 106 patients with available MRI scans (T1-weighted pre-Gd and STIR images) and CR of the dominant hand (Figure 2). All except ten patients had T1-weighted post-Gd images for assessment of synovitis and flexor tenosynovitis

In paper III, we included 85 patients with available clinical data (assessment of tender finger joints) and MRI scans (T1-weighted pre-Gd and STIR images) of the dominant hand performed on the same day or at the latest after 22 days (Figure 2). All except seven patients had T1-weighted post-Gd images for assessment of synovitis and flexor tenosynovitis. In total, 82, 83 and 84 patients completed the FIHOA, AUSCAN pain and AUSCAN stiffness scales, respectively. All patients completed the AUSCAN physical function and AIMS-2 hand/finger scales and measurements of grip strength.

3.3 Data collection

A broad spectrum of variables was collected at the follow-up examination of the Oslo hand OA cohort, including information about demographic and disease related variables. In addition, the patients underwent an extensive whole body joint examination, CR of both hands, US of both hands, MRI of dominant hand and collection of blood and urine samples. Table 4 summarises the most important measures in the three papers included in the current thesis, and this chapter will mainly focus on these measures.

3.3.1 Demographics and patient-reported outcomes

The hand OA patients who consented to participate in the study received a booklet of questionnaires (35 pages) by postal mail approximately one week ahead of the clinical examination. The completed booklet was returned when they subsequently came to the study visit. We used the questionnaires together with clinical interviews performed by study nurses to obtain extensive information about demographic and disease-related variables. Patient-reported outcome measures that were used in paper III are described in more detail.

Table 4. Variables used in the analyses in paper I-III.

	Paper I (n = 10)	**Paper II (n = 106)**	**Paper III (n = 85)**
Demographics			
Age	x	x	x
Sex	x	x	x
Patient-reported outcome measures			
Australian Canadian hand index			x
Functional index in Hand OA			x
Arthritis Impact Measurement Scales-2			x
Physical examination and performance-based measures			
Tender joint count			x
Grip strength			x
MRI			
Synovitis	x	x	x
Flexor tenosynovitis	x	x	x
Erosions	x	x	x
Cysts	x	x	x
Osteophytes	x	x	x
Joint space narrowing	x	x	x
Malalignment	x	x	x
Bone marrow lesions (BMLs)	x	x	x
Collateral ligament (CL) discontinuity	x	x	x
BMLs at CL insertions	x	x	x
Conventional radiography			
Kellgren-Lawrence		x	x
Osteophytes		x	
Joint space narrowing		x	
Erosions		x	
Cysts		x	
Malalignment		x	

The Australian Canadian (AUSCAN) hand index

AUSCAN is the most widely used patient-reported outcome measure in hand OA and assesses both pain (five items), stiffness (one item) and physical function (nine items) during the last 48 hours (115). We used the Likert scale version, which gives the patient a choice of five response options (0-4 scale, of which 4 represents worst health) for each of the 15 items. The pain dimension measures the amount of hand pain at rest, when gripping, lifting, turning and squeezing objects, while the stiffness dimension asks for stiffness in the morning. The physical dimension is capturing difficulties with the following tasks: turning taps, turning a round door knob or handle, doing buttons, fastening jewellery, opening a new jar, carrying a full pot with one hand, peeling vegetables and fruits, picking up large and heavy objects and wringing out washcloths. Subscale scores were obtained by calculation of the mean value of the assigned values scored on the questions within the subscale and then multiplied with the number of items in the subscale (in order to correct for missing values). At least three pain items and five physical function items had to be assigned by the patient to obtain the AUSCAN pain and physical function sum scores respectively.

The Function Index in Hand OA (FIHOA)

FIHOA is originally an investigator-administered hand OA-specific instrument and consists of ten questions about functional impairment on a four-point Likert scale (0-3 scale, of which 3 represents worst health) (118). In the Oslo hand OA cohort, the patients completed the questionnaire. Total score was obtained by calculation of the mean value of the assigned values scored on the questions and then multiplied with ten (in order to correct for missing values). At least six items had to be assigned.

The Arthritis Impact Measurement Scales-2 (AIMS-2)

AIMS-2 is a multidimensional instrument that was initially developed for RA, but it can also be used in other rheumatic joint diseases like OA (119). It consists of 57 items covering 12 dimensions of health status, of which one captures hand and finger function. This subscale consists of five questions on a five-point Likert scale (0-4, of which 4 represents worst health). The subscale score was obtained by calculation of the mean value of the assigned values scored on the questions within the subscale and then multiplied five (in order to correct for missing values). At least three items had to be assigned.

3.3.2 Physical examination and performance-based measures

One rheumatologist (Barbara Slatkowsky-Christensen) with 20 years experience in rheumatology performed the clinical joint assessment. Absence or presence of tenderness upon palpation / pain on moving was assessed in the bilateral thumb base, MCP, PIP (including the thumb) and DIP joints as described in the EULAR hand book (paper III) (183). The joint examination also included assessment of soft tissue swelling, bony enlargement and limited motion, but these joint abnormalities were not used as outcome measures in the current thesis.

Grip strength (kg) was assessed in both hands with a Jamar hand dynamometer (Therapeutic Equipment Corporation, Clifton, New Jersey, USA) with the patients sitting with the shoulder in neutral position and 90 degrees flexed elbow (125). The best performance out of two attempts was recorded for each hand. In this thesis, we used measurements of the hand that was imaged by MRI (paper III).

3.3.3 Magnetic Resonance Imaging (MRI)

An 1.0 T extremity MRI scanner (ONI, General Electric Healthcare, Waukesha, Wisconsin, USA) was used for all examinations. The patients rested in a comfortable chair during the examination with their hand resting in a cylindrical coil (diameter 10 cm). The hand was fixed to a plate and the space around the plate and hand was filled with rubber sponge to ensure extended fingers and reduce motion artefacts.

The image sequences were tested in a pilot study in collaboration with a musculoskeletal radiologist (Sølve Sesseng, SS) and MRI technicians. Coronal, sagittal and axial T1-weighted fat-saturated pre- and post-Gd (0.1 mmol Gd/kg body weight; Magnevist, Bayer Schering Pharma AG, Leverkusen, Germany) images were acquired from a 3D dual-echo Dixon technique (131) in addition to coronal and axial STIR images (Table 5). Both T1 and T2 differences may contribute to the contrasts on the STIR sequence, but in this protocol the T1 contrast was made dominant due to short TE time (Table 5).

Table 5. Details of the MRI sequences.

Sequence	Flip angle	Contrast	TR	TE	ST	Gap	FOV	Matrix	Time
3D GRE fat-sat.	15	Pre	20	5	1	0	130	224*224	5:52
3D GRE fat-sat.	15	Post	20	5	1	0	130	224*224	5:52
COR STIR	90	Pre	2850	16.3	2	0.2	130	256*192	4:45
AX STIR	90	Pre	3150	21	3	1	120	256*192	5:09

3D-GRE fat-sat = three-dimensional gradient echo with fat saturation, COR STIR = coronal Short Tau Inversion Recovery, AX STIR = axial Short Tau Inversion Recovery. TR = repetition time (milliseconds), TE = echo time (milliseconds), ST = slice thickness (millimetres), gap = gap between the slices (millimetres), FOV = field of view (millimetres), time = time (minutes:seconds) required to obtain sequences.

The development of the MRI scoring system for hand OA and its reliability are described in paper I. Three readers (Ida K. Haugen, IKH; Pernille Bøyesen, PB; Siri Lillegraven, SL) read ten sets of MRI scans unaware of clinical and radiographic data (not anonymous). The readers had different levels of experience; PB and SL (both medical doctors) had experience in reading MRI scans in inflammatory arthritic diseases and were members of the MRI group in OMERACT. IKH had no previous training in reading MRI scans but had experience in reading hand radiographs for presence and severity of OA (184). The reading was repeated after 1 week, and we calculated the intra-reader and inter-reader reliability. Prior to the second part of the reliability exercise, an external person anonymised, recoded and rearranged the ten MRI scans in a different order. The score sheets from the first reading were unavailable for the readers until the second reading was completed. All readers read the MRI scans independently at different workstations (screens of 24-27 inches). We used Picture Archiving and Communication System (PACS) Sectra (IDS5, SECTRA, Linköping, Sweden) and OsiriX (OsiriX, Geneva, Switzerland) software in the first and second part of the reliability exercise respectively. These software packages allow the reader to adjust window/level settings, such as the ability to zoom in/out, use a localiser to accurately place a specific lesion in two planes and measurement of distances.

