Osteoarthritis: the role of synovitis

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Cover: “Echo” (1874). Painting by Alexandre Cabanel.

Echo was a mountain nymph in the Greek mythology. She used to talk continuously and with her talk distracted the goddess Hera, in such a way that Hera was unaware of her husband Zeus’ numerous love affaires. Hera discovered that Echo was playing tricks with her and cursed her. Ever since, Echo could only repeat the words of others. This is an explanation for echo as an acoustic phenomenon.

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“Climb if you will, but remember that courage and strenght are naught without
prudence and that a momentary negligence may destroy happiness of a lifetime.
Do nothing in hast; look well to each step;
and from the beginning think what may be the end.”

Edward Whumper, 1865. Bedwong als eerste de Matterhorn in Zwitserland.

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General introduction

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder leading to high disease burden. From a survey, that studied the global burden of disease in 1990 and 2010, osteoarthritis was among the top 25 most prevalent diseases leading to disability, above diseases such as diabetes mellitus and COPD. This same survey showed that the prevalence of OA incremented around 25% from 1990 until 2010 indicating this to be an increasing problem.[1] Since the prevalence of OA rises with age, it is expected to increase further in the coming decades with ageing of the population.[2]

At present no treatment to cure or delay progression of OA is available. Until now treatment consists of patient education and symptom alleviation. In 2007 recommendations on the management of hand OA were formulated and the authors concluded that there is a lack of evidence of effectiveness of therapies. They warranted more hand OA research to be initiated.[3]

OA can occur in any joint, but the hand joints are among the most frequently affected. Hand OA has not been studied frequently, however. The reason for the lack of interest in this "forgotten disease" is probably the fact that the clinical burden has not been recognized fully until recently, leading to the assumption that hand OA is a mild disease.[4,5] Also, hand OA is a heterogeneous disorder and multiple hand joints are simultaneous involved. Clinical features fluctuate and often don't correlate with structural damage seen on radiographs,[6] the most frequently used imaging technique for the investigation of hand OA up till now. Also, progression of structural damage as seen on radiographs, is usually slow, taking years to develop. Therefore, to be able to investigate hand OA using radiographic progression as outcome measure, large study groups with long follow-up periods are necessary, making it complex to study.

There is a great need for the development of new instruments which can identify factors that have a better ability to correlate with clinical features as well as progression.

Aetiology

Hand OA is a heterogeneous disorder involving the whole synovial joint, leading to loss of cartilage, development of subchondral sclerosis, cysts and osteophytes. Soft tissues such as synovium, capsule and ligaments are also affected.

Although hand OA was already identified in ancient times,[7] it's aetiology is still largely unknown. It is regarded as the consequence of multi-factorial aetiology, which adds to the heterogeneity in OA phenotypes. Several risk factors for hand OA have been recognized. The most important risk factor is age. Hand OA is only seldom seen in persons under 40 years of age, but the prevalence is steeply increasing above 50 years of age.[8,4,9]

Another risk factor for OA is female gender. In a systematic review with meta-analysis the overall relative risk for men was 0.81 (95% confidence interval 0.73 to 0.90) when compared to women.[10]

It is further recognized that the occurrence of hand OA especially increases in women above 50 years of age. In this age period most women experience their climacteric transition, and therefore low oestrogen levels in post-menopausal women are thought to play role in OA development. However, in a systematic review on the association between female hormonal aspects and hand OA no clear relationship could be observed.[11]

Furthermore, obesity is associated with the presence of hand OA. This association was evidenced in a systematic review with an approximate relative risk of 1.9.[12]

Also, mechanical forces, for instance by occupational activities especially those that require extensive precision grip or forceful grip, and muscle strenght are implicated in hand OA development.[13,14]

Finally, family history is a widely recognized risk factor for hand OA.[15,16] Which genes are involved in hand OA is not clear. Many loci and genes have been under study, but many have not been replicated by others.

Diagnosis

Several sets of criteria are available to classify hand OA.[17] The most well-known are the classification criteria developed by the American College of Rheumatology (ACR).[18] These criteria identify subjects with clinical hand OA using hand pain or stiffness as major criterion. The ACR criteria set is developed and validated by comparing patients with clinical hand OA, as determined by experts, with patients suffering from other rheumatic disorders causing hand pain, such as rheumatoid arthritis. ACR criteria recommendations do not require radiographs to define hand OA (table 1.1). Recently, the classification criteria have been criticized. Zhang et al assigned the highest priority for the research agenda to define new classification criteria.[2]

Table 1.1 Classification criteria for osteoarthritis of the hands, according to the American College of Rheumatology.[18]

Hand pain, aching or stiffness AND 3 or more of the following features: • Hard tissue enlargement of two or more of ten selected hand joints* • Hard tissue enlargement of 2 or more DIP joints • Fewer than 3 swollen MCP joints • Deformity of at least 1 of 10 selected joints*

* The ten selected hand joints are the second and third DIP joints, second and third PIP joints and the first carpometacarpal joints of both hands.
Abbreviations: DIP=distal interphalangeal, PIP=proximal interphalangeal, MCP = metacarpophalangeal

Alternatively, hand OA can be classified on radiographic features with or without symptoms. Several scoring methods are available that are used to detect OA features on radiographs. A common score is that of Kellgren and Lawrence which assigns a global OA score (grade 0-4) to separate hand joints.[19] Hand OA is often defined as a KL score greater than 1. How many joints are required to have radiographic features for the classification of hand OA is currently not agreed upon. Other radiographic scoring methods, such as the method depicted in the OARSI atlas and the Verbruggen-Veys anatomical phases score, score specific features such as osteophytes, joint space narrowing (JSN), cysts or erosive evolution separately on joint level.[20]

Prevalence of hand OA

Hand OA is highly prevalent. However, since different definitions for hand OA can be used, prevalence estimates depend upon the hand OA criteria used as well as the population sampled.

When hand OA is defined by radiographic features, the highest prevalence of up to 81% of the elderly population can be found.[21,22]

When studying the clinical features of hand OA at physical examination, Heberden's nodes have been reported in 58% and Bouchard's nodes in 29.9% of the adults aged over 60 years in the United States.[23] The prevalence of symptomatic hand OA is lower. The age- and sex-adjusted prevalence estimates for hand OA following the ACR criteria in adults were between 2.0 and 6.2%.[8,4,23,24]

Clinical aspects

Hand OA is characterized by symptoms, such as pain or aching in and around hand joints, stiffness, loss of mobility, decreased grip strength, and disability. In addition, typical hallmarks, such as bony enlargements of finger joints and deformities, are found.[2] Bony enlargements in distal interphalangeal joints (DIPJs) and proximal interphalangeal joints (PIPJs), Heberden's and Bouchard's nodes respectively, can be associated with underlying structural abnormalities.[25,26,27,2] These typical hallmarks can be present without symptoms.

Not all hand joints are equally affected. OA is most prevalent in DIPJs, less so in first carpometacarpal joints (1st CMCJs) and PIPJs, and least prevalent in metacarpalphalangeal joints (MCPJs).[21,28,29] Hand OA often presents as poly-articular disease following a specific pattern. Clustering is seen primarily symmetrically and by row (DIPJ, PIPJs, MCPJs), and to a lesser extent by ray.[28]

Pain

Hand pain is one of the most important symptoms of hand OA. The cause of pain however is unclear. Although structural abnormalities as assessed on radiographs play a role, only limited associations were demonstrated.[6,30] Several alternative hypotheses

on the aetiology of pain can be thought of. Involvement of soft tissues, such as synovial inflammation, might play a role. Until recently, it has been very difficult to investigate this hypothesis due to the limited ability to visualize soft tissue in the small hand joints. This has changed over the last years due to the development of more sophisticated imaging techniques.

Pain in hand OA can also be caused by extra-articular mechanisms. It is now known that pain perception is also influenced by genetic predisposition, and psychological factors such as experience of patients, their expectations, their present mood, socio-economic environment and copings strategies.[31,32,30,33,34]

Inflammation

OA has always been characterized as a degenerative disease especially of cartilage. More recently, the role of inflammation in OA is recognized. In OA joints synovial thickening with effusion is frequently present.[35,36,37] The aetiology of inflammation is not completely understood although different mechanisms have been described. Mechanisms that could explain fluctuating inflammatory features could be mechanical stress and the presence of crystals. Mechanical stress can induce matrix degradation leading to the release of aggrecanases and collagenases and subsequently to activation of chondrocytes, which are capable of producing proinflammatory cytokines leading to inflammatory features.[38,39] Furthermore, crystals such as calciumpyrophosphate and/or hydroxyapatite, which are frequently found in OA, can lead to synovitis.[40] Other mechanisms that can lead to more persistent inflammation are age and obesity. Aging leads to change of chondrocytes during life. They develop features of senescence-associated secretory phenotype, including increased production of many cytokines, chemokines and matrix metalloproteinases leading to inflammatory features.[41] Adipose tissue is capable of producing adipokines, which are able to induce inflammation.[42,43] The different inflammatory processes that probably all play a role in OA might explain the difference in the course of inflammatory features in OA.

Prognosis

Several studies investigated the progression in hand OA and showed that it is a relatively slow process.[44] After 10 years, radiographic progression was estimated in 59% of hand OA patients. However, the progression of radiographic changes was relatively modest.[45] Regarding progression of OA and clinical symptoms, two studies have been performed that show that clinical deterioration is reported in about 50% of patients after 6 and 8 years.[46,47] Little is known about the risk factors of progression of hand OA. A recent systematic review on this topic revealed that with best evidence synthesis limited evidence was present for a positive association of an abnormal scintigraphic scan and radiographic progression.[48]

Hand OA subsets

Although the term "hand OA" suggests differently, hand OA is not just one disease but consists of several subsets.[2] Recognized subsets are interphalangeal joint OA (with and without nodes), thumb base OA and erosive OA.

Nodal OA

Nodal OA is defined as the presence of nodules in respectively DIPJ and/or PIPJ as descibed above. Distribution is mainly symmetrical and can involve multiple joints.

Thumb base OA

Thumb base OA is defined as OA in 1st carpometacarpal joint (CMCJ) with or without OA of the joint between the scaphoid and trapezium (STJ).[2] It often co-occurs with other sites in the hands.[49,50] OA in thumb base can be assumed when thumb base pain is present and tenderness, joint enlargement (e.g. squaring) and deformity are found on physical examination.[51] The prevalence in adults from the general population thirty years of age or older for radiographic OA of 1st CMCJs was reported to be 7% in men and 15% in women. It's prevalence rises with age.[52] Prevalences of symptomatic 1st CMCJ OA in adults from the general population above 60 years of age was estimated 1.9%.[22] Risk factors for thumb base OA are comparable to IPJ OA. In addition, it is suggested that hypermobility is an important risk factor as well.[53]

Up till now it is controversial what the specific role in clinical burden of thumb base OA is and limited studies are available. It appears that in symptomatic hand OA, when the co-occurrence of IPJ, 1st CMC OA and the number of joints involved is taken into account, 1st CMCJ OA contributes more to pain and disability than IPJ OA.[54]

Erosive OA

The term erosive OA was first used by Peter et al. in 1966 to describe 6 women with OA in IPJs with inflammation and development of erosive and osteoarthritic features on radiographs,[55] but its clinical and radiographic features had earlier been described by Kellgren and Crain.[56,19] Erosive OA is a radiographic subset of OA[2] based on central erosions and collapse of the subchondral bone plate. Erosive OA is considered to have a higher clinical burden and worse outcome than non-erosive hand OA, eventually leading to instability and ankylosis.[57] Whether erosive OA comprises a separate disease entity with specific risk factors and pathogenesis or a more severe stage of hand OA is unclear at the moment.[2] Erosive lesions are predominantly present in the DIPJs and to a lesser extent in the PIPJs.[58,59] The occurrence of erosive OA in the 1st CMCJ is relatively unexplored.[2]

The prevalence of erosive OA is estimated in the general population to be 3%.[59] The prevalence rises to 7-14% in populations with symptomatic hand OA,[60,61,62] and up to 25% when studying symptomatic hand OA in secondary care.[63,64] Erosive OA tends to

involve women more often than males,[55,65,66] however no significant differences were seen in prevalence between males and females.[59]

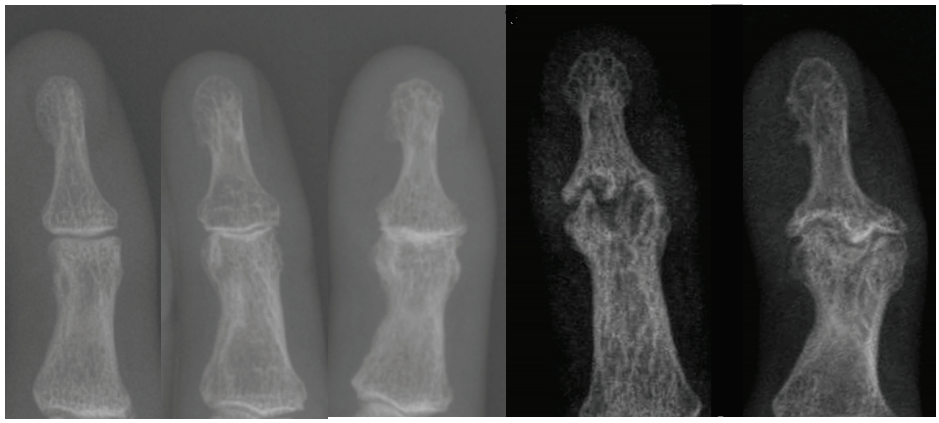
Imaging

In hand OA, structural abnormalities can be assessed using radiographs. This imaging modality is being used for diagnoses of OA (although no validated definition is present),[2] for assessment of structural progression over time and for research purposes. Several features of OA make the use of radiographs in clinical practice and research less convenient. First of all, progression of structural abnormalities is slow, as described above. Using structural features as assessed by radiographs as outcome measure is therefore costly and time consuming. Secondly, associations with clinical features such as pain, only show limited associations, thus making it difficult to use this imaging technique for this purpose.[6]

Frequently used methods to score structural features are the OARSI scoring system and the Verbruggen-Veys anatomical phases. The OARSI scoring system semi-quantitively or dichotomously scores osteophytes (0-3), JSN (0-3), subchondral sclerosis (0-1), malformation (0-1), cysts (0-1) and erosions (0-1).