All MRI scans were later read according to the proposed MRI scoring system (paper I) unaware of clinical and radiographic data (paper II and III): Osteophytes (grade 0-3;

distal/proximal part of the joint), JSN (grade 0-3), cysts (absence/presence; distal/proximal), malalignment (absence/presence; frontal/sagittal plane), synovitis (grade 0-3), flexor tenosynovitis (grade 0-3), BMLs (grade 0-3; distal/proximal), collateral ligament discontinuity (absence/presence; radial/ulnar) and BMLs at collateral ligament insertions (absence/presence; distal/proximal and ulnar/radial). Erosions (grade 0-3; distal/proximal) and bone attrition (absence/presence; distal/proximal) were scored separately in contrast to the proposed combined definition and grading. Two readers (IKH, PB) in consensus read the ten first MRI scans, while the remaining images were read by IKH alone. IKH re-scored ten randomly selected MRI scans after a period of at least 7 weeks, and the intra-reader reliability was assessed (paper II-III). All MRI scans were read on large screens (24 inches) with use of PACS Sectra software.

3.3.4 Conventional radiography (CR)

Digital bilateral hand radiographs with posteroanterior view were obtained in 102 of 106 patients, whereas 4 patients only imaged the right hand (same hand as imaged by MRI) (paper II).

The finger joints (DIP, PIP including the thumb, MCP and CMC-1) were graded according to the KL scale and the OARSI atlas (13, 170). The KL scale gives a global score of the DIP, PIP, MCP and CMC-1 joints on a 0-4 scale based on the presence and size of osteophytes, JSN, sclerosis, cysts and altered shape of bony ends: 0 = no OA, 1 = doubtful OA, 2 = definite minimal OA, 3 = moderate OA, 4 = severe OA (13). Epidemiological studies often use KL grade 2 or above as the definition of OA.

The OARSI atlas shows example images of different grades of individual radiographic OA features such as osteophytes (grade 0-3), JSN (grade 0-3), erosions (grade 0-1), pseudowidening (grade 0-1), cysts (grade 0-1), sclerosis (grade 0-1) and malalignment (grade 0-1). According to the published atlas, osteophytes and JSN should be scored in the DIP, PIP (including the thumb), CMC-1 and naviculotrapezial joints; malalignment, sclerosis and erosions in the DIP, PIP and CMC-1 joints; pseudowidening in the DIP joints; cysts in the PIP and CMC-1 joints. In this study, all features were scored in the DIP, PIP (including the thumb), MCP and CMC-1, as done for the KL scale.

IKH read the CR images on the same workstations as for the MRI scans with use of PACS Sectra software. The readings were performed blinded for clinical and MRI data. The same reader (IKH) re-scored thirty randomly selected radiographs (not anonymised) after a period of at least 2 weeks. These radiographs were also assessed by a second reader (Jessica Bijsterbosch, JB) from the Department of Rheumatology at Leiden University Medical Centre for calculation of inter-reader reliability. IKH and JB had previously collaborated in a multicentre study about the reliability of different radiographic scoring systems for hand OA. This study was led by rheumatologist Margreet Kloppenburg (MK), a leading expert in the field of hand OA, and her research group at Leiden University Medical Centre (184), and IKH was trained for reading hand radiographs in Leiden under supervision of a musculoskeletal radiologist (Iain Watt) and MK.

3.3.5 Blood samples

A blood sample was drawn from all patients. The erythrocyte sedimentation rate was used for the assessment of the ACR criteria for the hips (below 20 mm per hour) (185). Full-blood and serum have been frozen in a biobank for later use.

3.4 Statistics

All statistical analyses presented in this thesis were performed by IKH in collaboration with a statistician using the Statistical Package for the Social Sciences for Windows, versions 17.0 (SPSS, Chicago, IL, USA). P-values below a cut-off of 0.05 were considered statistically significant.

3.4.1 Descriptive analyses and group comparisons

We present the mean and standard deviation for variables with a normal distribution. Several variables, such as the number of affected joints or sum scores for the MRI features, had a skewed distribution with a right tail, and we present the median and interquartile range. We calculated the prevalence of MRI features across joints with different grades of radiographic severity (KL grades) (paper II) and the prevalence of tenderness in joints with

different grades of MRI pathology (paper III) as counts with percentages. The number of affected joints by MRI and CR was compared by Wilcoxon signed-rank test (paper II).

3.4.2 Reliability

We assessed the reliability of the MRI readings using three statistical methods (paper I): the intraclass correlation coefficient (ICC) as a relative measure of reader agreement in addition to the smallest detectable difference (SDD) and percentage exact and close agreement (PEA, PCA) as absolute measures of agreement. We have also presented the reliability of readings of MRI and CR with use of unweighted/weighted kappa (κ) in paper II and III.

ICC is used to measure reliability when data are considered to be on an interval level (186). In the current context, ICC can be conceptualised as the ratio of the variance between the two readings (of the same patient) to the total variance (all patients). We used the sum scores of the different MRI and radiographic features and calculated the single and average measure ICCs (SmICCs and AvmICCs) for intra-reader and inter-reader reliability respectively. AvmICC corrects for the number of readers. We considered the cases (here: patients) to be a random sample from a larger population, while the readers were entered as a fixed effect (i.e., not random selection). Thus, the analyses were performed with two-way mixed effect models. Agreement was defined in terms of absolute agreement (as opposed to consistency). ICC was interpreted similar to κ (see below) with 1.0 as perfect agreement but with no lower limit (negative estimates may occur).

The SDD represents the smallest difference that can be discriminated from the measurement error. The calculation of SDD was based on the Bland and Altman's 95% limits of agreement method; intra-reader SDD was calculated as 1.96 multiplied with the standard deviation of the mean difference between the two status scores (187), and inter-reader SDD as the pooled within-subject standard error of measurement (SEM) multiplied with $(1.96*\sqrt{2})$ and then divided by the square root of the number of readers ($\sqrt{3}$) (188, 189). SEM represents the square root of the error (residual) variance. SDD = 0 is perfect agreement, but there is no convention regarding any upper limit and it depends on the distribution of the data.

PEA was calculated as the percentage of occasions of which the scoring value was identical between all readers (i.e., inter-reader) or between the first and second reading (i.e., intra-

reader), and PEA = 100% is perfect agreement. PCA was similarly calculated as the percentage of occasions of which the difference was ≤1 (not applicable for features scored as absent/present), and should ideally approach 100%.

Cohen´s κ takes into account the agreement occurring by chance and is frequently used for assessment of reliability of categorical items if there are only two readers or readings (190). Interpretation of κ is often based on the guidelines by Landis and Koch (191): < 0: no agreement, 0–0.20: slight, 0.21–0.40: fair, 0.41–0.60: moderate, 0.61–0.80: substantial, and 0.81–1.0: almost perfect agreement. There are difficulties in interpretation of κ, since κ is affected in complex ways by the presence of bias between the readers/readings and by the distribution of data across the categories (192). Weighted κ is useful when there are ordered response categories and takes into account the seriousness of disagreement (193).

3.4.3 Test performance

Sensitivity and specificity are statistical measures of the performance of a binary classification test (here: MRI). Sensitivity measures the proportion of actual positives, which are correctly identified as such (a / a+c), while specificity measures the proportion of negatives correctly identified (d / b+d) (Table 6). We calculated the sensitivity and specificity of MRI in detection of structural OA features (dichotomised at joint level as absent/present) with CR used as reference (paper II).

As a measure of accuracy, we similarly calculated the PEA as the proportion of "true positive" and "true negative" results (a+d / a+b+c+d) (Table 6). For features that were scored on 0-3 scales with both modalities, we calculated the PEA across the categories and the PCA as the proportion of which the difference was $\leq$ 1 between the two modalities (paper II).

Table 6. Overview of test performance and accuracy of MRI.

		Conventional radiography ("gold standard")	
		Present	Absent
MRI (classification test)	Present	a	b
	Absent	c	d

3.4.4 Univariate and multivariate regression analyses

We calculated the odds ratio (OR) of having MRI pathology present in joints with different levels of radiographic severity with use of logistic regression analyses with Generalised Estimating Equations (GEE) models in order to adjust for several joints within one patient (i.e., within-subject dependency) (paper II). Joints with no radiographic OA (KL grade = 0) served as references, and the analyses were adjusted for age and sex.

We similarly calculated the OR of tenderness in joints with MRI pathology present using logistic regression analyses with GEE models (paper III). Joints without the current MRI feature served as reference, and the analyses were adjusted for age and sex (corrected univariate analyses). Variables with a p-value < 0.25 in corrected univariate analyses were included in a multivariate model (adjusted for age and sex), and the variables were removed from the model one by one with backward selection. The final model included variables that were associated with joint tenderness with a p value ≤ 0.10 (adjusted for age and sex). The multivariate analyses were also repeated with forward selection of variables.

We used an unstructured correlation matrix (paper II and III), which means that the model uses the data to estimate the covariance between the repeated measurements (here: several joints within one person). For one exception (paper II) we used an independent correlation matrix, which is a simpler model, due to inability of the model to finalise the estimation process.

3.5 Legal and ethical aspects

The study was conducted according to the ethical principles of the Declaration of Helsinki. All participants gave their written informed consent prior to entering the study. The regional ethical committee approved the study, and the Data Inspectorate approved the storage of data.

4. Summaries of results

4.1 Paper I

Hand osteoarthritis and MRI: Development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score

In this paper, we introduced a novel MRI scoring system for the DIP and PIP joints in hand OA and tested the intra-reader and inter-reader reliability. The scoring system contained the following features: Synovitis (Gd enhancement, grade 0-3), flexor tenosynovitis (Gd enhancement, grade 0-3), erosions (including subchondral bone collapse, grade 0-3), osteophytes (grade 0-3), JSN (grade 0-3), BMLs (grade 0-3), cysts (grade 0-1), malalignment (grade 0-1), collateral ligament discontinuity (grade 0-1) and BMLs at the insertion sites of the collateral ligaments (grade 0-1). Erosions, osteophytes, BMLs and cysts were assessed in the proximal and distal part of the joint separately, whereas malalignment was assessed in the frontal and sagittal plane.

We proposed a definition for each of the features and their grades and developed an atlas with example images in order to facilitate the scoring.

In the reliability exercise, three readers read ten MRI scans independently, and the readings were repeated after one week after anonymisation and rearrangement of the images. Inter-reader reliability was very good for synovitis, erosions, osteophytes, JSN, malalignment (frontal plane) and BMLs (ICCs ≥ 0.83, PCA ≥ 89%), and good for flexor tenosynovitis (ICC = 0.64, PCA = 80%) and collateral ligament discontinuity (ICC = 0.79, PEA = 63%). Cysts, malalignment (sagittal plane) and BMLs at the insertion sites of the ligaments showed high PEA (≥ 85%), but poor to moderate ICCs (0.00–0.59), which was probably due to low prevalence. The estimates for intra-reader reliability were of similar magnitude as the estimates for inter-reader reliability but lower for synovitis (ICC = 0.48).

Our results suggest that the proposed Oslo MRI score for hand OA can reliably assess hand OA features, but further validation is needed.

4.2 Paper II

Comparison of features by MRI and radiographs of the interphalangeal finger joints in patients with hand osteoarthritis

The main objectives of this paper were to examine the spectrum of MRI pathology, to investigate the construct validity of MRI-defined structural hand OA features with CR as reference, and to explore the association between MRI-defined pathology and radiographic severity in 106 patients with hand OA.

The patients had contrast-enhanced MRI and CR of the DIP and PIP joints of the dominant hand available. The MRIs were scored according to the proposed Oslo hand OA MRI score (presented in paper I). However, we chose to score erosions and attrition separately as opposed to the proposed combined scoring. The hand radiographs were scored according to the KL scale and the OARSI atlas for individual radiographic features.

We found very good agreement between MRI-defined attrition and radiographic central erosions (PEA = 92%, $\kappa = 0.75$), whereas MRI detected almost twice as many joints with attrition and/or erosions as compared to joints with radiographic central or marginal erosions. MRI and CR agreed about absence or presence of erosions/attrition in 71% of the joints; the sensitivity of MRI was very high (95%), whereas the specificity was lower (63%). MRI also detected almost twice as many joints with osteophytes as compared to CR. The agreement between MRI and CR was only moderate (PEA = 37%, weighted $\kappa = 0.50$) due to poor specificity of MRI (22%), although the sensitivity was perfect (100%). PCA was very high (94%) indicating that MRI detected many small osteophytes in joints that appeared radiographically normal. MRI and CR detected similar number of joints with JSN, cysts and malalignment, but the agreement on individual joint level was poor to moderate.

The prevalence of most MRI features increased with radiographic severity, but moderate to severe synovitis was more frequent in joints with mild OA (OR = 2.1, 95% CI 1.4 to 3.2) than in moderate/severe OA (OR = 1.4, 95% CI 1.0 to 2.2) (joints without OA as reference).

We concluded that MRI detected more erosions than CR, suggesting that erosive hand OA may be more common than previously indicated by CR. Synovitis was most common in mild OA, but whether this is due to burn-out of inflammation in late disease must be further investigated.

4.3 Paper III

Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis.

The main objective of this paper was to explore the associations between MRI features and measures of pain and physical functioning in 85 patients with hand OA.

The patients fulfilled questionnaires about hand pain and physical functioning, underwent a clinical examination with assessment of joint tenderness and measurement of grip strength as well as contrast-enhanced MRI of the dominant hand within 22 days after the clinical examination. The MRI scans were scored according to the proposed Oslo hand OA MRI score (presented in paper I).

In our multivariate model, we found that the following MRI features were associated with tenderness in the same joint (adjusted for age and sex): Osteophytes (OR = 1.4, 95% CI 0.9 to 2.1), erosions (OR = 1.4, 95% CI 1.0 to 1.9), bone attrition (OR = 2.5, 95% CI 1.5 to 4.1), moderate/severe synovitis (OR = 2.4, 95% CI 1.6 to 3.8) and BMLs (OR = 1.5, 95% CI 1.0 to 2.3). Synovitis and BMLs were also associated with joint tenderness independent of radiographic severity (multivariate model with both features, adjusted for KL grade, age and sex).

We found no significant associations between the amount of MRI pathology and the AUSCAN pain, AUSCAN physical functioning or AIMS-2 hand/finger subscales. The sum score of MRI-defined attrition was associated with FIHOA (B = 0.58, 95% CI 0.18 to 0.97), while the sum score of osteophytes was associated with grip strength (B = -0.39, 95% CI -0.58 to -0.21).

We concluded that MRI-defined synovitis, BMLs, erosions and attrition were associated with tenderness in the same joint, whereas the associations to patient-reported pain and physical functioning and grip strength were limited. Synovitis and BMLs may represent targets for therapeutic interventions in hand OA.

5. General discussion

5.1 Methodological aspects

Methodological limitations of the studies included in this thesis may contribute to bias, defined as systematic deviations from the truth. Bias is the result of problems in the design and conduct of the study. The following sections describe how these limitations may have affected our results, and methodological strengths are also addressed.

5.1.1 Study design

In all three papers we used a cross-sectional study design.

In paper I, we applied a cross-sectional test-retest design and calculated the intra-reader and inter-reader reliability for status scores. We were not able to assess the reliability for change scores due to the lack of longitudinal data. In the reliability exercise, the retest was performed approximately one week after the first scoring session, and all cases had been anonymised, recoded and reorganised in a different order. Despite a limited number of patients (n = 10), we considered it unlikely that the readers remembered the scores from the first reading.

In paper II and III, we examined the validity of MRI against CR and measures of pain and physical function in a cross-sectional setting. The strengths of this cohort include the extensive data collection with information about imaging findings, clinical examination and patient-reported outcomes. To our knowledge, the Oslo hand OA cohort is currently the largest hand OA cohort with MRI data worldwide.

We found that MRI was more sensitive than CR in detection of structural features such as osteophytes and erosions, and that structural features as well as synovitis were frequently present in joints without definite radiographic OA (paper II). These results may suggest that MRI detects OA features at an earlier time point than CR. However, whether these joints develop future radiographic OA features remains speculative due to the lack of longitudinal data. Longitudinal studies are also needed in order to examine whether MRI is more sensitive in detection of OA progression and whether synovitis can predict future radiographic OA. Although not part of this thesis, we are planning a follow-up examination

(including MRI) of these patients, allowing us to explore the value of MRI in a longitudinal setting.

MRI-defined erosions, attrition, synovitis and BMLs were cross-sectionally associated with joint tenderness (paper III). Multiple OA features are commonly co-occurring, which may lead to a high risk of confounding in a cross-sectional study. We tried to limit the risk of confounding by doing multivariate analyses with inclusion of all MRI features that were associated with joint tenderness in the same model. Confirmation of these associations in future longitudinal studies is needed to further increase the validity of the results. It should be explored whether progression of these features is associated with pain onset or worsening. However, simultaneous progression of other structural lesions may also confound such findings. The problem of confounding by structural OA progression may be circumvented by exploring whether reduction or complete resolution of synovitis and BMLs is accompanied by less joint tenderness.

5.1.2 Representativity of the study sample

Selection bias is a systematic error due to a non-random sample of a population, causing a higher likelihood of inclusion in the study for some members of the population than others. When the assumptions of randomness and representativity cannot be assumed, we can only draw limited conclusions (194). Selection bias may affect both the internal and external validity of our results. Internal validity refers to whether the obtained results reflect the "truth" within the study population, whereas external validity refers to the generalisability of the study results (194).