The Verbruggen-Veys method is based on scoring osteoarthritic joints in progressive, consecutive phases. Five anatomical phases are distinguished, being the normal (N), stationary (S), joint space loss (J), erosive (E) and remodeled (R) phases. The sequence of evolution from N to S to J to E to R phases is proposed to reflect the natural history of erosive OA.[20]

Radiographs are unable to visualize soft tissue such as synovitis and effusion. Other imaging methods have been introduced in recent years such as MRI and ultrasonography (US), that are able to assess soft tissues.



N phase S phase J phase E phase R phase

Figure 1.1 Anatomical phases of the Verbruggen-Veys score.

US is an easy procedure, non-invasive, with good availability and minimal discomfort for the patient, and is able to study soft tissue in hand OA.

In 2007 a preliminary scoring system for hand OA was developed by a group of experts.[67] In this score grayscale (GS) synovitis (a composite measure of synovial thickening and effusion), power Doppler signal (PDS) and osteophytes were assessed. All US features were scored using a semiquantative scale: 0=none, 1=mild, 2=moderate and 3=severe. Examples of US images are depicted in figure 1.1 and 1.2.

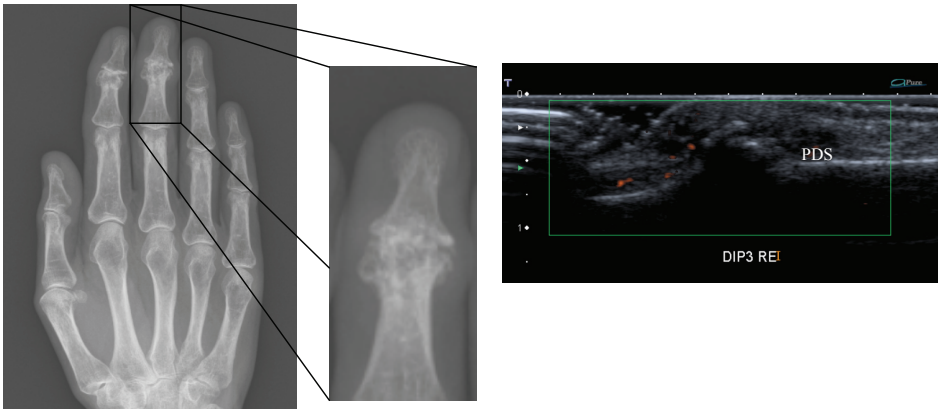


Figure 1.2 Images of erosive distal interphalangeal joint of the right hand. On the right the radiograph with in the window the affected joint, on the left the US image. Synovial thickening with power Doppler signal, and osteophytes grade 3 are depicted.

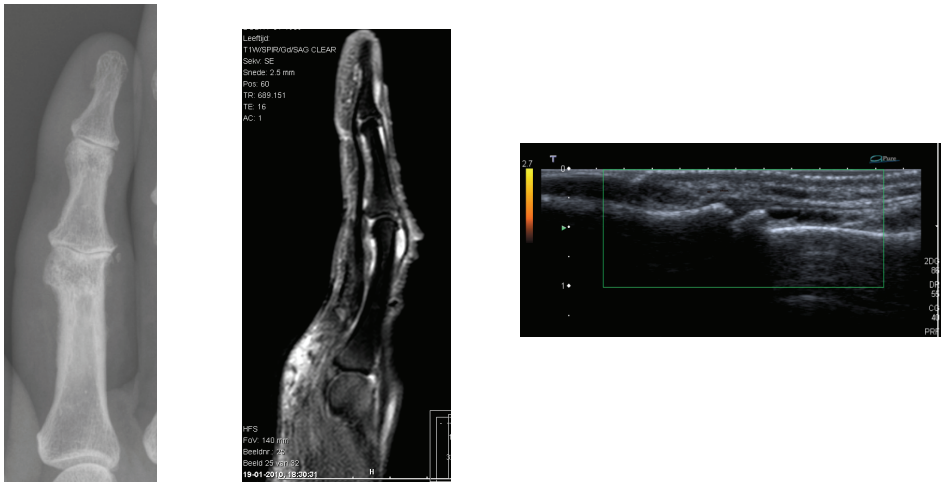


Figure 1.3 Images of the second finger of the right hand of an OA patient. On the left the radiograph of the same finger. In the middle a T1 weighted sagittal MRI image with gadolinium enhancement showing synovitis and on the right the ultrasound image of the DIP joint showing an osteophyte, effusion and synovial thickening.

Few studies on US in hand OA have been published. These studies showed that inflammatory features were frequently present in symptomatic hand OA.[36,68]

For hand OA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone.[69,35,70] Recently, a MRI scoring method supported by an atlas was proposed, which facilitates research with MRI in hand OA. The Oslo Hand OA MRI score (OHOA-MRI score) was developed as a reliable method to assess key features in hand OA.[71]

Aim of this thesis

As is outlined above, OA is a challeging disease. Due to it's heterogeneity and slow progression of structural features it is complex to study. Also, clinical features fluctuate frequently and they associate poorly with structural features as assessed on radiographs, the golden standard imaging modality uptill now. The origine of the clinical features, especially pain, is therefore not clear, and is likely to be multifactorial. It is now recognized that the whole joint is involved in OA, and that synovitis is frequently found. The role of synovitis is not elucidated yet.

The aim of this thesis is therefore to investigate the role of inflammatory features in OA, especially hand OA. For this reason we aimt:

1. to investigate the role of inflammatory features in pain in OA.
2. to investigate the role of inflammatory features in progression of structural features in OA.

The ultimate goal by increasing our knowledge on OA and the role of inflammatory features is to elucidate whether inflammation could be a target for treatment in OA and finally to develop new treatments for OA.

The ECHO study

The studies described in this thesis made especially use of data derived from the ECHO study. The ECHO study (acronime of EChografie bij Hand Osteoarthritis) was set up by M.C. Kortekaas as a collaborative prospective follow-up research project by the departments of Rheumatology and Radiology. The study population consisted of patients with symptomatic hand OA according to the ACR criteria.

In total, 64 patients were included for baseline assessment between May 2008 and January 2010. A subgroup of the study population was reassessed after 3 months, and all patients were invited for a follow-up visit after 28 months. These follow-up visits occurred between January 2011 and April 2012.

At all visits patients underwent ultrasonography, pain scores and physical examination. At baseline and after 28 months, radiographs were made and standardized questionnaires were completed in addition.

Thesis outline

Association of OA features and pain.

Since the cause of pain in OA is unclear, the associations between pain and radiographic features are weak and soft tissue and subchondral abnormalities are thought to be involved in pain, we summarized the evidence concerning the association of pain with MRI abnormalities in the knee. In **Chapter 2** we performed a systematic review of studies investigating the associations that are present between MRI findings in knee OA and knee pain. For this review we investigated eight commonly reported MRI findings, being cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition.

In **Chapter 3** we investigate the presence of inflammatory features by ultrasonography in patients from the ECHO study. In addition we investigated the association of US features, being GS synovitis, and in addition synovial thickening and effusion separately, and PDS, with joint specific pain, and with patient reported outcomes by questionnaires being physical function and health related quality of life (HRQoL) in hand OA.

In earlier studies using conventional radiographs limited associations between hand pain and radiographic features were demonstrated.[21] Beside the involvement of soft tissue as a cause of pain, another explanation for the limited associations could be that relationships were studied using global scores for pain and summated scores for structural abnormalities. Since all features of separate hand joints are combined into one score per patient, associations might be concealed. Also, since pain is a subjective experience influenced by genetic predisposition and psychosocial factors it is important to take in account patient effects. In hand OA this can be done by comparing affected with non-affected joints within the same patient using generalized estimating equation (GEE) analyses. In earlier studies the latter has not been performed.

In **Chapter 4** we investigate the association between structural radiographic abnormalities, being osteophytes and JSN, and pain in hand OA. To prevent the above mentioned potential limitations, associations were studied at patient level and at individual joint level controlling for person confounding using both ultrasonography and conventional radiography.

Associations of OA features and progression.

Up till now the natural evolvement of inflammatory features in hand OA has not been investigated before in prospective follow-up studies. Therefore it is not known how these features evolve over time and what the implication of their presence is. The clinical course in hand OA varies over time with passing episodes of soft tissue swelling. Therefore it is expected that inflammatory features also change over time. Since pain varies over time as well, one could hypothesize that fluctuation in pain

is due to variation in inflammation. On the other hand, pain is a difficult feature to understand, since it is a subjective experience influenced by genetic predisposition and psychosocial factors.[32,72,30,33,34]

Although few studies have used inflammatory US features to monitor treatment effect during a short follow up period,[73,74] no short–term observational follow up studies have been performed to investigate how, on joint level, inflammatory features and their relation with pain evolve over time. Therefore, in **Chapter 5** we investigate how inflammatory US features and pain develop over a three months period.

How these inflammatory features behave over long-term follow-up and what the clinical implication of their presence is, has not been investigated either. In knee OA, inflammatory US features, such as effusion, have been shown to be involved in progression of structural features as assessed by replacement of a joint prosthesis.[75] Whether inflammation is involved in structural progression in hand OA, has not been studied before. Therefore, in **Chapter 6** we investigate whether inflammatory US features are associated with structural damage after long-term follow-up of 2 to 3 years. Also the course of inflammatory US features over long-term follow-up is studied.

Erosive OA is a subset of hand OA associated with a higher clinical burden than non-erosive disease.[2] Unfortunately, the processes that lead to erosive development are still unknown. In an earlier study it was shown that erosive development in erosive OA is clustered in certain patients and in certain families, suggesting that underlying systemic processes are involved.[65] Based on this observations and the observation that during the clinical course inflammatory features are often seen in erosive OA, we hypothesized that inflammatory features are implicated in erosive evolution. In **Chapter 7**, we therefore investigate the presence of inflammatory US features in erosive and non-erosive interphalangeal joints in patients with erosive OA in comparison to interphalangeal joints from patients with non-erosive hand OA.

In addition, in **Chapter 8** we investigated the association of inflammatory US features and erosive progression over 2.3 year follow-up in hand OA.

Reliability and validity of MRI in hand OA

In knee OA, magnetic resonance imaging (MRI) has proven to be a valid imaging modality which enables visualization of the subchondral bone, including BMLs and soft tissues.[76,77] For hand OA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone.[78,70,69] Recently, the Oslo Hand OA MRI score (OHOA-MRI score) supported by an atlas was developed as a reliable method to assess key features in hand OA, which facilitates research with MRI in hand OA.[71] In **Chapter 9** we tested reliability and criterion validity in a severe hand OA population.

Finally, we summarize the results of the studies in this thesis and present our conclusions and future perspectives in **Chapter 10**.

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2

Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review

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ABSTRACT

Objective

To systematically evaluate the association between MRI findings (cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition) and pain in patients with knee osteoarthritis (OA) in order to establish the relevance of such findings when assessing an individual patient.

Methods

The Medline, Web of Science, Embase and Cumulative Index to Nursing & Allied Health Literature (CINAHL) databases up to March 2010 were searched without language restriction to find publications with data on the association between MRI findings of knee OA (exposure of interest) and knee pain (outcome). The quality of included papers was scored using a predefined criteria set. The levels of evidence were determined qualitatively using best evidence synthesis (based on guidelines on systematic review from the Cochrane Collaboration Back Review Group). Five levels of evidence were used: strong, moderate, limited, conflicting and no evidence.

Results

A total of 22 papers were included; 5 had longitudinal and 17 cross-sectional data. In all, 13 reported a single MRI finding and 9 multiple MRI findings. Moderate levels of evidence were found for BML and effusion/synovitis. The OR for BML ranged from 2.0 (no CI was given) to 5.0 (2.4 to 10.5). The OR of having pain when effusion/synovitis was present ranged between 3.2 (1.04 to 5.3) and 10.0 (1.1 to 149). The level of evidences between other MRI findings and pain were limited or conflicting.

Conclusions

Knee pain in OA is associated with BML and effusion/synovitis suggesting that these features may indicate the origin of pain in knee OA. However, due to the moderate level of evidence these features need to be explored further.

INTRODUCTION

Knee is the major site of osteoarthritis (OA), the most common rheumatic disorder which is characterised by pain that leads to significant restriction in patients' daily activity.[1,2] Despite its importance, the source of pain remains unclear.[3] To treat OA optimally, knowledge of the source of pain is important since new therapies can be specifically targeted.

An important element in understanding pain is to know which structures produce it inside the knee since the pathology of knee OA involves the whole knee joint.[3] To assess knee structures in vivo imaging modalities are needed. On radiographs, hallmarks of knee OA such as bony outgrowth and cartilage loss, which are visualised as osteophytes and joint space narrowing, respectively, do not show a consistent association with knee pain.[4] Other potential sources include abnormalities in subchondral bone, ligamentous damage, meniscal injury and synovitis.[5] However, these potential sources cannot be assessed on conventional radiographs. More advanced imaging techniques are needed currently best exemplified by MRI.