Initially 209 participants were included in the Oslo hand OA cohort. The participants were recruited from the outpatient clinic at Diakonhjemmet Hospital in 2001-03 and had most frequently been referred from their general practitioner due to hand OA or questions about differential diagnoses such as inflammatory rheumatic diseases. In total 275 patients with hand OA were initially identified as eligible for the study. Of those, 209 (76%) consented to participate in the baseline data collection (questionnaires/interview, clinical examination and CR of both hands).

In this thesis, we used data from the follow-up examination in 2008-09, of which 128 of the 209 original participants (61%) attended. Whether the non-responders did not meet due to

improvement (i.e., the patients did not see any need to participate in the study) or worsening of symptoms (i.e., the patients were too physically impaired to meet at or travel to the hospital for examination) is unknown.

Hence, the participants were possibly selected at baseline based on structural disease, high amount of inflammation or severe symptoms, which were our exposure and outcome variables in paper II-III. For example, we can anticipate that persons with Heberden´s nodes (as signs of structural disease) or hand pain are more likely to seek their general practitioner and thereafter be referred to the rheumatology clinic. Conditioning on the common effect (here: seek doctor) may affect the association between the exposure (here: structural disease) and outcome (here: pain) (i.e., the internal validity). The majority of participants in this cohort fulfilled the ACR clinical hand criteria, which means that the majority had both hand pain and also bony enlargement of the finger joints. Hence, the association between the exposure variables (here: MRI features as measures of structural disease) and outcome variables (here: pain) is not only the result of the causal effect of exposure on outcome (195). This may have affected our results on the analyses performed at patient level examining the association between the amount of MRI pathology and measures of hand pain and function (paper III). The association between MRI features and tenderness in the same joint is probably less affected by selection bias, and these analyses performed at individual joint level were therefore the main focus in this thesis.

The generalisability of our results (i.e., the external validity) to the general population of hand OA patients is limited due to the selection process described above and the overrepresentation of women and elderly patients. Hence, caution should be applied in the interpretation of the results on a population level.

Hand OA is often considered as a women's disease. However, we recently studied the prevalence, incidence and progression of radiographic hand OA in the general population of Framingham and found that radiographic hand OA was only slightly lower in men (38%) compared to women (44%) with age between 40 and 84 years. OA in certain joint groups (MCP and wrist joints) and age groups (below 60 years) was even slightly higher in men. Hence, radiographic hand OA seemed to be a disease of both sexes in contrary to the common conception of hand OA as a women´s disease. However, despite similar prevalence estimates of radiographic disease, we found that symptomatic hand OA was twice as prevalent in women (16%) as in men (8%) (3). Similar sex differences have been shown in

clinical and experimental studies of several chronic pain conditions (196), suggesting differences in pain sensitivity, cognitive/affective mechanisms and/or pain reporting between men and women. Higher occurrence of erosive hand OA and possibly more severe structural disease in women may also contribute to the observed differences of symptomatic hand OA between women and men. Although symptomatic hand OA is more common in women than men, we had a higher women-to-men ratio in the Oslo hand OA cohort than seen in most population-based studies of hand OA (3, 197, 198). One possible explanation for the high women-to-men ratio in this study may be that women are more likely to seek medical care and were therefore more likely to be recruited in this study.

Notification and exclusion of patients with differential diagnoses are important for the diagnosis of hand OA (11). Those with diagnoses of inflammatory joint diseases such as PsA, RA and gout as well as hemochromatosis were not included in the Oslo hand OA cohort. However, the initial symptoms and signs of hand OA may be difficult to distinguish from inflammatory joint diseases, and in total 4 patients were excluded during the period between baseline and follow-up due to (possible) diagnosis of either RA or PsA. One single criterion on its own has limited sensitivity and specificity for differentiation between hand OA and inflammatory joint diseases, and the diagnosis should therefore be based on a composite of multiple features such as age, sex, joint distribution and bony enlargement of the finger joints (11). Laboratory test may also assist the process. Studies have shown that patients with erosive hand OA do not have anti-cyclic citrullinated peptide (anti-CCP) antibodies or rheumatoid factor isotypes (199, 200). However, neither rheumatoid factor, anti-CCP nor urate were measured in this study.

One main advantage of the Oslo hand OA is the comprehensive data collection. Clinical examination and imaging assessment require allocation of space and trained staff (such as rheumatologists, nurses and radiology technicians), and especially the MRI scans are associated with high costs. A similar detailed assessment would be more difficult and very expensive to perform in a large population-based cohort that was selected neither on the exposure nor the outcome variables.

Other studies examining the validity of MRI features in hand OA patients have been performed in Leeds (United Kingdom), Ghent (Belgium) and Leiden (the Netherlands), and all studies used similar study designs with patients recruited from the outpatient clinics. Grainger *et al.* compared high-resolution MRI (hrMRI) and CR in 15 patients (14 women)

with hand OA based on the ACR criteria, who were recruited from the outpatient clinic (150). Wittoek *et al.* (Ghent University) also recruited 14 patients (10 women) from their rheumatology outpatient clinic, and all participants fulfilled the ACR clinical criteria for hand OA (201). Kwok *et al.* (Leiden University Medical Centre) similarly recruited 16 patients (10 women) with hand OA from the outpatient rheumatology clinic, and all fulfilled the clinical ACR criteria (202). Hence, all studies have similarities with the Oslo hand OA cohort with regard to patient enrolment. At the publication date, the Oslo hand OA cohort is by far the largest hand OA cohort with hand MRI of the participants.

5.1.3 Self-reported measures and clinical examination

The data collection in the Oslo hand OA cohort aimed to include similar dimensions of assessment that had been frequently used in outcome research for RA, including patient-reported outcomes, functional performance-based tests, clinical joint assessment and imaging. In line with an opinion paper by Kloppenburg *et al.* regarding the need for research in hand OA, our data collection included components of both disease activity, function and damage (203).

Self-reported measures of pain and physical functioning are frequently used in rheumatology research and within the field of OA. The advantage of self-reported instruments is that they are often more feasible in a busy clinical setting, as they do not require the presence of any trained staff and allocation of space. In this thesis, a large range of instruments were completed by the patients, such as the AUSCAN, FIHOA, AIMS-2, Health Assessment Questionnaire (HAQ), Short Form (SF)-36 (115, 118, 119, 204, 205). Other hand OA specific measures like the SACRAH, Cochin and Michigan questionnaires were not included in the data collection in order to prevent a too comprehensive booklet for the patients (116, 117, 206). In this thesis (paper III), we focused on questionnaires about hand pain and functioning like the AUSCAN, FIHOA and AIMS-2. Hence, HAQ and SF-36 were not included.

Factors such as educational level and the motivation of the patients as well as their personal preferences and perception of normality may affect how the patients complete the questionnaires. Thus, self-reported measures may therefore not always correlate with objective measures of physical functioning. Within ICF, self-reported instruments measure the functioning from the perspective of a person's life, while objective hand function tests

measure the capacity of a person to perform a certain task (112). Although measurement of grip strength gives an objective performance-based measure, it only measures some aspects of hand functioning. The ability to perform tasks requiring hand manipulation is for example not assessed by grip strength. The Moberg Pick-up test was also performed in our cohort (126), but the test was not included in the analyses in the current thesis. We chose to focus on grip strength since this is a more well-established instrument.

One single rheumatologist (BSC) with more than 20 years experience within the field of rheumatology performed the clinical joint examination in order to avoid inter-rater bias. Tender joints by palpation/movement, bony enlargement, soft tissue swelling and limited motion were assessed, but only tender joints were used as an outcome measure in this thesis (paper III). Self-reported pain in the individual hand joints was not assessed. Compared to self-reported measures of hand pain, the clinical examination of joint tenderness probably limits the role of psychosocial factors related to pain reporting.

5.1.4 Magnetic resonance imaging (MRI)

We know from numerous studies that hand OA has a predilection of the DIP, PIP and thumb base joints (3, 19, 20). The MCP joints are less frequently affected, and MCP OA seems to be more prevalent in men than women (3). Erosive hand OA is typically occurring in the DIP and PIP joints (3), although erosive OA of the thumb base has also been reported (29). The joints are usually symmetrically affected (198), and there are inconsistent results regarding whether OA is more common in the dominant hand (65-67). In the Framingham study, we found slightly higher prevalence of OA in the DIP and PIP joints in the right hand, whereas thumb base OA was more common in the left hand (3).