Several studies have investigated MRI findings related to pain but to our knowledge, no summarisation of data has been performed in a systematic manner. Such a review requires a focused research question, an explicit research strategy and a system to evaluate the quality of evidence.[6] Therefore, we sought to evaluate the relationship between MRI findings in knee OA and knee pain. We summarised eight commonly reported MRI findings: cartilage defects, bone marrow lesions (BML), osteophytes, meniscal lesion, effusion/synovitis, ligamentous abnormalities, subchondral cysts and bone attrition (table 2.1).

Table 2.1 Definitions of the lesions associated with knee OA viewed on MRI.

Lesion	Definition
Cartilage defects	Cartilage abnormalities scored on MRI images using semi-quantitative method or determined using quantitative method.
Bone marrow lesion (BML)	Ill-defined lesion in the medullary space with high signal on T2-weighted imaging or low-signal on T1-weighted imaging scored using semi-quantitative method.
Osteophytes	Focal bony protrusion that extended from bone cortical surface scored for presence or using semi-quantitative scoring methods.
Meniscal abnormalities	Tear of meniscus or meniscus lesion or subluxation scored semi-quantitatively.
Effusion/synovitis	Effusion: Fluid in synovial space scored for presence or scored using semi-quantitative method. Synovitis: synovial layer scored on the presence of thickening or scored semi-quantitatively. Synovitis and effusion scored together using semi-quantitative method.
Ligaments abnormalities	Tear of ligaments or lesion of the ligaments scored semi-quantitatively.
Subchondral cysts	Marginated circular area filled in with fluid under the cartilage scored for presence or scored using semi-quantitative method.
Bone attrition	Flattening or depression of the articular cortex scored using semi-quantitative method.

Materials and methods

The present review is a systematic review of observational studies. Therefore, we adhered to a protocol developed from a widely recommended method for systematic review/meta-analysis of observational studies (MOOSE).[7] We included studies with data on the association between MRI features of knee OA (exposure of interest) and knee pain (outcome). The following studies were excluded: reviews, abstracts, letters to the editor, case reports, case series and studies concerning study population with other underlying musculoskeletal diseases.

Data sources, searches and extraction

Using the following key words: 'knee', 'knee pain', 'MRI', 'osteoarthritis' in combination with all possible key words concerning MRI features we wanted to investigate, we searched the following medical databases up to March 2010: Medline (from 1966), Science Citation Index through Web of Science (from 1945), Embase (from 1980) and, Cumulative Index to Nursing & Allied Health Literature (CINAHL) (from 1982). No language restriction was applied and no search of unpublished studies was performed. Additionally, the reference lists of all relevant identified articles were screened and

Google Scholar was searched to find additional papers. Complete search strategies can be obtained from the authors on request.

Two reviewers, EY (a PhD student) and MCK (a rheumatologist) independently screened the titles of retrieved references for obvious exclusion and read the remaining abstract to determine eligible studies. Differences were solved by discussion or by consulting a third reviewer (MK, a senior rheumatologist).

From eligible papers, information was collected on the following categories: (i) type of study, performed by looking at the method of data analysis (when a study provided data on the association between MRI features change in time with change in pain level in time, the study was considered to be a prospective cohort study; if this analysis was not available, such as in a case-control study, the study was regarded to be of a cross-sectional design); (ii) study population (patient characteristics, size, gender and age); (iii) definition of knee OA; (iv) assessment of MRI findings; (v) assessment of pain; (vi) potential confounders; and (vii) results of the association between MRI features and pain.

Assessment of study quality

Independently, the same two reviewers assessed the methodological quality of included studies using a predefined criteria set which was previously used in systematic reviews in the area of musculoskeletal disorders (see table 2.2).[8,9] Several domains were assessed: population, selection bias, assessment of determinants on MRI, assessment of the outcome, follow-up analysis and data presentation.

For each criterion met in the article, a '1' was given; otherwise, a '0' was given. We defined rules on how to assess specific situations. A study could describe multiple MRI features but not all were assessed reproducibly (criterion 5) or using standardised criteria (criterion 6). For such a study, the criteria are scored as a proportion of MRI features which were assessed reproducibly or using standardised criteria from the total MRI features investigated.

Differences in scoring were resolved by discussion or by consulting the third reviewer. Maximum scores possible were 11 for prospective cohort and 9 for cross-sectional study design. The total score for a study (in %) is the total score given for a study divided by the maximum possible score. The mean of the quality scores of all studies, which was 62%, was used to classify studies as high or low quality.

Table 2.2 Criteria for the quality evaluation of the included studies.

Item Criteria	Applicable for
Study Population: Definition of Study Population	
1. Sufficient description of characteristics of the study population. Sufficient is when age, sex and settings are mentioned.	C/ CS
Study Population: Selection Bias	
2. Clear description of selection of study subjects.	C/ CS
3. Participation rate >=80% for study population.	C/ CS
Assessment of findings on MRI	
4. Findings were assessed reproducibly. If multiple findings were assessed, the score will be the number of findings assessed reproducibly divided by all findings studied.	C/ CS
5. Findings were assessed using validated criteria. If multiple findings were assessed, the score will be the number of findings assessed by using standardized criteria divided by all findings studied.	C/ CS
6. MRI readers were blinded to clinical findings.	C/ CS
7. The sequence of scans were unknown to the MRI readers.	C
Assessment of the outcome: Knee Osteoarthritis Pain	
8. Presence of pain was assessed using validated scales.	C/ CS
Follow-up	
9. No difference in characteristics between withdrawal and completers group.	C
Analyses and Data Presentation	
10. Appropriate analysis techniques were used.	C/ CS
11. Adjusted for possible confounders. At least adjustments should be made for age and sex	C/ CS

C: prospective cohort studies and CS: cross-sectional studies

Rating the body of evidence

The summary of evidence for each MRI feature was given by using best evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.[10] This is an alternative to pooling of association sizes when the included studies were heterogenous.[8] The synthesis has five levels of evidence: (1) strong, when general consistent findings were reported in multiple high-quality cohort studies; (2) moderate, when one high-quality cohort study and at least two high-quality cross-sectional studies show general consistent findings or when at least three high quality cross-sectional studies show general consistent findings; (3) limited, when general consistent findings were found in a single cohort study, or in maximum two cross-sectional studies; (4) conflicting, when no consistent findings were reported; and (5) no evidence, when no study could be found. This synthesis puts more weight on a prospective cohort design which is appropriate for our review question since it takes into account the change in determinant (MRI feature) and change in outcome (pain).

Sensitivity analyses by defining other cut-offs (median score of all studies instead of mean) of high quality studies were performed. We also present the number of positive studies without quality assessment to give readers the opportunity to compare this with the best evidence synthesis results.

A study that investigated multiple features was counted as a single study for each MRI feature investigated. A study was regarded as positive if it showed a significant association between an MRI feature and knee pain. When a study included subfeatures of an MRI finding, that is, tear and subluxation for meniscal lesion, the study was regarded as positive when at least one of these showed positive association. Since effusion and synovitis cannot be readily differentiated on non-enhanced MRI,[9,11] we analysed these features together.

RESULTS

Literature flow

After screening their title, 2144 of 2629 identified references were excluded (figure 2.1). From the 485 remaining references, 19 papers were included. We selected the most recent publication[12] of two publications with overlapping results.[12,13] Four

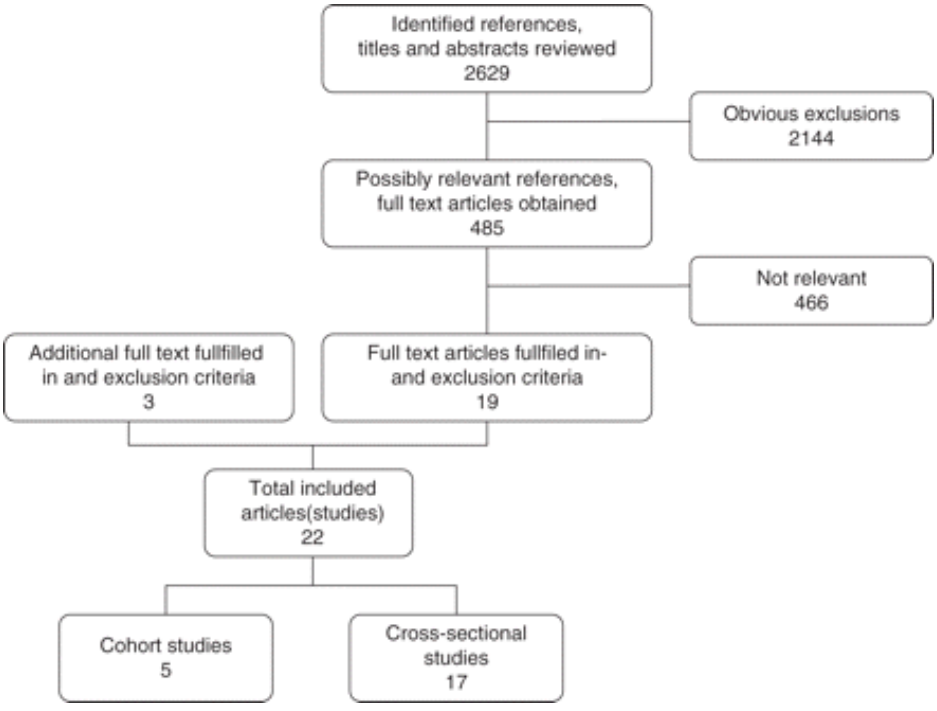

Figure 2.1 Results of literature research

Table 2.3 Characteristics of included studies (listed alphabetically by first author surname)

Studies	Study population	Features assessed	Pain assessment	Statistical analysis	Quality score (%)
Cohort studies					
Hill *et al*[12]	Patients with knee OA (ACR criteria). n=270 (42% women); mean age 67±9 years. BOKS, USA.	Effusion/synovitis	VAS	Linear regression	68
Kornaat *et al*[20]	Generalised patients with OA. n=182 (86% women); median age 60 years (range: 43–77). GARP study, The Netherlands.	BML	WOMAC pain	Linear mixed model	64
Pelletier *et al*[21]	Patients with knee OA (ACR criteria) from outpatient rheumatology clinic, n=27 (52% women), mean age 64±9.6 years. Canada.	Synovitis	WOMAC and VAS pain	Spearman correlation	36
Raynauld *et al*[14]	Patients with knee OA (ACR criteria). n=40 (88% women); mean age 62±8 years. Canada.	Cartilage	WOMAC and VAS pain	Spearman correlation	64
Wluka *et al*[16]	Patients with knee OA (ACR criteria). n=132 (54% women); mean age 63 years (range 41–86) Australia.	Cartilage	WOMAC pain	Spearman correlation	64
Cross-sectional studies					
Anandacoomarasamy *et al*[35]	Obese patients with knee OA from general population (ACR criteria), n=77 (68% women), mean age: 51±12.7 years, Sydney, Australia.	Cartilage	WOMAC pain	Spearman correlation	67
Amin *et al*[22]	BOKS, USA. See above. n=265 (43% women); mean age 67±9 years.	ACL tear	VAS	Student t test	67
Bhattacharyya *et al*[18]	Cases: BOKS, USA. See above. n=154, mean age: 65 years. Controls: no knee pain, n=49 mean age: 67 years.	Meniscal tear	VAS	Student t test	67
Dunn *et al*[23]	Patients suspected for clinical OA. n=55 (55% women); mean age 63±3 years. USA.	Cartilage	WOMAC pain	Spearman correlation	22
Felson *et al*[24]	BOKS, USA. See above. n=401 (33% women in knee pain group, 48% in no pain group); mean age: 62 years (range: 22–91).	BML	Presence/ absence of pain	Logistic regression	75
Fernandez-Madrid *et al*[25]	Case: patients with knee OA (ACR criteria). n=52 (67% women); mean age 55±14 years. Control: general population. n=40 (62% women), 49±15 years. Detroit, USA.	Cartilage, osteophytes, subchondral lesions, effusion/ synovitis, meniscal tears	Presence/ absence of pain	χ^2 test	72
Hayes *et al*[26]	Four groups (each n=30, 100% women): no pain, no radiographic knee OA, mean age 45±1 years; no pain, radiographic knee OA, 46±1 years; pain, no radiographic knee OA, 47±1 years; pain, radiographic knee OA, 47±1 years. Southeast Michigan Osteoarthritis cohort, USA.	Cartilage, osteophytes, subchondral cysts, BML, effusion/synovitis, meniscal tear, ACL tear	Presence/ absence of pain	Fisher exact test of general association	56