The patients in this study underwent bilateral hand radiographs, while only the DIP and PIP joints of the 2^{nd}-5^{th} finger of the dominant hand were imaged by MRI. The MCP joints were in most patients uncovered or incompletely covered due to limited FOV, whereas imaging of the thumb base joint would have required a separate acquisition. The selection of sequences was based on the current recommendations for RA and PsA (158, 162), and the sequences were developed in collaboration with an MRI technician and a musculoskeletal radiologist (SS). Based on the recent papers by Tan *et al.* (110, 207), we aimed to get an adequate visualisation of the collateral ligaments. Sequences were tested on healthy controls and patients in a pilot study. The decision about which joints to scan by MRI and the final

selection of sequences were based on considerations about joint distribution, burden on the patients, feasibility and economical costs.

We obtained T1-weighted images with a 3D GRE sequence. This sequence allows acquisition of nearly isotropic voxels and is therefore ideal for accurate quantitative assessment of cartilage thickness and volume in the knee. In this thesis, the sequence was selected due to low scanning time and adequate visualisation of the ligaments. However, the technique has some disadvantages. The sequence provides only limited contrast between cartilage and fluid, and it was not possible to differentiate between cartilage and synovial fluid or between the two cartilage layers due to the small size of the finger joints. To reduce motion artefacts, the patients´ hands were fixed within the coil and we used an extremity coil, which is more comfortable for the patients than a whole-body scanner.

3D GRE images were acquired pre- and post administration of Gd contrast. The decision of using contrast-enhanced images was based on the current recommendation for RA, suggesting that the use of contrast increase the sensitivity for detection of synovitis (142). It has also recently been suggested that contrast-enhanced MRI is more accurate for assessment of synovial inflammation and especially infiltration than T2-weighted images in knee OA (208), and a scoring system for synovitis with use of contrast-enhanced MRIs was recently developed (156). The main disadvantage of using Gd contrast is the risk of nephrogenic systemic sclerosis, especially in elderly patients with decreased kidney function. OA is more commonly occurring in elderly patients, and the patients in this thesis were in the range of 57 to 78 years. All participants had a blood test for creatinin levels, as a measure of the kidney function, prior to the MRI examination.

The development of synovial membrane enhancement following the injection of intravenous Gd depends on the speed by which the Gd moves through the circulation to the small synovial membrane vessels and diffuse into the interstitium of the synovial membrane. If the joint is scanned too early after the contrast injection, the enhancement will be less pronounced, potentially leading to underestimation of the severity of synovitis. If the scanning is delayed, there will be a slowly decreasing intensity of the enhancement, especially in cases of synovial effusion as the contrast will equilibrate between the synovial membrane and effusion (132). In this particular situation, the thickness of the synovial membrane may be overestimated (since the space occupied by effusion is mistakenly

included). In this thesis, the post-Gd images were acquired immediately after administration of the intravenous Gd contrast.

Bone damage and formation were evaluated on the GRE images. Cortical bone is seen as signal void on the GRE sequences due to the relative lack of hydrogen protons in this tissue. Hence, the contrast against cartilage and other structures such as the synovial fluid and membrane is important for the evaluation of bone erosions/attrition and osteophytes. However, soft tissue structures such as collateral ligaments and tendons also have a dark appearance on the GRE images, and it can therefore be difficult to distinguish osteophytes from thickened ligaments and tendons.

Fat suppression is necessary for depiction of BMLs and can be provided by a STIR sequence. In this thesis, BMLs were assessed with use of coronal and axial STIR images. The primary advantage of the STIR sequence is the ability to produce uniform fat suppression, which limits the risk of misinterpretation of regions with inadequate fat suppression as BMLs (129). However, the inversion pulse also degrades the signal-to-noise ratio of the remaining signal by 40-50%, and the technique is relatively inefficient in terms of time (129). The slice thickness was 2-3 mm, and the STIR images were not used for assessment of other features than BMLs. Thick slices (i.e., larger voxels) increase the risk of partial volume artefacts. Partial volume artefacts occur when a structure (here: bone) is only partly within the voxel, and they are especially marked at the interface between tissues with different signal intensity such as the bone and inflamed synovium. Due to the small size of the finger joints, perhaps only one or two coronal slices had voxels that only contained bone. Both the axial and coronal planes were used for better insurance of true BMLs. High signal intensity of the bone in imaging sections that contained adjoining soft tissue (i.e., on the way “out” or “into” the bone) was interpreted as partial volume artefacts and not BMLs.

Knowledge about the normal anatomy is important in order to not overestimate the presence of pathology. The collateral ligaments insert into bony recesses at the phalangeal heads, and presence of inflamed synovium adjacent to these bony recesses may possibly mimic the presence of marginal erosions as in RA (132). Furthermore, the “magic angle” phenomenon may lead to false appearance of increased signal intensity of the collateral ligaments (133), leading to overestimation of disrupted ligaments. Nutrient foramina, which are usually located on the palmar side in the middle third of the shaft, may also be misinterpreted as erosions (209).

5.1.5 Conventional radiography (CR)

In this thesis, only the radiographs with posteroanterior view were scored for presence and severity of OA features and used in our analyses. Traction spurs at the insertion sites of the extensor tendons are most easily seen on lateral and oblique images, and the use of images with posteroanterior view only may have led to an underestimation of bone proliferation.

The images were scored according to the KL scale and OARSI atlas. The KL scale has been criticised for too much emphasis on osteophytes (176), as narrowed/sclerotic joints cannot be classified as having OA unless osteophytes are present. In the original paper from 1957, the different grades were described as: 0 = no OA, 1 = doubtful OA, 2 = minimal OA, 3 = moderate OA, 4 = severe OA, and example images were shown (13). In the atlas from 1963, also written descriptions of the example images were included. However, the definition of the grades differed between hand joint groups. As an example, a DIP joint with KL grade = 2 was described as "definite osteophytes at two points…., but good joint space", while a PIP joint with KL grade = 2 was described as "definite osteophytes at two points and possible narrowing of joint space" (14). The latter description is similar to the description of a knee joint with KL grade = 2. Furthermore, according to a later publication by Lawrence in 1977, a joint should be scored as having KL grade = 2 when there is "a definite osteophyte, but unimpaired joint space", and grade 3 and 4 in case of moderate and severe JSN respectively (175). Hence, it remains unclear how to grade joints with possible or mild JSN. In this thesis, we chose to classify joints as having KL grade = 2 based on the presence of definite osteophytes with or without accompanying possible/mild JSN (as described for the PIP and DIP joints respectively). Joints with only mild JSN but not definite osteophytes were therefore scored as normal (n = 248). We decided to score joints with moderate to severe JSN but no osteophytes as KL grade = 1 (n = 65). Thus, several of the joints with KL grade 0-1 had JSN. This means that OA pathology may be present in joints with KL grade 0-1 since the atlas does not allow scoring of these features as definite OA. This limitation of the KL scale should be kept in mind when interpreting the results in paper II.

5.2 Main results

5.2.1 Development of an MRI scoring system for hand OA

The development of the MRI scoring system for hand OA (paper I) was based on a similar process as had been done for the RAMRIS and PsAMRIS in OMERACT (158, 162).

The first step in the development of the MRI score included selection of pathological features based on a literature review and informal group discussions. The next step was to perform reliability exercises (three in total), of which the results from the last exercise were presented in paper I. Only inter-reader reliability was assessed in the first two exercises, and the results from the second exercise were presented at the EULAR congress in 2010 (210). We did additional training for features with low reliability, and modifications of the features were performed if necessary.

Since OA is a disease affecting the whole joint, we started with a broad inclusion of features, such as structural key hand OA features, inflammatory features and BMLs. We also initially assessed extensor tendinitis, since this feature was included in the initial exercises of PsAMRIS (162). Based on recent studies by Tan *et al.* we included assessment of different forms of collateral ligament pathology (110, 207), such as normal/disrupted, non-thickened/thickened and non-inflamed/inflamed ligaments. During/after the first two exercises, we excluded ligament thickening, ligament inflammation and extensor tendinitis from the scoring system due to no/infrequent appearance and/or low reliability. The MCP joints were also excluded from the scoring system after the first exercise due to incomplete/varying coverage by the FOV.

The final definition of bone damage included both assessment of focal bone loss ("erosions") and attrition of the joint plate ("subchondral bone collapse"). We realised that the initial definition of erosion ("a sharply marginated bone lesion, which is visible in two planes with a cortical break seen in at least one plane") did not capture the typical central erosions, which are often seen as "seagull wing" configurations. Hence, according to our final definition, grade 1 included either 1-2 small erosions and/or subchondral bone collapse. Despite this combined definition, we chose to score these two features separately for paper II-III. This decision was based on the awareness of previous studies suggesting different pathogenic processes behind these two features (150). Further, the presence of

subchondral bone collapse alone was only scored as a grade 1, and it is questionable whether presence of small erosions and possibly severe collapse of the joint plate can be equated. In paper II and III, we changed the wording from "subchondral collapse" to "attrition" in order to have the same wording as used for knee OA (151), and in order to have a wording based on the appearance and not the possible underlying pathogenic mechanisms. Initially, we proposed a grading of erosions on a 0-10 scale based on the volumetric bone loss (similar to PsAMRIS) (162). However, most of the erosions in our first two reliability exercises were scored as grade 1, even though the joints were considered as severely damaged (210). Hence, we changed the grading to a 0-3 scale, which was rather based on the size and numbers of erosions. One could possibly argue that a combined score of attrition and erosions as originally proposed is preferred in order to increase the feasibility of the scoring system. A combined score based on the volumetric size of erosions and the percentage of the joint plate that is erosive may represent one possible solution, which should be included in the future research agenda.

BMLs, cysts and erosions may have a similar appearance but were included as separate features in our scoring system. By definition, BMLs have a more diffuse border than cysts and erosions, and they are most easily detected on STIR or fat-suppressed T2-weighted sequences. The definitions of cysts and erosions were similar, as the difference was only the absence or presence of a cortical break respectively. However, the small size of the DIP and PIP joints and a field strength of only 1.0 T may complicate the judgement about whether a thin cortical rim is present or not. The cause of cysts in OA is not entirely clear but is most probably due to synovial fluid intrusion or bone remodelling (or a combination) (35-37). Hence, the erosions, cysts and BMLs are possibly inter-related. Cysts and erosions may also be surrounded by BMLs making the distinction more difficult. In knee OA, cysts and BMLs have been combined into one feature in the BLOKS and MOAKS (153, 154). Whether these features have similar prognostic and clinical value in hand OA should be explored before one can consider merging the two features into one.

We used all available MRI planes for assessment of bone formation. Hence, both "real" intra-articular osteophytes at the joint margins and traction spurs at the insertions of the extensor tendon were scored as osteophytes despite different underlying mechanisms (167). The initiation of the "real" intra-articular osteophytes is associated with proliferation of mesenchymal cells from the periosteum and synovium at the joint margins, which subsequently differentiate into chondrocytes. These cells undergo hypertrophy and create

skeletal outgrowths after a process of endochondral ossification. The chondral hyperplasia will in practice grow in the direction of least resistance, and anatomical studies of the finger joints have shown that a "window" exists between the extensor tendon and the collateral ligaments (106). It has been suggested that local biomechanical factors are important to the formation of osteophytes, and there is evidence that the osteophytes in fact contribute to maintenance of joint stability. Hence, it is unclear whether osteophytes represent pathological joint alterations or normal remodelling processes secondary to the OA changes in the joint (32, 38).

Enthesophytes around the finger joints are seen as bone formation at the insertions of the extensor tendons and possibly along the midshaft, as physiological responses to excessive tension or contracture, and can be identified by its location within a collagenous structure (106). Previous studies have suggested an association between enthesopathic changes and OA (211), but Gibson *et al.* found no association between enthesopathic changes in the hand and knee (212, 213). Whether these enthesopathic changes play a role in hand OA is unclear.

Direct assessment of the cartilage in these small finger joints was difficult due to suboptimal resolution of the MRI scans. The cartilage appears grey on the STIR images and may be difficult to delineate from the black cortical bone. On the GRE fat-saturated images, the cartilage is bright and can be easily delineated from the bone. However, it was in this study not possible to delineate the two layers of cartilage and the synovial fluid. Hence, even if MRI is capable of directly visualise the cartilage, JSN was defined based on the inter-bone distance in our proposed scoring system (paper I).

In summary, we have proposed a preliminary MRI scoring system for hand OA, which contains both structural and inflammatory OA features. The proposed scoring system is extensive and time-consuming (paper I). We did not measure the exact time that was required for assessment of one MRI scan, but 30-60 minutes was usually necessary depending on the severity of disease seen on the MRI scans (i.e., longer time was required for patients with severe disease). Increased feasibility can potentially be obtained by exclusion of non-relevant features, collapse of features and scoring at joint level (i.e., not the proximal and distal part of the joint separately).

5.2.2 Reliability of the MRI scoring system for hand OA

In this thesis, the status scores were assessed independently, and we used SDD in order to test whether the differences between two independent status scores differed from zero. SDD should not be confused with smallest detectable change (SDC), which is used in longitudinal settings when the images are presented to the reader in pairs with or without known time sequence (i.e., the two obtained scores are not assessed independently) (189).

The intra-reader reliability for inflammatory features was only moderate (paper I), while the inter-reader reliability (based on the results from the first reading) was good to very good. This is possibly due to the use of different radiographic imaging software for the first and second reading (PACS and OsiriX respectively). The intra-reader reliability (IKH) reported in paper II and III was very good for synovitis but moderate for flexor tenosynovitis. In this case, the same software (PACS) was used for both the first and second reading. These results suggest that use of different imaging software may affect the impression of Gd enhancement and should preferably be invariable in a study. In summary, synovitis can probably be assessed with good reliability, while the assessment of flexor tenosynovitis is less reliable and possibly redundant.

5.2.3 Spectrum and severity of MRI findings in hand OA

Key hand OA features, such as osteophytes, JSN and erosions, were frequently present (paper II). This section will focus on synovitis and BMLs, which cannot be visualised by CR. Structural features, which can be visualised by both MRI and CR, will be discussed in the next section.

OA has traditionally been considered as a non-inflammatory disease. However, inflammation is increasingly recognised in both early and late stages of the disease contributing to symptoms and progression of OA (214). In this thesis, we found a very high prevalence of MRI-defined synovitis with Gd enhancement (grade 1-3: 66% of the joints, grade 2-3: 22% of the joints) (paper II). This number is substantially higher than the number of joints with MRI-defined synovitis reported by Wittoek *et al.* (20%) (201), whereas Kwok *et al.* reported even higher numbers (202).

Several studies have examined the prevalence of US-detected synovitis in patients with hand OA (215-219). In line with our results, Keen *et al.* demonstrated grey scale synovitis

(a combination of synovial thickening and effusion) in 53% of the joints (215). Other studies have suggested that joint effusion is more prevalent than synovial thickening (216, 217), while power Doppler activity is less common (215-218). However, results are not completely consistent across studies (219). The differences between the US studies may be due to varying disease severity in the patient populations, the US technique and interpretation of the findings. All US studies reported lower prevalence estimates of synovitis than in this thesis (paper II), despite the fact the presence of MRI-detected synovitis by definition required both synovial thickening and Gd-enhancement (paper I). A higher sensitivity of MRI in comparison to US in detection of synovitis has also been reported by Wittoek *et al.* (201).

We found a high proportion of mild MRI-defined synovitis also in joints with no/doubtful OA (KL grade ≤ 1) (paper II), as previously shown for US-detected effusion and synovitis in hand OA (217) and also for MRI-detected synovitis in knee OA (220). Synovitis was most common in joints with mild radiographic OA (KL grade = 2). Wittoek *et al.* found that US-detected effusion, synovitis and power Doppler activity were common in all phases of radiographic OA (17), but most prevalent in erosive joints (E phase) and slightly lower in joints that were remodelled (R phase) (217). Similar results were shown for MRI-defined synovitis by Kwok *et al.*, although the prevalence of synovitis was very high in all phases (202). These results may suggest a "burn-out" of inflammation in later stages of the disease or possibly more easily detection of synovitis in joints with more anatomical space. However, the association between synovitis and damage needs to be further investigated in longitudinal studies. In knee OA, Benito *et al.* showed that cell infiltration and vascular proliferation were more frequent in synovial biopsies from patients with early OA (less than 1 year symptom duration) than in severe late OA (221). However, other studies have shown that synovitis is most frequent in severe knee OA (222, 223).

Previous MRI studies have shown that the thin synovial membrane in the MCP and wrist joints can show low-grade post-Gd enhancement also in persons without clinical OA or inflammatory disease (224, 225). Similarly, studies of healthy controls using US have found synovial hypertrophy and effusion of the DIP and PIP joints (215, 218). However, the selection of the control groups may have biased the results, and some cases among the healthy individuals might be in a very early stage of hand OA. Hence, our definition of synovitis was based on the thickness of the synovial membrane in combination with Gd enhancement. Whether the thickness of the synovium was greater than normal was based on

comparison with images in the atlas. However, one may question whether grade 1 represents pathology or is within the normal variations.