Studies	Study population	Features assessed	Pain assessment	Statistical analysis	Quality score (%)
Hernández-Molina *et al*[27]	Patients with knee OA (K&L ≥2). n=1273 (48% women); mean age: 65±9 years. Framingham OA study cohort, Massachusetts, USA.	Bone attrition	Presence/ absence of pain	χ^2 test	78
Hill *et al*[28]	Cases: BOKS, USA. See above. n=360, 33% women, mean age: 68 years. Controls: no knee pain. n=73, 65% with K&L ≥2 and JSN≥1, 57% men, 66 years.	ACL tear	Presence/ absence of pain	χ^2 test	50
Kornaat *et al*[29]	GARP. See above. n=205 (80% women); median age 60 years (range: 43–77).	Cartilage, osteophytes, subchondral cysts, BML, effusion, meniscal defects	Presence/ absence of pain	Logistic regression	78
Link *et al*[30]	Patients with knee OA (ACR criteria). n=50 (60% women); mean age 64±11 years.	Cartilage, BML, meniscal tear, ACL tear	WOMAC pain	Wilcoxon rank sum test	47
Lo *et al*[36]	Patients with knee OA (Knee pain or stiffness and osteophytes OARSI atlas score 1–3), n=160 (50% women), mean age 61±9.9. OA initiative.	BML, effusion/synovitis	WOMAC pain	Logistic regression	78
Pelletier *et al*[31]	Knee OA (radiographic) from general population. Subset from clinical trial on Risendronate in North America. n=110 (64% women); mean age 62±7 years.	Cartilage	WOMAC pain	Spearman correlation	39
Phan *et al*[32]	Patients with knee OA (ACR criteria), n=34 and general population, n=6, 60% women, mean age: 58±16 years.	Cartilage, BML	WOMAC pain	Correlation not specified	67
Sengupta *et al*[33]	BOKS. See above. n=217 (30% women); mean age 67 ±9 years.	Osteophytes	10-point pain scale	Logistic regression	78
Sowers *et al*[34]	Southeast Michigan Osteoarthritis cohort, USA. See above.	Cartilage, BML	VAS pain	Wilcoxon or Maentel–Haenszel test of general association	78
Torres *et al*[19]	Patients with knee OA (K&L ≥2 and 'a little difficulty' in one or two WOMAC physical function scale). n=143 (88% women); mean age 70±10 years.	Cartilage, osteophytes, bone cysts, bone attrition, BML, synovitis, meniscal tears, ligament abnormalities (MCL, LCL and ACL)	VAS pain	Median quantile regression	78

ACR clinical and radiographic criteria requires knee pain and osteophytes on radiograph.[50]

ACL, anterior cruciate ligament; ACR, American College of Rheumatology; BMI, body mass index; BML, bone marrow lesion; BOKS, Boston OA of the knee study; GARP, Genetic Arthrosis Progression Study; JSN, joint space narrowing; K&L, Kellgren and Lawrence Osteoarthritis Scoring System for knee radiographs; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; n, number of study population; OA, osteoarthritis; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster University.

publications[14,17] came from the same authors and used the same patient population. We therefore selected two of them.[14,16] These two selected studies defined cartilage loss as determinant and pain as outcome, contradictory to the two others which defined the determinant and outcome conversely. After additional searching, another three papers were found.[16,18,19] In total, 22 papers were selected. In all, 5 studies reported longitudinal data[12,14,16,20,21] and 17[18,19,22-36] were cross-sectional studies.

Characteristics of included studies

Of the 22 analysed papers, 8 published associations of multiple MRI features (table 2.3),[19,25,26,29,30,32,34,36] the others investigated only a single MRI feature.

Of these papers (table 2.3), 10 were results from 3 studies: the Boston Osteoarthritis Knee Study (BOKS),[12,18,22,24,28,33] the Southeast Michigan OA (SEM) cohort[26,34] and the Genetic Arthrosis Progression Study (GARP).[20,29] Most studies used a General Electric MRI system (in 14 publications).[12,13,16,18,19,22-24,26,28,30,32-34] A Siemens MRI system was used in four publications[14,25,27,31] and a Philips MRI system was used in two publications.[20,29] Two studies[35,36] used a 3 T magnetic field system, all others used a 1.5 T system. Only one study[35] used MRI contrast agent.

Patients investigated in the included studies were of both sexes and older than 50 years, except for one which studied women alone with mean age of 47 years (table 2.3).[26] Almost all studies defined knee OA by using clinical and radiographic criteria of American College of Rheumatology, which requires at least knee pain and osteophyte on radiograph. Only five studies defined knee OA purely radiographically.[19,23,26,27,31]

Study quality assessment

We agreed on 212 of 227 (93%) quality assessment items scored (see table 2.2). Most disagreement focused on the clarity of description of the study population (criterion 2) and participation rate (criterion 3).

In general, many publications either did not assess MRI findings using standardised and validated criteria or they did not inform the reader about this (criterion 5). In many prospective cohort studies the researchers were not blinded for the time order of MRI scans (criterion 7) and differences between withdrawal and completed groups were not described (criterion 10). In cross-sectional studies, the most common limitations were participation rate (criterion 3) and lack of adjustment of possible confounders such as age and sex (criterion 11).

Association between MRI features and pain (best-evidence synthesis)

Cartilage defect

Six studies[19,26,29-32] investigated cartilage defects using semiquantitative scores, five[14,16,23,25,34] used quantitative methods and one used quantitative method on contrast-

enhanced MRI.[35] The level of evidence on the association between cartilage defects and pain was conflicting: three[16,19,34] of five high-quality studies showed a positive association with pain. When all 12 studies which investigated cartilage defects[14,16,19,23,25,27,29-32,34,35] were summarised, 50% showed a positive association independent of study quality.

Bone marrow lesions

The evidence about the association between BML and pain was moderate. Four[19,24,34,36] of five high-quality studies showed an association between BML and pain. One high-quality cohort study showed no association.[20] Three of the four high-quality cross-sectional studies that demonstrated a positive association presented an OR as quantitative measure of association. The OR ranged from 2.0 (adjusted for effusion and synovitis)[36] to 5.0 (unadjusted, 95% CI 2.4 to 10.5).[34] One study reported a β coefficient of 3.72 (95% CI 1.76 to 5.68).[19] When all eight studies investigating BML[19,20,24,26,30,32,34,36] were taken into account 63% reported a positive association between BML and pain.

Osteophytes

Neither of the two high-quality studies showed a positive association between osteophytes with pain.[29,33] According to best evidence synthesis this gives limited level of evidence on the no association between osteophytes and knee pain.

Meniscal lesions

Only one[19] of three high-quality cross-sectional studies showed a positive association resulting in a conflicting level of evidence for the association between meniscal lesions and pain.[18,19,29] When all studies were taken into account; 33% showed a positive association.

Synovitis/joint effusion

A moderate association was found for effusion/synovitis, since all four[12,19,29,36] high-quality studies showed a positive association. One of which was a high-quality cohort study.[12,19,29] This study performed separate analyses for effusion and synovitis: the analysis between effusion and pain showed no association whereas the association between synovitis and pain was positive. We regarded this study as positive, because we deemed a study as a positive study when at least one of the subfeatures showed a positive association. Four high-quality studies reported quantitative measures of association. Three reported the OR of having pain when effusion/synovitis was present, ranging between 2.6 (adjusted for synovitis and BML)[36] and 10.0 (adjusted for age, sex BMI and intrafamily effects, 99% CI 1.13 to 149).[29] One other study reported β regression of 9.82 (95% CI 0.38 to 19.27).[19] When no quality assessment was performed, 86% of included studies[12,19,21,25,26,29,30,36] showed a positive association with pain.

Ligament disease

Two studies[28,30] classified ligament abnormalities as presence or absence of tears, and three studies[19,22,26] used semiquantitative scores. Since only two high-quality studies[19,22] were available, which showed positive association, this resulted in a limited level of evidence for a positive association between ligament abnormalities and pain. When all five studies[19,22,26,28,30] were taken in account, only 40% showed a positive association.

Subchondral cyst

Subchondral cysts were not associated with pain. Two high-quality studies showed no association and this resulted in a limited level of evidence.[19,29]

Bone attrition

Conflicting evidence was found on the association between bone attrition and pain. One[19] of two high-quality cross-sectional studies,[19,27] showed a positive association.

Sensitivity analysis

When we used median score of all studies instead of mean score as the cut-off of high quality studies, the level of evidence of the association of all MRI finding investigated remained the same. The number of positive studies without quality assessment is shown in table 2.4.

Table 2.4 Best evidence synthesis (MRI features arranged from top to bottom according to the number of studies included)

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Cartilage defects (level of evidence: conflicting)						
Scored using semi-quantitative scores						
Pelletier[31]	CS	r= 0.09, p=0.38	-	na	6/12 (50%)	3 (1C, 2CS)/ 6 (2C, 3CS (50%
Phan[32]	CS	r is not mentioned, NS	-	na		
Torres[19]	CS	β=1.03 (95%CI 0.6-1.5)	0.53 (0.08-0.98)	age and BMI		
Hayes[26]	CS	+-ve, p=0.001	-	na		
Kornaat[29]	CS	-	OR 1.1 (99% CI: 0.4-3.1)	age, sex, BMI, intrafamily effects		
Link[30]	CS	+-ve, p<0.05	-	na		
Scored quantitatively						
Raynauld[14]	C	r= -0.25 (WOMAC), NS r= 0.12 (VAS), NS	-	na		
Wluka[16]	C	r= 0.28, p=0.002	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Sowers[34]	CS	+-ve, p<0.0001	-	na		
Dunn[23]	CS	+-ve, p<0.05	-	na		
Scored using other methods (i.e. quantitatively after giving contrast agent)						
Anandacoomarasamy[35]	CS	R=-0.21, p=0.07	-	na		

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Bone Marrow Lesion (level of evidence: moderate)						
Kornaat[20]	C	-	mean difference (increasing BML)=2 (95%CI:-8 to 11)	Age, sex BMI, intrafamily effects	5/8 (63%)	4 (CS)/5 (1C, 4CS) (80%)
Hayes[26]	CS	+-ve, p=0.001	-	na		
Felson[24]	CS	-	OR 3.31 (95% CI 1.5-7.4)	age, sex, radiological and effusion score		
Link[30]	CS	p>0.05	-	na		
Lo[36]	CS	+, RR BML scores vs no BML= 1: 1.3 2: 2.1 3: 2.3 p for trend 0.0009	+, 1: 1.2 2: 1.9 3: 2.0 p for trend 0.006	effusion and synovitis		
Phan[32]	CS	r is not mentioned, NS	-	na		
Sowers[34]	CS+	OR 5.0 (95% CI 2.4-10.5)	-	na		
Torres[19]	CS+	β=5.0 (95% CI 3.0-7.0)	β=3.7 (95%CI 1.8 to 5.7)	age and BMI		

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Osteophytes (level of evidence: moderate)						
Presence					2/6 (33%)	0/2 (CS) (0%)
Fernandez-Madrid[25]	CS	NS	-	na		
Hayes[26]	CS	+-ve, p<0.001	-	na		
Kornaat[29]	CS	-	OR 1.05 (99%CI 0.4-2.9)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	β= 1.2 (95% CI 0.6-1.7)	β= 0.5 (95%CI 0.07-0.94)	age and BMI		
Signal strength						
Sengupta[33]	CS	-	PR=0.94 (0.8 to 1.1)	age, gender, BMI		
Meniscal lesion (level of evidence: conflicting)						
Bhattacharyya[18]	CS	-	p=0.7	age	2/6 (33%)	1/3 (CS) (33%)
Fernandez-Madrid[25]	CS	NS	-	na		
Hayes[26]	CS	+-ve, p<0.001	-	na		
Kornaat[29]	CS	-	Tears: OR=1.26 (99% CI 0.6-2.7) Subluxation: OR=1.03 (99% CI 0.5-2.2)	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Torres[19]	CS	Tears: β= 3.3 (95% CI 0.9-5.8) Subluxation: β= 15.0 (95% CI -0.3-30.3)	Tears: β= 2.0 (95% CI 0.6-3.4) Subluxation: β= 2.2 (-6.9 to 11.3)	Age and BMI		

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Effusion and synovitis (level of evidence: moderate)						
Hill[12]	C	-	Effusion: OR=1.2 (95%CI: -8.1 to 10.5)	age, gender, BMI, cartilage score at baseline, effusion score, BML score, change in effusion and BML score.	6/8 (80%)	4 (1C, 3CS)/ 4 (1C, 3CS) 100%
Fernandez-Madrid[25]	CS	Effusion: +-ve, p<0.001 Synovitis: NS	-	na		
Hayes[26]	CS	Effusion: +-ve, p<0.001 Synovitis: +-ve, p<0.001	-	na		
Kornaat[29]	CS	-	Effusion: OR 10.0 (99% CI: 1.1-1.5)	age, sex, BMI, intrafamily effects		
Link[30]	CS	Effusion: p>0.05	-	na		
Lo[36]	CS	Effusion: RR BML scores vs no BML= 1: 1.8 2: 2.4 3: 3.1 p for trend <0.0001 Synovitis: 1: 1.9 2: 1.9 3: 2.3 p for trend 0.20	Effusion: 1: 1.7 2: 2.0 3: 2.6 p for trend 0.0004 Synovitis: 1: 1.4 2: 1.5 3: 1.9 p for trend 0.22	Synovitis and BML		
Torres[19]	CS	β= 15.0 (95% CI -8.2-38.2)	β= 9.8 (0.4-19.3)	age and BMI		
Pelletier[21]	C	Effusion: r=0.07, +-ve, p=0.71 (WOMAC) r=0.01, +-ve, p=0.93 (VAS)	-	na		

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Knee ligament abnormalities (level of evidence: limitied)						
Amin[22]	CS	-	ACL: +-ve, p<0.05	age, BMI, gender and cartilage scores	2/5 (40%)	2/2 (CS) (100%)
Hill[28]	CS	ACL: +-ve, p=0.0004	-	na		
Link[30]	CS	ACL: p>0.05 MCL: p>0.05	-	na		
Torres[19]	CS	β (95% CI) ACL: 5.0 (-13.0 to 23.0) MCL: 0 (-11.9 to 11.9) LCL: 15.0 (-8.2-38.2)	 ACL: 6.8 (-5.4 to 19.0) MCL: -6.1 (-14.0 to 1.7) LCL: 29.5 (17.8 to 41.1)	age and BMI		
Hayes[26]	CS	ACL and PCL: p=0.23 MCL and LCL: p=0.86	-	na		

Studies	Study design	Association (sizes)		Adjusted confounders	Number of studies: positive/ total (%)	
		Crude	Adjusted		All	High quality
Subchondral cysts (level of evidence: limited)						
Hayes[26]	CS	+-ve, p<0.001	-	na	1/5 (20%)	0/2 (CS) (0%)
Kornaat[29]	CS	-	OR 1.7 (99% CI: 0.8-3.6),	age, sex, BMI, intrafamily effects		
Link[30]	CS	p>0.05	-	na		
Fernandez-Madrid[25]	CS	NS	-	na		
Torres[19]	CS	β=2.5 (95% CI -0.4-5.4)	β= 0.8 (-0.5-2.1)	age and BMI		
Bone attrition: level of evidence: conflcting						
Hernández-Molina[27]	CS	OR 3.3 (95% CI 2.5-4.5)	OR 1.2 (95% CI 0.7-2.0)	Age, gender, K/L grade, BMI, presence of BML and effusion	1/2 (50%)	1/2 (CS) (50%)
Torres[19]	CS	β=3.3 (95% CI 1.8-4.9)	β=1.9 (0.7-3.1)	age and BMI		

Author's name in *italic* indicates high-quality studies; positive in front of p values indicates significant positive association sizes. R:)Spearman's or Pearson's) correlation coefficient between MR feature of interest and pain in continuous scale (WOMAC pain subscale or VAS); in a cohort study the correlation coefficient showed the association between changes of the MRI features with the changes in pain during the follow-up. OR, odds of having pain (in cross-sectional studies) or increasing pain (in cohort studies) when a MRI feature is present or increasing comparing to the odds when MRI feature is absent. β is regression coefficient representing the increase in knee pain severity associated with increase in lesion score, PR, prevalence (odds) ratio.

ACL, anterior cruciate ligament; BMI, body mass index; BML, bone marrow lesion; C, cohort; CS, cross-sectional studies; K&L, Kellgren and Lawrence; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; na, not applicable; NS, not significant; PCL, posterior cruciate ligament; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster University Scoring system.

DISCUSSION

Pain is the most disabling symptom of OA. Knowledge about the structures that cause pain is crucial, because in the future it may be possible to specifically target interventions. For a long time, research on the structural cause of pain has been focused on cartilage defects, even though cartilage does not have pain fibres.[3] Further, research on structures that produce pain in the knee was hampered by the limited ability of radiographs to visualise knee structures extensively. MRI has been shown to be superior to plain films. It demonstrates the whole joint organ. Since several initial reports seemed positive about the association between MRI findings and pain, we therefore investigated the evidence between the MRI findings and knee pain in patients with knee OA. Our findings will be relevant to researchers, clinician and radiologists reporting MRI studies.

We identified a moderate level of evidence for a positive association for BML and effusion/synovitis with pain in knee OA. The level of evidence was limited for a positive association for knee ligamentous abnormalities. We found limited levels of evidence for no association for osteophytes and subchondral cysts. Conflicting levels of evidence were found for cartilage defects, meniscal lesions and bone attrition. We did not investigate studies found during the literature search which investigated features beyond the scope of this review: patella alignment,[37] peripatellar and other periarticular lesions,[38] popliteal or synovial (Baker's cyst).[13,26,29]

In our review, we used a priori defined qualitative levels of evidence to reach a summary. We consider this as a strength because we provide an alternative to quantitative statistics, which could not be calculated as the topic of our review included several aspects of studies that were heterogenic. However, simply counting positive studies also has several drawbacks. It does not take into account the size of the studies, and the decision on 'positive or negative' studies was based only on statistical significance. In meta-analysis, it is theoretically possible that individual studies are negative but the pooled effect is positive.[39] Another technical limitation of our review is the use of quality scores to asses the methodological quality of the studies. It could be that when different quality score sets were used, the interpretation of the results could be influenced.[40] Other limitations of this review mostly reflect the limitations of the studies investigated. First, no publication bias could be assessed using a funnel plot due to the limited number of studies that reported their results in RR or OR.[41] Therefore, we do not know whether preferentially positive findings were published. Second, the quality of included studies was not excellent. There are several obvious examples of limitations of the studies. MRI scan interpretation is by nature subjective, as few, if any, quantitative methods exist. Attempts at standardisation may not be generally used. Also, most scans were read unblinded to order. It is possible that MRI readers define the later findings as more severe than the first findings. This could lead to misclassification.

The moderate associations found in the review have the consequence that more research is needed.[42] Epidemiological studies about BML and effusion/synovitis could strengthen the levels of association. An ideal epidemiological study design would be a case-crossover study where individual MRI findings in the presence of knee pain at one time point are compared with MRI findings in the same patient without knee pain at another time point. The ideal data analysis would give an association size and permit adjustment for confounders, including age and sex, and also for other MRI features when multiple MRI findings are studied simultaneously.

The causal relationship between BML and effusion/synovitis and pain in knee OA needs further study. Our knowledge is now limited to the fact that BML, defined as ill-defined hyperintensities on T2-weighted MRI,[43] comprises normal tissue, oedema, necrosis and fibrosis in histological slices.[44] Further, although knee OA is not considered as an inflammatory arthritis per se, research on the role of inflammation in knee OA and the potential use of anti-inflammatory treatments in knee OA should also be pursued in the light of the possible association between effusion/synovitis with knee pain in knee OA. Evaluation of effusion and synovitis can be improved by using contrast enhancement, since it can highlight inflammation and improve the distinction between synovitis and effusion.[12,19] Gadolinium contrast diffusion is affected in synovitis tissue, where the blood flow and permeability are changed.[45] In the present review, no included papers performed contrast-enhanced MRI.

Beyond the knee itself further research needs to be focused on the origin of pain in OA and representation in the central nervous system. Some observations have shown that pain in arthritis is also characterised by abnormal pain response (hyperalgaesia)[46] and functional MRI has the potential to study hyperalgaesia and other pain response.

Knowing which structures in the knee are associated with knee OA will add to our understanding of OA and, in the long term, will lead to rational therapeutic targets for OA. This will mean improvement in patient care, since at this moment the therapeutic options against OA are limited.[47] At present, the clinical implication of BML is not clear, despite being a common finding in knee OA, being present in 78% of patients with knee OA with pain and in 30% of patients with knee OA without pain.[24] BML is plainly not pathognomonic of knee OA as it is also found in a range of conditions such as trauma, osteoporosis and rheumatoid arthritis.[48] Moreover, BML is also not a static finding. Almost every BML in knee changes in size over a period of 3 months.[49] The clinical implications of effusion/synovitis may be clearer, since they might permit the potential use of anti-inflammatory drugs in treatment of OA. Effusion/synovitis is common in knee OA. Moderate effusion being seen in 36% of patients with knee OA and synovitis present in (84%) of knees.[26]

The finding that ligamentous abnormalities may associate with pain is of special interest. While the exact aetiology and management of these finding remains unclear it may be that surgical intervention could in theory be aimed at repair of these structures

to alleviate pain. However, based on present knowledge, surgical intervention for symptomatic treatment is not currently indicated.

In summary, this systematic review has shown that BML and effusion/synovitis were associated with knee OA pain. However, the level of evidence is moderate and these features need to be explored further.

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3

Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound

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ABSTRACT

Objectives

To investigate the association of ultrasound (US) features - grayscale (GS) synovitis, synovial thickening, effusion and power Doppler signal (PDS) - with symptoms in hand osteoarthritis (HOA).

Methods

Fifty-five consecutive patients (mean age 62 years, 87 % women) with HOA, fulfilling the American College of Rheumatology criteria, were assessed for pain upon palpation and filled in Australian/Canadian Osteoarthritis Index (AUSCAN) scores, visual analogue scale pain and Short Form-36 (SF-36). US was performed in all metacarpophalangeal, proximal interphalangeal, distal interphalangeal, first interphalangeal and first carpometacarpal joints, and features were semiquantitatively scored (0-3). Generalised estimating equations were used to calculate OR (95%CI) for the association between US features and pain per joint adjusted for relevant confounders. The association between US features summated scores and self-reported outcomes was studied by linear regression analysis

Results

GS synovitis, effusion, synovial thickening and PDS were demonstrated in 96%, 91%, 73% and 86% of patients, respectively. US features were dose-dependently associated with pain upon palpation (OR 4.5 (2.2 to 9.0), 4.4 (2.0 to 9.4), 4.9 (2.2 to 11.0) and 4.1 (2.2 to 7.9)). GS synovitis was associated with AUSCAN pain, stiffness and SF-36, and effusion with AUSCAN pain.

Conclusions

GS synovitis, effusion, synovial thickening and PDS are associated with pain in HOA, suggesting a role for inflammation. Further follow-up studies are warranted.

INTRODUCTION

Hand osteoarthritis (HOA) causes considerable pain and disability.[1,2] The source of the pain in HOA is still unclear. Radiographic OA features show only a modest association with symptoms in HOA.[3] Radiography, however, is unable to visualise soft tissue such as synovitis and effusion. Ultrasound (US) is an easy non-invasive procedure, with good availability and minimal discomfort for the patient and can be used to study soft tissue in HOA.

Few studies on US in HOA have been published. They show that inflammatory features are often in symptomatic HOA.[4,5] The association between pain and US features is still largely unknown.

The aim of the present study was to investigate the presence of inflammatory features and the association of US features - grayscale (GS) synovitis, synovial thickening, effusion and power Doppler signal (PDS) - with pain, function and health related quality of life (HRQoL) in HOA.

Materials and methods

Patient population and OA diagnosis

Consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Center, a secondary consultation centre for the region, in Leiden, the Netherlands from May 2008 until May 2009. Local medical ethics committee approval was obtained.

All patients met the American College of Rheumatology criteria for HOA and were at least 45 years of age.[6] Exclusion criteria were: trauma or an operation of the hands up to 6 months before inclusion or an intra-articular injection up to 3 months before inclusion, oral corticosteroids 1 month prior to inclusion, positive rheumatoid factor, carpal tunnel syndrome or another inflammatory joint disease. All patients gave informed consent.

Clinical assessment

Demographic characteristics were collected by standardised questionnaires. From all patients 100 mm visual analogue scale (VAS) and Australian/ Canadian Osteoarthritis Index (AUSCAN) pain, function and stiffness subscales over the last 48 h were obtained.[7]

HRQoL was assessed by the Short Form-36 (SF-36) physical component summary score (PCS), which was derived using norm-based data from the Dutch population. This means the score is standardised to a mean of 50 with a standard deviation of 10.[8]

During physical examination, first carpometacarpal joints (CMCJs), first interphalangeal joints (IPJs), metacarpalphalangeal joints (MCPJs), proximal interphalangeal joints (PIPJs) and distal interphalangeal joints (DIPJs) from both hands

were examined using the Doyle index.[9] No analgesics were allowed for 72 h preceding the clinical and US assessment.

Ultrasound procedure

US was performed on the same day as the clinical assessment by two ultrasonographers (MCK, WYK) in consensus, using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear array transducer. PDS was assessed with a pulse repetition frequency (PRF) of 13.2 kHz and a medium wall filter. Gain was adjusted until background signal was removed.

Hand joints were scanned on the dorsal side in longitudinal and transverse planes.[10] Features had to be present in both planes.

Each joint was scored for GS synovitis defined as a composite of effusion and synovial thickening, as described.[10]

In addition to GS synovitis, synovial thickening and effusion were scored separately. Synovial thickening and effusion were scored in accordance with the scoring system for rheumatoid arthritis.[11] The definition of synovial thickening and effusion followed the Outcome Measures in Rheumatoid Arthritis Clinical Trials definitions.[12] Synovial thickening is defined as an abnormal hypoechoic intra-articular material that is non-displaceable and poorly compressible and may exhibit PDS. Effusion is defined as an abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible and does not exhibit PDS.

All US features were scored using a semiquantitative scale: 0=none, 1=mild, 2=moderate and 3=severe.[10]

PDS and synovial thickening grade 3 was only seen in two and eight joints respectively. Therefore grade 2 and 3 were combined in the analyses.

Intraobserver variability was tested by performing a second US in 10% of (randomly chosen) patients on the same day after at least 5 h. In between, at least one other US assessment was performed.

The ultrasonographers were blinded to clinical findings.

The intraobserver variability, taking in account the severity of the score, depicted by the intraclass correlation coefficient was 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Statistical analysis

The association of US features with pain upon palpation of separate hand joints was studied using generalised estimating equations (GEE). Relative risks were presented as OR with 95%CI. In multivariate analyses, adjustments were made for patient effects and confounders. To investigate whether US features were independently associated with pain, adjustments were made for other US features. We compared summated scores of US features with self-reported pain, disability and HRQoL using linear

regression analysis, adjusting for age, sex, body mass index (BMI) and US features when appropriate.

Data were analyzed using SPSS for Windows, V.16.0.

RESULTS

Study population

Fifty-six patients with HOA were recruited. One patient had received an intra-articular injection and was excluded. Hence 55 patients were analysed. Demographic and clinical characteristics are described in table 3.1. Mean age was 62 years and 87% were female. Mean AUSCAN and VAS pain scores were 9 and 50, respectively.

Table 3.1 Demographic and clinical characteristics of 55 patients with hand osteoarthritis (HOA)

Variable	HOA patients (n=55)
Age (years), mean (SD)	62.0 (8.9)
Female, number (%)	48 (87.3)
BMI (kg/m2), mean (SD)	27.6 (4.5)
Symptom duration (years), median (range)	5.0 (0-55)
Painful joints upon palpation (no), median (range)	9.0 (0-30)
VAS pain (mm), mean (SD)	50 (22.6)
AUSCAN pain (0-20), mean (SD)*	9.1 (4.2)
AUSCAN stiffness (0-4, mean (SD)*	1.8 (1.1)
AUSCAN function (0-36), mean (SD)*	14.8 (7.5)
SF-36 PCS (0-100), mean (SD)*	44.6 (8.6)

* 52 completed AUSCAN scores and 49 completed SF-36 were available
BMI=body mass index, VAS=visual analogue scale, AUSCAN=Australian/ Canadian Osteoarthritis Index, SF-36=Short-Form 36, PCS=Physical health scale.