We found a low prevalence of BMLs (13% of the joints) (paper II) compared to findings reported by Wittoek and Kwok *et al.* (54% and 27% respectively) (201, 202). Both these studies were performed with use of a 3.0 T MRI scanner, which may have contributed to higher sensitivity in detection of BMLs. Furthermore, Wittoek *et al.* had a slice thickness of only 1 mm, while Kwok *et al.* had similar slice thickness as in our study (3 mm). We found the highest prevalence of BMLs in joints with KL grade 3-4, and moderate to large BMLs were very uncommon in joints without radiographic OA (paper II). These results are in line with previous studies in knee OA, suggesting that BMLs are manifestations of bone trauma related to increased biomechanical loading (e.g., meniscal pathology and malalignment) (226-229). Histological studies in knee OA have confirmed the presence of necrotic, remodelled trabeculae, bone marrow necrosis and/or fibrosis, which are consistent with ongoing local bone trauma and repair (146).

We found that the collateral ligaments appeared disrupted in 41% of the normal joints (KL grade = 0), and in 90% of the joints with radiographic moderate/severe OA (paper II). These results are in line with the results from Tan *et al.* showing that ligament abnormalities were present at hrMRI scans in both early (symptom duration less than 1 year) and chronic hand OA (symptom duration more than 1 year) (110). Other structural abnormalities, such as BMLs, erosions and osteophytes, were seen in close anatomic relationship to the ligaments, and Tan *et al.* hypothesised that the collateral ligaments could possibly play a role in the pathogenesis of OA. However, ligament abnormalities were also frequent in the elderly controls, and these abnormalities could therefore possibly also be age-related (110).

Flexor tenosynovitis was infrequently present (19% of the joints) and was not associated with radiographic severity (paper II). These findings may suggest that flexor tenosynovitis is not related to the OA process.

Histology represents the gold standard for the examination of BMLs and synovitis. Tan *et al.* also performed a combined MRI and histological study (207), but interpretation of the results is limited by the fact that the MRI scans and histological sections were not from the same subjects. Lewis *et al.* correlated the MRI appearance of the PIP joints of cadavers with histology of the same specimens (230). However, they focused on normal anatomy and did

not explore the histological content of MRI-defined BMLs or synovitis. Hence, the histological content of the MRI-defined BMLs and synovitis in hand OA remains unclear.

5.2.4 Validity of MRI against CR

MRI was in this study more sensitive than CR in detection of erosions and osteophytes but not of JSN, cysts and malalignment (paper II). These results are discussed in this section in the context of other studies, and possible explanations for our findings are presented.

The classification of erosive hand OA has traditionally been based on the presence of radiographic central erosions, which typically show classic "seagull wing" patterns. We found good agreement between MRI-defined attrition and radiographic central erosions (paper II). However, significantly more joints had MRI-defined erosions and/or attrition (52% of the joints) than marginal or central erosions detected by CR (25% of the joints). These numbers are in line with previous MRI studies in hand OA (150, 201, 202) supporting the validity of our results.

The hand radiographs were initially only scored for central erosions according to the OARSI atlas (170). We chose to re-evaluate all joints without radiographic central erosions for presence of marginal erosions in order to not underestimate the prevalence of radiographic erosions. However, marginal erosions were found in only 39 of 677 joints. Erosions may be located on the dorsal or volar side of the joint and may therefore be less visible on CR.

We chose to score MRI-defined attrition and focal erosions separately, since they perhaps have a different pathogenesis. Previous studies on radiographic hand OA have shown that cartilage loss precedes radiographic erosive evolution (17, 34), suggesting that biomechanical factors may play a role in the development of these erosions. However, studies using hrMRI have also identified periarticular/marginal erosions (110, 150), which were associated with pathological collateral ligaments and synovitis. These marginal erosions have traditionally not been assessed in hand OA, and future longitudinal studies should explore their role in hand OA with regard to the pathogenesis of OA and prognostic value. Small erosion-like lesions in the metacarpal and wrist bones have also been shown in healthy controls, but they were mainly not contrast-enhancing (224).

MRI was in our study more sensitive than CR in detection of osteophytes (86% and 39% of the joints respectively) (paper II). Kwok *et al.* had similar findings (202), whereas Wittoek *et al.* found similar numbers of joints with osteophytes on MRI and CR (201). The higher sensitivity of MRI could possibly be explained by the multiplanar demonstration of the joint by MRI. All these three studies used radiographs with traditional posteroanterior view, which can project "real" intra-articular osteophytes at the medial and lateral joint margins. The sagittal planes of MRI and radiographs with oblique or lateral view are able to visualise traction spurs. Consistent with the findings reported by Tan *et al.* (207), we frequently found osteophytes at the insertion site of the extensor tendon. Although the pathogenesis of the intra-articular osteophytes and traction spurs may differ, they were combined into one feature reflecting bone formation in order to not introduce a too extensive scoring system.

In contrast to our findings, Wittoek *et al.* did not find a higher sensitivity of MRI in detection of osteophytes and argued that this could be due to the signal void of densely packed calcium in osteophytes (201). However, delineation of the dark osteophytes is still possible if adjoining tissue demonstrate high signal intensity. One limitation of the study by Wittoek *et al.* is the lack of a standardised scoring method for the assessment of osteophytes. Thus, it remains unclear how they defined osteophytes and which sequences and planes that were used for this assessment. Too conservative scoring of radiographic osteophytes according to the OARSI atlas may also have contributed to the difference between MRI and CR. The OARSI atlas shows examples of clear definite osteophytes, and doubtful ossicles at the corners were not scored as present osteophytes (170).

The dark appearance of bone on the GRE fat-saturated sequence complicated the distinction between bone proliferation and soft tissue such as ligaments and tendons, which may have led to an overestimation of bone proliferation. If the bone proliferations contain trabecular bone (i.e., only large osteophytes), a non-fat suppressed sequence could have simplified the distinction between bone and soft tissue (162).

The agreement between MRI-defined JSN and radiographic JSN was moderate. JSN was more common on CR (80% of the joints) than on MRI (68% of the joints), which may be due to apparent radiographic JSN in normal joints with flexion deformities. On the other hand, MRI is able to demonstrate intra-articular osteophytes (and thus cartilage defects) that are not visualised on CR, which may contribute to the decreased specificity of MRI.

Cysts were infrequently seen by both MRI and CR, but the agreement was poor. The majority of the joints with cysts only on CR demonstrated erosions on the MRI scans. As previously discussed, it might be difficult to judge whether a cortical break is present or not on the MRI.

Malalignment was similarly more common on CR (12% of the joints) than MRI (7% of the joints). The higher sensitivity of CR may be due to a too strict definition of MRI-defined malalignment ($\geq$ 15 degrees angulation in the frontal plane). No cut-off for the angulation is defined in the OARSI atlas (170).

We used CR as our comparator ("gold standard") in this study. However, we know from studies in RA that CR is inadequate for defining erosions and is therefore not optimal for comparison with MRI (104). The most convincing comparators for MRI features would have been histological evidence or computed tomography (CT), but these were not available in the cohort used in this thesis. Histology of joints is usually only available from cadavers or after surgery. Computerised tomography (CT) provides multiplanar imaging with the advantages of good visualisation of bony anatomy, and future studies should therefore ideally use CT as the gold standard for assessment of erosions, cysts and osteophytes.

5.2.5 Associations between MRI findings and measures of pain

A systematic review from 2006 revealed evidence for a positive association between radiographic hand OA and hand pain, but large variation among studies was also reported (231). These results may suggest that other structures than those seen by CR are important for the experience of pain in hand OA.

All MRI features (except cysts) were associated with tenderness upon palpation in the univariate analyses (paper III). However, it is important to notice that OA is a disease affecting the whole joint organ. Several features are associated with each other and therefore often co-occurring, which may lead to problems with confounding. Hence, we performed multivariate analyses in order to more accurately assess the direct associations between the various MRI features and joint tenderness. Our final multivariate model included osteophytes, erosions, bone attrition, synovitis and BMLs (paper III). These findings support the notion that the occurrence of pain is multifactorial with contributions from several features in the whole joint organ.

Subchondral bone, a richly innervated tissue, is thought to be involved in pain generation, which was supported by a positive association between bone formation and damage with joint tenderness (although the association was not statistically significant for osteophytes). Osteophytes may cause joint pain either by stretching nerve endings in the periosteum/capsule or be a result of microfractures of the bone trabeculae within the spur (232). Our results are in line with a recent study by Kortekaas *et al*. showing an association between radiographic and US-detected osteophytes and tenderness upon palpation in finger joints in hand OA, which was independent of radiographic JSN and US-detected inflammation (233). The OR detected in this study was of higher magnitude compared to our results, which may be explained by residual confounding in their model (since BMLs and attrition/erosions were not included in the model) (233). Keen *et al.* also found that tender and painful joints were more likely to demonstrate US-detected osteophytes (215). However, Yusuf *et al.* concluded that there was limited evidence for an association between MRI-defined osteophytes and pain in a systematic review of knee OA (234).