Prevalence of US features

Nearly all (96%) patients with HOA had GS synovitis in at least one hand joint; the median number of affected joints per patient was 6 (table 3.2). Effusion, synovial thickening and PDS were less commonly seen (91%, 73% and 85%, respectively). Twenty per cent of all hand joints showed GS synovitis, consisting mainly of effusion.

US features were equally distributed between left and right hands, and were predominantly found in first CMCJ, second and third PIPJ and DIPJ (see supplement table S3.1). Twenty-five per cent of all hand joints showed at least one inflammatory US feature. In 5.2% two features were present, and in 2.3% three US features were present.

Table 3.2 Prevalence of ultrasound (US) features in 55 patients with hand osteoarthritis (HOA)

US features	HOA patients (n=55)
Grayscale synovitis*	
Patient, no (%)	53 (96.4)
Affected joints, median. (range)	6.0 (0-13)
Total score, median (range)	8.0 (0-24)
Effusion*	
Patients, no. (%)	50 (90.9)
Affected joints, median (range)	6.0 (0-13)
Total score, median (range)	7.0 (0-24)
Synovial thickening*	
Patients, no. (%)	40 (72.7)
Affected joints, median. (range).	2.0 (0-9)
Total score, median (range)	2.0 (0-14)
Power Doppler signal*	
Patients, no. (%)	47 (85.5)
Affected joints, median. (range).	2.0 (0-8)
Total score, median (SD)	3.0 (0-11)

* Maximum score per patient for affected joints is 30, the maximum total score is 90.

Association of US features and pain upon palpation in hand joints

All US features showed a dose-dependent association with pain after adjustment for age, gender and BMI: OR (95% CI) for GS synovitis 4.5 (2.2 to 9.0), effusion 4.4 (2.0 to 9.4), synovial thickening 4.9 (2.2 to 11.0) and PDS 4.1 (2.2 to 7.9). Further adjustment for US features revealed that GS synovitis was associated with pain independently of PDS (OR 4.0 (1.9 to 8.2), and that effusion and synovial thickening were associated with pain independently of each other and PDS (OR 3.7 (1.8 to 7.6) and 2.5 (1.1 to 6.3) respectively). PDS was no longer associated with pain after further adjustments (table 3.3).

Table 3.3 Association of ultrasound (US) features and pain upon palpation in 55 patients with hand osteoarthritis (HOA)

US feature score	N	Adjusted OR * (95% CI)	Adjusted OR ** (95% CI)
GS synovitis			
0	1289	1	1
1	244	2.2 (1.6-3.0)	2.1 (1.5-2.8)
2	84	5.4 (3.2-8.8)	4.7 (2.8-7.8)
3	33	4.5 (2.2-9.0)	4.0 (1.9-8.2)
Effusion			
0	1337	1	1
1	227	2.3 (1.6-3.0)	2.0 (1.5-2.6)
2	61	4.9 (3.0-7.9)	3.8 (2.3-6.1)
3	25	4.4 (2.0-9.4)	3.7 (1.8-7.6)
Synovial thickening			
0	1529	1	1
1	76	2.3 (1.4-3.8)	1.3 (0.7-2.4)
2+3	37+8	4.9 (2.2-11.0)	2.6 (1.1-6.3)
PDS			
0	1511	1	1
1	107	1.9 (1.3-2.7)	1.4 (1.0-2.1)
2+3	30+2	4.1 (2.2-7.9)	2.0 (0.8-4.9)

*Adjustment made for age, gender, BMI; **in addition the following adjustments were made: GS synovitis for PDS, effusion for synovial thickening and PDS, synovial thickening for effusion and PDS, PDS for synovial thickening and effusion.
PDS=power Doppler signal, GS=grayscale, BMI=body mass index.

Association of US features and self-reported pain, function or HRQoL.
A statistically significant association was demonstrated for GS synovitis with AUSCAN pain, stiffness and SF-36 PCS. Of the other features only effusion showed an association with AUSCAN pain. (see supplement table S3.2).

DISCUSSION

The majority of patients with HOA show inflammation on US. In individual joints, we showed a dose-dependent association between inflammatory features and pain. In addition, GS synovitis, effusion and synovial thickening were independently associated; PDS was not. GS synovitis was also associated with AUSCAN pain and stiffness and with SF-36 PCS, as was effusion with AUSCAN pain.

Few studies have investigated the relationship between US features and pain in HOA. Keen et al. showed no association between self-reported pain and US features.[4]

However, patient effects were not taken into account. In the present study, after adjustments for patient effects and confounders, associations between pain and inflammatory features were revealed.

In our study, 96% of patients showed GS synovitis, 91% effusion, 86% PDS and 73% synovial thickening. Vlychou et al. showed synovial thickening in 87% of all studied patients, although the presence of PDS was comparable.[5] However, that study was performed in erosive HOA patients, which may account for the difference. Further studies to compare the presence of inflammatory signs in several HOA subsets are warranted.

On average, patients in this study had fewer joints showing GS synovitis than found by Keen et al (6 versus 12).[4] Whether this is due to a difference in HOA phenotype or difference in US technique, is difficult to determine. Patients in the study of Keen had a slightly higher VAS pain score. PDS scores were, however, similar in the two studies.

In this study, GS synovitis, as well as effusion and synovial thickening separately, were studied. In earlier studies of HOA, either GS synovitis was scored or effusion and synovial thickening. GS synovitis is often chosen because it is thought that separation of effusion and synovial thickening is not straightforward.[10] We show that it is technically possible to study effusion and synovial thickening as separate entities.

This study has potential limitations. Firstly, symptoms such as pain and stiffness depend upon personal factors which were not assessed. However, in this study design, painful joints were compared to non-painful joints in the same patient, thereby minimising the confounding effect from personal factors.

Secondly, only the dorsal sides of the joints were examined. This was done in accordance with a protocol formulated by experts in the field.[10] It is possible that GS synovitis is underestimated by scanning only the dorsal side

In this study, strong, dose-dependent associations were found between inflammatory US features and pain in separate hand joints. These findings are promising for elucidating the aetiology of pain in HOA. The association between US features and pain can give rise to further research for therapeutic strategies. However, repeat studies to confirm the association of US features and pain are needed.

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Supplement table S3.1 Distribution of ultrasound (US) features by joint in 55 patients

	DIP				PIP					MCP					CMC	Total (%)
	2	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**(n=1540)**
Left																
No of joints with syn. thickening	2	4	2	1	3	8	10	6	5	2	1	1	0	0	11	56 (6.8)
No of joints with effusion	18	19	16	18	19	9	16	8	14	4	3	1	0	1	18	164 (19.9)
No of joints with PDS	4	2	2	3	9	10	9	4	0	4	4	1	0	1	12	65 (7.9)
No of joints with 2 US features	*2*	*4*	*1*	*2*	*6*	*4*	*5*	*2*	*4*	*1*	*0*	*1*	*0*	*0*	*7*	*39 (4.7)*
No of joints with 3 US features	*1*	*0*	*0*	*0*	*0*	*3*	*5*	*1*	*0*	*1*	*3*	*0*	*0*	*0*	*5*	*19 (2.4)*
Right																
No of joints with synovitis	7	3	2	1	6	7	8	6	4	0	4	0	0	0	17	65 (7.9)
No of joints with effusion	19	19	13	16	18	10	12	14	5	2	5	1	0	0	16	150 (18.2)
No of joints with PDS	5	3	1	2	3	9	8	7	3	5	5	2	1	1	19	74 (9.0)
No of joints with 2 US features	*5*	*3*	*0*	*2*	*5*	*5*	*6*	*6*	*1*	*0*	*0*	*0*	*0*	*0*	*14*	*47 (5.7)*
No of joints with 3 US features	*1*	*0*	*0*	*0*	*0*	*4*	*2*	*2*	*0*	*0*	*4*	*0*	*0*	*0*	*6*	*19 (2.4)*

DIP=distal interphalangeal joint, PIP=proximal interphalangeal joint, MCP=metacarpal phalangeal joint, CMC=carpometacarpal joint, syn.=synovial, PDS=power Doppler signal.

Supplement table S3.2 Association, depicted as β-coefficients, between ultrasound features and self-reported pain, function and quality of life in 55 patients with hand osteoarthritis

	β-coefficients (95% confidence intervals)*				
	Pain		AUSCAN function	AUSCAN stiffness	SF-36 PCS
US features	**VAS**	**AUSCAN**			
GS synovitis	0.3 (-0.1,3.7)	0.5 (0.2,0.9)	0.3 (-0.1,1.2)	0.3(0.003,0.2)	-0.4 (-1.7,-0.3)
Effusion	0.2 (-1.0,3.1)	0.5 (0.2,0.9)	0.3 (-0.1,1.3)	0.2 (-0.04,0.2)	-0.3 (-1.5,0.1)
Synovial thickening	0.3 (-0.6,5.9)	0.1 (-0.4,0.7)	0.1 (-0.6,1.6)	0.3 (-0.02,0.3)	-0.2 (-2.1,0.4)
PDS	-0.1 (-5.3,2.4)	-0.2 (-1.2,0.2)	-0.1 (-1.6,1.1)	-0.2 (-0.3,0.1)	0.1 (-0.9,2.1)

*Adjusted for age, gender, BMI, and in addition adjustments were made for other US features: GS synovitis for PDS, effusion for synovial thickening and PDS, synovial thickening for effusion and PDS, PDS for effusion and synovial thickening.
US=ultrasound, VAS=visual analogue scale, AUSCAN=Australian/ Canadian Osteoarthritis Index, SF-36=Short-Form 36, PCS=Physical health scale, GS=grayscale, PDS=power Doppler signal, BMI=body mass index.

4

Osteophytes and joint space narrowing are independently associated with pain in finger joints in hand osteoarthritis

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ABSTRACT

Objective

To study the associations between structural abnormalities on ultrasound (US) or conventional x-rays (CR) and pain in hand osteoarthritis (HOA).

Material and methods

In 55 consecutive patients with HOA (mean age 61 years, 86% women), fulfilling the American College of Rheumatology criteria, pain in 30 separate hand joints was assessed upon palpation; osteophytes were assessed by US and CR and joint space narrowing (JSN) by CR. Associations between structural abnormalities and pain per joint were analysed using generalized estimating equations to account for patient effects and adjusted for age, sex, body mass index, US inflammatory features and other remaining structural abnormalities.

Results

In 1649 joints, 69% and 46% had osteophytes on US and CR, respectively and 47% had JSN. Osteophytes and JSN showed independent associations with pain per joint adjusted: OR for osteophytes: 4.8 (95% CI 3.1 to 7.5) for US and 4.1 (95% CI 2.4 to 7.1) for CR; for JSN: 4.2 (95% CI 2.0 to 9.0)

Conclusions

Osteophytes and JSN are independently associated with pain in individual HOA joints taking in account patient effects.

INTRODUCTION

In hand osteoarthritis (HOA), the most predominant structural abnormalities -cartilage loss and marginal bony enlargements- have been studied mainly by conventional x-rays (CR) as osteophytes and joint space narrowing (JSN). Recently, ultrasound (US) studies have been performed[1,2,3] and suggest that US has a higher sensitivity for osteophytes than CR. However, US has difficulties detecting JSN when bony irregularities overlie the joint space,[1] and therefore seems less suitable as imaging modality for JSN.

HOA can cause considerable pain, and one could assume that structural abnormalities play a role in the aetiology of this clinical feature. However, in earlier CR studies limited associations were demonstrated.[4] An explanation for the limited associations could be that relationships were studied using global scores for pain and summated scores for structural abnormalities. Since all the signs of separate hand joints are combined into one score per patient, associations might be concealed. Second, since pain is a subjective experience influenced by genetic predisposition[5] and psychosocial factors such as the experience and expectations of patients,[6,7] it is important to take in account patient effects. In HOA this can be done by comparing affected with non-affected joints within the same patient using generalized estimating equation (GEE) analyses. This was not performed in previous studies.

We have investigated the association between structural abnormalities and pain in HOA. To prevent the above mentioned potential limitations, associations were studied at the patient level and at the individual joint level controlling for person confounding using both US and CR.

Methods

Patient population and osteoarthritis diagnosis

Consecutive patients fullfilling the American College of Rheumatology criteria for HOA[8] and at least 45 years of age were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre, The Netherlands, from May 2008 to February 2010. For HOA this is a secondary consultation centre for the region.

Local medical ethics committee approval and patients' informed consent were obtained.

Exclusion criteria were presence of rheumatoid factor, other inflammatory joint disease or disorders such as carpal tunnel syndrome, trauma or operation on the hands within 6 months, intra-articular injection within 3 months, or oral corticosteroids within 1 month prior to inclusion.

Clinical assessment

Hand pain over the last 48 h was assessed by a 100 mm visual analogue scale (VAS) and by the subscale of the Australian Canadian Osteoarthritis Hand Index (AUSCAN).[9] Function was assessed using AUSCAN subscale. AUSCAN responses are rated on a five-point Likert scale ranging from 0 (none) to 4 (extreme).

All 1st carpometacarpal (CMCJs), 1st interphalangeal (IPJs), metacarpalphalangeal (MCPJs), proximal interphalangeal (PIPJs) and distal interphalangeal (DIPJs) were examined for pain upon lateral pressure (0=none, 1=tender, 2= wincing, 3=withdrawal) using a validated Doyle Index for the hands.[10,11] No analgesics were allowed 72 h before the clinical and US assessment.

Ultrasound procedure

US and clinical assessment were performed on the same day by two ultrasonographers (MCK and WYK) in consensus, who were blinded to clinical findings and CR scores, using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear array transducer. Power Doppler Signal (PDS) was assessed with a pulse repetition frequency of 13.2 KHz and medium wall filter. Gain was adjusted until background signal was removed.

All joints were scanned from the dorsal side only in longitudinal and transverse planes, covering the dorsal and lateral sides of the joint, in accordance with a preliminary US scoring system for HOA.[12] Features had to be present in both planes.

Each joint was scored for osteophytes, PDS, effusion and synovial thickening on a 4-point scale as described previously.[13]

Intraobserver variability was tested by performing a second US in 10% randomly selected patients on the same day after at least 5 h, with at least one other US assessment in between. The intraobserver variability, taking in account the severity of the score, depicted by the intraclass coefficient (ICC) was 0.71 for osteophytes 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Radiographic assessment

Dorsal-volar hand x-rays were obtained within 16 weeks of the US assessment. The x-rays were scored for osteophytes (0-3) and JSN (0-3)[14] by one observer (MCK) blinded to patient characteristics and US outcomes. The intrareader variability, based on 10 randomly selected x-rays, depicted by the ICC was 0.73 for osteophytes, 0.67 for JSN.

Statistical analysis

With linear regression analysis the relationship between structural abnormality summated scores and AUSCAN pain, VAS pain and summated score of the Doyle Index was studied, adjusting for age, sex, body mass index and inflammatory US features.

With GEE the relationship of structural abnormalities and pain at joint level was studied taking into account patient effects. RRs were presented as OR (95%CI).

Data were analysed using SPSS for Windows, version 16.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Study population

Sixty-four patients were recruited. Nine patients were excluded (one received an intra-articular injection after screening and in eight the time between US and CR exceeded 16 weeks). In the remaining 55 patients, one 5th MCPJ was excluded due to an operation in the past, hence 1649 joints were studied.

The demographic characteristics of the patients are shown in table 4.1. Excluded patients did not differ significantly from the included patients (data not shown).

Table 4.1 Demographic characteristics of 55 patients with hand osteoarthritis.

Variable	HOA patients (n=55)
Mean (SD) age (years)	61.4 (9.3)
Women, n (%)	47 (85.5)
Mean (SD) body mass index (kg/m^2)	27.7 (4.5)
Median (range) symptom duration (years)	5.0 (0-55)
Median (range) VAS pain (mm)	51.0 (0-99)
Mean (SD) AUSCAN pain (score:0-20)	9.1 (4.5)
Median (range) AUSCAN function (score: 0-36)	17.0 (0-33)

HOA, hand osteoarthritis; VAS, visual analogue scale; AUSCAN, Australian Canadian Osteoarthritis Hand Index

US and CR findings

Of the 1649 studied joints, 69% had osteophytes on US and 46% on CR; 47% of joints were narrowed. The distribution is shown in the supplement table S4.1.

The median number of osteophytes and the median summated osteophyte score per patient were higher on US than on CR (21 vs 11 and 44 vs 15, respectively).

Association of clinical outcomes with osteophytes and JSN on US and CR

Neither summated osteophytes score assessed by US or CR, nor summated JSN score showed an association with global pain scores (table 4.2).

Table 4.2 Association between structural abnormalities and pain in 55 patients with hand osteoarthritis.

	Osteophytes		JSN
	US	**CR**	**CR**
VAS pain	-0.2 (-3.0 to 0.8)	-0.2 (-0.5 to 0.2)	0.0 (-0.6 to0.5)
AUSCAN pain	-0.2 (-2.1 to 0.4)	-0.1 (-0.3 to 0.1)	0.0 (-0.7 to 0.4)
Doyle Index for the hands	0.0 (-2.2 to 1.6)	0.0 (-0.3 to 0.3)	0.0 (-0.6 to 0.5)

Linear regression analyses with summated osteophytes score by US or CR, and summated JSN score, as dependent variables. Beta coefficients (95% CI) adjusted for age, sex and body mass index and inflammatory ultrasound signs (effusion, power Doppler signal and synovial thickening).
JSN, joint space narrowing; US, ultrasound; CR, conventional x-ray; VAS, Visual analogue scale; AUSCAN, Australian Canadian Osteoarthritis Hand Index

Table 4.3 Association between structural abnormalities and pain upon palpation (presence vs absence) in separate small hand joints# using US and CR in 55 patients with hand osteoarthritis.

Score	**US**		**CR**	
	OR (95% CI)*	**OR (95% CI)****	**OR (95% CI)***	**OR (95% CI)****
Osteophytes				
0	1	1	1	1
1	1.6 (1.2-2.3)	1.6 (1.2-2.3)	2.2 (1.7-2.9)	2.0 (1.5-2.7)
2	2.8 (1.8-4.4)	2.7 (1.8-4.1)	3.9 (2.6-5.9)	3.2 (2.1-4.8)
3	6.2 (4.0-9.4)	4.8 (3.1-7.5)	4.8 (2.7-8.4)	4.1 (2.4-7.1)
JSN				
0			1	1
1			2.0 (1.4-2.8)	1.8 (1.3-2.4)
2			5.3 (3.1-9.1)	4.3 (2.6-7.2)
3			6.4 (2.7-14.8)	4.2 (2.0-9.0)

Small hand joints: DIPJs, PIPJs, 1st IPJs, MCPJs and 1st CMCJs.
* General estimating equations analyses adjusted for age, sex and body mass index.
** General estimating equations analyses adjusted for age, sex, body mass index and synovial thickening, effusion and power Doppler signal as assessed by ultrasound and osteophytes or JSN.
US, ultrasound; CR, conventional x-rays; JSN, joint space narrowing

Association of pain in individual joints with osteophytes and JSN on US and CR
A strong dose-dependent relationship was found between pain in individual joints, taking into account patient effects and osteophytes, on both US and CR (table 4.3). Associations were still significant after adjustment for inflammatory US features and JSN.

JSN assessed by CR showed a strong dose-dependent association with pain in individual joints taking in account patient effects, which remained significant after adjustment for inflammatory US features and osteophytes. This means that both osteophytes and JSN are independently related to pain in HOA.

DISCUSSION

The study reveals a strong dose-dependent association between pain and structural abnormalities assessed on joint level with US or CR, taking into account patient effects in patients with symptomatic HOA. Associations were absent when summated scores of structural abnormalities and global pain scores were analysed. Both osteophytes and JSN are independently associated with pain. To the best of our knowledge, this is the first report to demonstrate this association for JSN. These findings are important for our understanding of HOA and for elucidating the aetiology of pain.

This study supports the hypothesis that analyses on joint level, taking into account patient effects, such as genetic and psychosocial factors, are important for identifying associations between structural abnormalities and pain in HOA. This is in line with an earlier study in knee osteoarthritis (OA), which investigated subjects with knees discordant for pain status, and showed that radiographic OA was strongly associated with pain when controlling for person confounding.[15] Also, in an earlier study assessing inflammatory signs and pain in HOA, associations were found when analyses were performed on the joint level and corrected for patient effects, but not when summated scores of inflammatory signs and global pain scores were used.[13]

JSN was found to be associated with pain upon palpation. This was not just another way to find OA as detected by osteophytes, since the association was independently of osteophytes. In earlier studies using CR, JSN has not been studied as separate feature in the association with pain. One US study showed only a trend for an association between JSN and painful versus painless joints, possibly because patient effects were not taken into account in the analyses.[1] The fact that JSN is independently associated with pain is especially interesting since, in a recent article, JSN was shown to be an important predictor for the development of erosive HOA.[16]

This study shows that US detects more osteophytes than CR. This could be explained by detection of osteophytes located on the dorsal or palmar sides of the joints rather then the lateral sides. The osteophytes located at the palmar and dorsal sides can easily be missed by CR. Whether US reflects the true number of osteophytes is difficult to say, since it is not clear what the gold standard is. Cross-validation with MRI or CT scanning could be helpful.

There are several potential limitations to this study. First, joints were only studied with US on the dorsal and lateral sides, thereby potentially underestimating the amount of osteophytes. Also, a linear array transducer was used instead of a hockey stick transducer, which is more difficult to handle when joints are deformed. A drawback of hockey stick transducers is, however, the lower resolution of these transducers.

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Supplement table S4.1 Distribution of joints with osteophytes in 55 patients with hand osteoarthritis assessed by ultrasound (US) and conventional radiographs (CR).

Right hand				Osteophytes		Left hand				
5	**4**	**3**	**2**	**1**		**1**	**2**	**3**	**4**	**5**
				52	CMC US	52				
				27	CMC CR	38				
4	8	6	16	35	MCP US	27	14	5	2	4
2	2	12	13	25	MCP CR	21	8	6	1	3
47	50	49	51	49	PIP US	48	47	49	51	50
30	20	26	26	37	PIP CR	42	27	33	19	28
51	51	51	55		DIP US		54	54	54	52
39	33	40	46		DIP CR		42	39	28	43

CMC=Carpometacarpal, MCP=metacarpal, PIP=proximal interphalangeal, DIP= distal interphalangeal.

5

Follow-up study of inflammatory ultrasound features in hand osteoarthritis over a period of 3 months: variable as well as constant

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ABSTRACT

Objective

To study inflammatory ultrasound (US) features and pain over a 3-months period in hand osteoarthritis (HOA).

Design

In 25 consecutive HOA patients (mean age 60 years, 76% female), fulfilling the American College of Rheumatology (ACR) criteria, visual analogue scale (VAS) pain scores were collected at baseline and 3 months. In 750 (all first carpometacarpal (CMC), metacarpalphalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP) and first interphalangeal (IP)) joints, pain was assessed upon palpation and synovial thickening, effusion and power Doppler signal (PDS) were scored with standardized methods by US.

Associations between inflammatory features and painful joints were analysed using generalized estimating equations to account for patient effects, adjusting for confounders, and presented as odds ratios (OR) with 95% confidence intervals (95%CI)

Results

Inflammatory US features were seen in (nearly) all patients. The median number (range) of inflammatory joints per patient did not change over time: 9 (0-16) to 9 (2-18). In 18.7% of joints inflammatory features were present at both time points; in 20.5% inflammatory features occurred only at baseline or follow-up. Pain decreased over time: median VAS pain: 49 to 39 mm; median number of painful joints 8 to 3. Synovial thickening, effusion and PDS were associated with pain upon palpation both at baseline and follow-up: OR 2.9 (1.4 to 5.7), 2.7 (1.7 to 4.3), 3.6 (2.1 to 6.3) and 7.3 (3.2 to 16.5), 3.3 (2.3 to 4.7), 4.1 (2.1 to 7.9), respectively.

Conclusions

In HOA inflammatory US features are stable over time at patient level, but vary on joint level. Pain diminished after 3 months, while associations between painful joints and inflammation seem to increase, emphasizing the multifactorial aetiology of pain.

INTRODUCTION

Hand osteoarthritis (HOA) is a prevalent disease, causing considerable pain and disability,[1] which aetiology is still largely unknown. Recent studies showed that in HOA inflammatory features are frequently present and that these features are associated with pain.[2,3] It is, however, not known how these inflammatory features behave over time and what the implication of their presence is.

The clinical course in HOA varies over time with passing episodes of soft tissue swelling. Therefore, it is expected that inflammatory features also change over time. Since pain varies over time as well, one could hypothesize that fluctuation in pain is due to variation in inflammation. On the other hand, pain is a difficult feature to understand, since it is a subjective experience influenced by genetic predisposition and psychosocial factors.[4,5]

Since inflammatory ultrasound (US) features are present and are associated with pain, this could be a target for therapy. Few studies have used inflammatory US features to monitor treatment effect on clinical and inflammatory features in HOA. Keen et al. investigated the efficacy of intra-muscular methylprednisolone in an open study in patients with HOA over a period of 3 months and observed a decrease of global pain, but no difference in inflammatory features on patient level.[6] Klauser et al. injected 78 clinically severe osteoarthritic hand joints with hyaluronic acid. Inflammatory features and pain decreased after 4 weeks; no control joints were investigated.[7]

No short–term observational follow-up studies have been performed to investigate how, on joint level, inflammatory features and their relation to pain evolve over time, which is important to study treatment effects. Therefore, the objective of the present study is to investigate how inflammatory US features and pain evolve. Since up till now, clinical trials investigated the effect of a drug for short periods, we examined evolution during a 3-months period.

Materials and methods

Patient population and OA diagnosis

Consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre, a secondary consultation centre for the region, from December 2008-January 2010. All patients participated in the ECHO study (EChografie in Hand Osteoarthritis), a cross-sectional study described previously.[2] When this study was started and inflammatory features appeared to be frequent, the objective of the present study was formulated and local medical ethics committee approval obtained for this amendment. Therefore only the last 25 patients were eligible for inclusion.

Patients met the American College of Rheumatology criteria for HOA[8] and had to be ≥ 45 years of age. Exclusion criteria were: trauma or operation of the hands

within 6 months, an intra-articular injection within 3 months prior to inclusion, oral corticosteroids one month prior to inclusion, positive rheumatoid factor, carpal tunnel syndrome or any other inflammatory joint disease such as rheumatoid arthritis, psoriatic arthritis or crystal arthropathy. All patients gave written informed consent.

Clinical assessment

Demographic characteristics were collected by standardized questionnaires. One-hundred millimetre visual analogue scale (VAS) hand pain was obtained at baseline and 3 months.