MRI-defined bone attrition and erosions were the only structural features that were significantly ($p < 0.05$) associated with joint tenderness. Previous studies on radiographic hand OA have shown that patients with erosive hand OA experience more pain and functional limitation than patients with non-erosive OA (29, 235). However, the patients with erosive hand OA had also a higher burden of disease, and most differences disappeared or were diminished after correction for the number of finger nodes (235). Our results are also in line with cross-sectional studies in knee OA showing an association between bone attrition and knee pain (236, 237).

This thesis is the first to show an association between BMLs and tenderness in hand OA, which remained borderline statistically significant in the multivariate model. BMLs may cause pain due to “bone angina”, i.e., stagnation of blood flow through the thickened subchondral bone trabeculae, which are the consequence of healing and remodeling of microfractures (238, 239). Hunter *et al.* confirmed a link between elevated intraosseous venous pressure and BMLs in knee OA (240). However, the pathophysiology behind the observed association between BMLs and pain is still elusive (241).

We found a significant association between MRI-defined synovitis and pain in hand OA, which supports previous studies using US (215, 216). However, the analyses in these previous studies were not adjusted for structural features and the direct effect of

inflammation on pain is therefore difficult to evaluate due to possible confounding. We found significant associations between synovitis and joint tenderness independent of other MRI features and radiographic severity, which strengthens the hypothesis of inflammation as a target in hand OA (89, 90). Keen *et al.* performed a four-week observational study on parenteral corticosteroids in hand OA, but they found no statistically significant reduction in US-detected synovitis (242). However, whether MRI synovitis is more sensitive to change and corresponds to clinical improvement needs to be assessed in future studies.

BMLs and synovitis seem to be the features that are most consistently associated with pain in knee OA (156, 220, 234, 243-248). A recent systematic review concluded that knee pain in OA was associated with BMLs and effusion/synovitis with moderate evidence, while the level of evidence for other MRI features was limited or conflicting (234). However, results are conflicting especially for BMLs (249-251), and several studies are limited by inadequate adjustment for demographic factors, other MRI features and/or radiographic severity, which may represent confounding factors. The lack of correlation between the severity of synovitis and the severity of knee pain further emphasise that not only synovitis contributes as a source of OA pain (246).

We found no independent association between JSN and pain, which was expected since the cartilage has no neural innervations. Cartilage damage in itself is therefore an unlikely source of pain in OA. However, a recent study by Kortekaas *et al.* showed an association between radiographic JSN and pain, independent of osteophytes and US-detected inflammation (233). Keen *et al.* also found that tender and painful tender joints were more likely to have US-detected JSN (215). These observed associations between JSN and pain are probably indirect and may possibly be mediated through attrition (central erosions), synovitis and/or BMLs acting as intermediate factors on the path between JSN and pain.

Flexor tenosynovitis did not remain in the final multivariate model for the association to joint tenderness. Based on our results showing moderate reliability, infrequent appearance and no association to radiographic severity or joint tenderness (paper I-III), this feature can possibly be removed from the proposed scoring system (paper I).

In line with previous studies using US and CR (215, 233), we found significant associations between MRI features and tenderness at the individual joint level, while the associations between the amount of MRI abnormalities and patient-reported pain (as measured by

AUSCAN) were much weaker (paper III). First of all, person-related psychosocial factors influence the report of pain and physical disabilities (241), while this influence is smaller on the analyses at individual joint level. Anxiety and depression are strong predictors of functional impairment and pain in OA and may therefore represent confounding factors for the association between OA features and pain (252). A study in knee OA elegantly showed that radiographic knee OA was strongly associated with pain when the analyses were performed in subjects that were discordant for pain status, and hence the analyses were controlled for person confounding (253). Secondly, we had information about MRI pathology in the DIP and PIP joints of the dominant hand only. Hence, MRI pathology in the non-dominant hand as well as in the MCP and thumb base joints of the dominant hand may also have affected the level of self-reported symptoms (254). Thirdly, studies have also shown great variations in OA pain, also within the same day (255, 256). Moreover, peripheral and central mechanisms of sensitisation may occur, leading to increased pain sensation (hyperalgesia and allodynia) and possibly pain responses from regions of the body remote from the inflamed joint (i.e., referred pain). The pain may also be influenced by the use of analgesia, and patients with severe disease may also report low levels of pain during activities if they avoid specific activities due to the awareness of pain.

5.2.6 Associations between MRI findings and measures of physical function

Previous studies of radiographic hand OA have shown inconsistent results for an association between radiographic hand OA and hand function, ranging from no association to moderate association (231). We found only limited evidence for an association between MRI features and markers of impairment and activity, but structural features such as bone formation and bone damage seemed to be most important for these associations (paper III).

The lack of significant associations may, as mentioned in the previous chapter, be due to person-related psychosocial factors that influence the self-reported physical disabilities (241), avoidance of specific activities due to pain or inability to perform the specific tasks, the use of remedies and imaging of the DIP and PIP joints of the dominant hand only.

Objective hand function tests are less related to person-related psychosocial factors as compared to self-reported questionnaires. In this thesis (paper III), we examined the association between the MRI features and grip strength as an objective measure of hand

function. Previous studies have shown that grip strength is more closely related to OA in the more proximal joints including the MCP joints. Chaisson *et al.* found that high grip strength was a risk factor for incident OA in the thumb base and MCP (64), and it is possible that OA in these joints will have more impact on the impairment of grip strength than the DIP and PIP joints (58, 257). Thumb base involvement in symptomatic hand OA has also been associated with higher levels of self-reported physical disability than OA in the interphalangeal joints (254). However, in contrast to previous studies, we found a stronger association between radiographic OA in the DIP joints and grip strength than for OA in the thumb joints and grip strength (data not shown in paper III).

FIHOA was the only questionnaire among the self-reported instruments that was able to show significant associations to the MRI features, which may indicate that characteristics of the various outcome measures can affect the results. We have previously examined the construct validity of the AUSCAN physical, AIMS-2 hand/finger and FIHOA subscales. None of the subscales were unidimensional, since they contained features about tasks requiring grip strength as well as tasks requiring precision grip representing two separate constructs. The contribution of grip strength and precision items varied across the instruments with the AUSCAN having relatively more items concerning grip strength and the AIMS-2 and FIHOA having relatively more precision items (122).

6. Conclusions

6.1 Answers to research questions

We were able to provide answers to the specific research questions presented in section 2.2:

- To address the general aim, we developed an atlas presenting example images of MRI features with different grades of pathology in DIP and PIP joints in hand OA (paper I).
- The intra-reader and inter-reader reliability for status scores of MRI features in hand OA were generally good to very good (paper I).
- Structural MRI features such as osteophytes, JSN, erosions/attrition, ligament discontinuity as well as synovitis were frequently present in hand OA patients. Malalignment, cysts, BMLs and flexor tenosynovitis were less common (paper II-III).
- MRI pathologies were generally most common in DIP and PIP joints with moderate/severe radiographic OA, whereas synovitis was most common in mild radiographic OA. Structural hand OA features such as osteophytes, JSN and erosions as well as mild synovitis were common also in joints rated without/doubtful radiographic OA (paper II).
- Agreement between MRI-defined attrition and radiographic central erosions was substantial, while the agreement was weaker when both central and marginal erosions were assessed. Moderate agreement was found for detection of osteophytes and JSN, but the percentage of close agreement was very high. Only poor to moderate agreement between MRI and CR was shown for cysts and malalignment (paper II).
- MRI was much more sensitive than CR in detection of erosions and osteophytes, while the specificity was lower. The sensitivity and specificity in detection of MRI-defined JSN was good in comparison to radiographic JSN. The specificity of MRI for detection of cysts and malalignment was very good, while the sensitivity was lower. Several radiographic cysts were scored as erosions on MRI (paper II).
- MRI-defined attrition, erosions, synovitis and BMLs showed the strongest associations to tenderness in the same joint (paper III).

– The amount of MRI features was not associated to patient-reported pain. There was a tendency towards an association between structural MRI features and patient-reported functioning and grip strength (paper III).

6.2 Clinical implications

This thesis provides results that are of potential importance to clinicians. We have shown that both structural and inflammatory features could reliably be assessed by MRI.

MRI proved to more sensitive in detection of structural hand OA features compared to CR. Further, both structural features as well as synovitis were frequently detected by MRI in joints with no or only doubtful radiographic OA, suggesting that OA may be present even though CR shows limited findings.

Synovitis, erosions, attrition and BMLs were associated with pain in hand OA independent of other structural features. Whether these could represent targets for treatment in hand OA should be further explored.

We believe that MRI can contribute the better knowledge about the sources of pain in hand OA and possibly represent an outcome measure in clinical trials.

7. Errata

There was no overlap between the slices provided by the Dixon sequence (paper I, page 1034).

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9. Papers I-III

I

II

III