During physical examination, the Doyle index (scores ranged 0-3)[9] was assessed at baseline and 3 months by a specialized and trained nurse in 30 hand joints, being first carpometacarpal joints (CMCJs), first interphalangeal joints (IPJs), metacarpalphalangeal (MCPJs), proximal interphalangeal joints (PIPJs) and distal interphalangeal joints (DIPJs) from both hands. For the analyses, pain scores were dichotomized in painful versus non-painful joints. No analgesics (including non-steroidal anti inflammatory drugs) were allowed 72 h prior to the clinical and US assessment.

Radiographic assessment

Dorsal-volar radiographs of both hands were scored for osteophytes (0-3) and joint space narrowing (JSN) (0-3) using the OARSI atlas[10] at baseline by a trained reader (MCK).

In addition all PIPJs and DIPJs were scored following the Verbruggen and Veys score.[11] Erosive HOA was defined by the presence of at least 1 joint in E (=subchondral erosion) or R (= remodelling of subchondral plate) phase.

Films were blinded for patient characteristics and US outcomes. The intra-reader reliability depicted by the intra-class coefficient (ICC) was 0.86 for osteophytes, 0.76 for JSN and 0.80 for the anatomical phases.

Ultrasound procedure

US was performed on the same day as the clinical assessment by one experienced ultrasonographer (MCK), scoring together in consensus in the presence of a second ultrasonographer (WYK) at all visits, using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear array transducer. Both ultrasonographers were blinded to clinical findings.

Power Doppler signal (PDS) was assessed with a pulse repetition frequency of 13.2 kHz and a medium wall filter. Settings were optimized by the application specialist of the manufacturer of the machine.

All 30 hand joints were scanned on the dorsal side in longitudinal and transverse planes and scored for PDS, synovial thickening and effusion as described previously[j] using a semi-quantitative scale: 0=none, 1=mild, 2=moderate and 3=severe (maximal total score 90).[2] Features had to be present in both planes.

Intra-observer reliability was good to almost perfect.[2]

Statistical analysis

Differences in demographics, self-reported pain, and summated US features between baseline and 3 months were calculated using Wilcoxon signed rank test. Proportion statistics was performed using McNemar analyses.

The association of US features with painful joints was studied using generalized estimating equations (GEE). Odds ratios (OR) were presented with 95% confidence intervals (95%CI). Adjustments were made for patient effects and confounders. We compared summated scores of US features with VAS pain and summated painful joints using Spearman's rank correlation.

Data were analysed using SPSS for Windows, version 20.0 (IBM SPSS statistics, New York, USA).

RESULTS

Study population

Twenty-five Patients were included (mean (SD) age 60 (8.8) years, 16 (76%) women, mean (SD) body mass index (BMI) 28.0 (4.3) kg/m2). Ten patients had erosive HOA. Of two patients data on physical examination and VAS were missing at baseline (60 joints). All patients had osteophytes and JSN in at least one joint on radiographs. The median (range) number of joints with osteophytes and JSN per patient was 16 (2-25), and 19 (3-22), respectively.

US scores at baseline and after 3 months of follow-up

Nearly all patients (24 (96%) at baseline and 25 (100%) at 3 months) showed inflammatory features during the disease course. The median number of joints per patient and median total score per patient with effusion, PDS or synovial thickening did not change over 3 months (table 5.1). However, a change in the actual joints that showed inflammatory US features between baseline and 3 months was seen. Hundred fifty-four of 750 (20.5%) joints had inflammatory signs only at one time point (either baseline or follow-up), 60.8% (456 joints) lacked inflammatory signs both at baseline and 3 months and 18.7% (140 joints) had these signs at both time points.

Effusion was most frequent at baseline and 3 months: 157 and 181 joints respectively. One-hundred and two joints showed effusion at both time points. Synovial thickening was seen in 93 and 92 joints at baseline and follow-up, respectively, 47 joints showed synovial thickening at both time points. PDS was found in 70 and 58 joints at baseline and follow-up, respectively, and 27 joints at both baseline and at 3 months.

So, although there is no change in the total number of joints and total severity score in US features of inflammation after 3 months of follow-up, there is a change observed in joints that show inflammatory features at baseline and after 3 months.

Table 5.1 Clinical and US scores in 30 hand joints of 25 patients with hand osteoarthritis at baseline and after 3 months of follow-up.

	Baseline* N=25	**3 months* N=25**
VAS, mm	49 (1-79)	36 (1-76)[a]
Painful joints upon palpation per patient, no.	8 (1-23)	3 (0-16)[a,b]
Patient with inflammatory US feature, no.	24	25
Joints per patient with any US inflammatory feature, no.	9 (0-16)	9 (2-18)
PDS		
Affected joints, no.	3 (0-7)	2 (0-9)
Total score[c]	3 (0-11)	2 (0-14)
Effusion		
Affected joints, no.	6 (0-14)	7 (0-17)
Total score[c]	6 (0-25)	8 (0-27)
Synovial thickening		
Affected joints, no.	3 (0-12)	3 (0-13)
Total score[c]	5 (0-23)	4 (0-19)

no.= number, VAS=visual analogue scale, US=Ultrasound, PDS=power Doppler signal
*All values are medians (range), unless stated otherwise.
[a] N=23, due to missing data of two patients
[b] Significant difference (p=0.01) between baseline and 3 months, calculated using Wilcoxon signed rank test.
[c] Maximal total score 90

Clinical scores at baseline and after 3 months

As depicted in table 5.1, global pain as measured with VAS pain (median) decreased in 3 months' time, although no statistical significance was reached (median VAS pain 49 to 36, p=0.16). Total number of painful joints per patient showed a statistically significant decrease (8 to 3, p=0.01). Hundred ninety-nine of 690 individual joints were painful at baseline and 106 of 750 at follow-up, which was statistically significant (p<0.0001).

The association between pain and inflammatory features as assessed by US

Previously, we showed in 55 HOA patients that inflammatory US features are associated with pain in hand joints[2]. Results at baseline of the present study were in accordance with those of the total group. These cross-sectional associations were still present after 3 months and tended to be stronger (table 5.2). In this table adjusted OR's are reported. Crude analyses were calculated as well and rendered comparable results.

When analyses were performed on patient level by correlating summated inflammatory US features with VAS pain and summated total painful joints at baseline and follow-up, no correlations were found (data not shown).

Association between inflammatory US features at baseline and painful joints upon palpation at 3 months follow-up

Strong associations between all inflammatory features at baseline and the presence of pain upon palpation in a joint were found after 3 months (table 5.2).

Again when analyses were performed on patient level no correlations were found (data not shown).

Table 5.2 The association between US inflammatory features and painful joints upon palpation in 25 patients with HOA: both at baseline and follow-up, and the prediction of painful joints at follow-up by US features at baseline

US features	Association between baseline US features and painful joints Adjusted OR* (95% CI)	Follow-up US features and painful joints Adjusted OR* (95% CI)	Baseline US features and painful joints after 3 months Adjusted OR* (95% CI)
Synovial thickening	2.9 (1.4, 5.7)	7.3 (3.2, 16.5)	2.0 (1.1, 3.9)
Effusion	2.7 (1.7, 4.3)	3.3 (2.3, 4.7)	4.8 (2.2, 10.5)
PDS	3.6 (2.1, 6.3)	4.1 (2.1, 7.9)	3.8 (2.7, 5.4)

* Adjusted for age, sex and BMI

DISCUSSION

The present study shows that in HOA patients summated inflammatory US features remained stable over a 3-month period. At joint level 19% of hand joints had persistent inflammatory features, while they fluctuated in 20%. Remarkably, pain reduced over time, while the associations of inflammatory features with pain remained and even tended to grow stronger after three months.

Mechanisms that could explain fluctuating inflammatory features in OA have been described. Mechanical stress can induce matrix degradation leading to the release of aggrecanases and collagenases and subsequently to activation of chondrocytes, which are capable of producing proinflammatory cytokines leading to inflammatory features[12].

Furthermore, crystals such as calciumpyrophosphate and/or hydroxyapatite, which are frequently found in OA, can lead to synovitis.[13]

Other mechanisms that can lead to more persistent inflammation are age and obesity.

Aging causes changes in chondrocytes leading to the development of an senescence-associated secretory phenotype that increase production of many cytokines, chemokines and matrix metalloproteinases.[14] Adipose tissue is capable of producing adipokines, which are able to induce inflammation.[15]

In the present study, the decrease in pain can't be explained by a decrease of inflammation.

An alternative explanation could be a lowered mechanical load and diminished psychological factors like uncertainty and fear resulting in perceiving less pain at 3 months. All participants received education about the disease and principles of chronic pain, joint protection, and use of assistive devices and splints by a clinical nurse specialist.

Furthermore, bias could have occurred due to the fluctuating natural course of the disease. Participants seek medical help when they experience a lot of complaints. At this time they were included in the present study. The decrease in pain could then be a natural spontaneous decrease in complaints (regression to the mean). In the clinical trial by Keen et al[6]., self-reported pain decreased after three months, as in the present study. The question can be raised whether this decrease in pain was due to methyl-prednisolone use, or to this mechanism. Knowledge on these issues and findings are important, and need further research, since imaging modalities studying inflammatory features are considered to be a very promising tool to study for instance the efficacy of possible disease modifying OA drugs. In order to draw solid conclusions towards responses of these drugs, thorough knowledge of the natural course of disease is mandatory.

Although patients reported decreased pain after follow-up, the association of pain on palpation with US features tended to increase. A possible explanation could be a decrease of other causes, such as psychosocial and mechanical causes, of pain that are not directly related to inflammation. This observation emphasized the multifactorial origin of pain.

A drawback of this study is the small patient population, which likely explains the lack of statistical significance for the decrease in VAS pain after 3 months and the lack of association between summated inflammatory features and VAS pain. However, 750 joints are studied in these patients allowing enough power to investigate the inflammatory features at joint level, also after adjusting for within-patient effects and confounders.

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6

Inflammatory ultrasound features show independent associations with progression of structural damage after over two years of follow-up in patients with hand osteoarthritis

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ABSTRACT

Objective

To study the development of inflammatory features and it's relation to structural damage over a 2.3 year period in patients with hand osteoarthritis (HOA).

Methods

Synovial thickening, effusion and power Doppler signal (PDS) in distal interphalangeal (DIP), proximal interphalangeal (PIP), 1st carpometacarpal (CMC), metacarpal phalangeal (MCP) and 1st interphalangeal (IP) joints were assessed using ultrasonography in 56 consecutive HOA patients (mean age 61.2 years, 85.7% female) fulfilling American College of Rheumatology (ACR) classification criteria, at baseline and follow-up. Radiographic progression of osteophytes and joint space narrowing (JSN) was scored using the OARSI atlas.

With generalized estimating equations (GEE) OR with 95% CIs were calculated for the associations between inflammatory ultrasound features and radiographic progression taking in account patient effect, age, gender, Body Mass Index, baseline osteophytes and JSN scores, and other inflammatory ultrasound features.

Results

Of 1680 joints, 8.4%, 8.7%, and 19.8% had synovial thickening, PDS or effusion at baseline, respectively. 7.1% and 5.7% of joints had progression of osteophytes and JSN, respectively. Independent associations were found between synovial thickening, effusion and PDS (grade 2-3 versus 0), and progression of osteophytes (OR (95%CI): 2.6 (1.02 to 6.5), 3.5 (1.7 to 7.4) and 5.7 (1.5 to 21.1)) and of JSN (OR (95%CI): 3.4 (1.3 to 8.4), 3.3 (1.5 to 7.6) and 3.1 (1.01 to 9.2)). Persistent inflammatory features at baseline and follow-up showed stronger associations with radiographic progression than fluctuating inflammatory features in comparison to no inflammatory features.

Conclusions

Inflammatory features, especially when persistently present, are independently associated with radiological progression in HOA after 2.3 years, indicating a role of inflammation in the aetiology of structural damage in HOA.

INTRODUCTION

Hand osteoarthritis (OA) is a highly prevalent musculoskeletal disorder leading to pain, disability and structural damage of the hand joints.[1] Which are the underlying pathogenic processes that play a role in disease development and progression are far from understood. MRI and ultrasound have shown that inflammatory features are frequently found in hand OA and are associated with pain.[2,3] After short-term follow-up of 3 months, the total inflammatory burden in the hand joints as assessed by ultrasound remain stable, although on joint level fluctuation can be seen.[4] However, it is unknown how these inflammatory features behave over long-term follow-up and what the clinical implication of their presence is. In knee OA, inflammatory ultrasound features, such as effusion, have been shown to be involved in progression of structural progression as assessed by replacement of a joint prosthesis.[5] Whether inflammation is involved in structural progression in hand OA, has not been studied before.

The objectives of the present study are to investigate whether inflammatory ultrasound features are associated with structural radiological damage after long-term follow-up of 2 to 3 years and to investigate the course of inflammatory ultrasound features over long-term follow-up.

Patients and methods

Patient population and OA diagnosis

In this prospective longitudinal observational study, consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre, a secondary consultation centre for the Leiden region, The Netherlands, from May/June 2008 until January 2010. Follow-up visits were performed between January 2011 and April 2012. Patients were included after informed consent; the local medical ethics committee of the Leiden University Medical Centre gave approval.

All patients met the American College of Rheumatology classification criteria for hand OA and were at least 45 years of age.[6] Exclusion criteria were: trauma or operation of the hands within 6 months, or an intra-articular injection within 3 months prior to inclusion, oral corticosteroids one month prior to inclusion, positive rheumatoid factor, carpal tunnel syndrome or another inflammatory joint disease (i.e. crystal arthropathy, such as gout or chondrocalcinosis with clinical symptoms, rheumatoid arthritis, psoriatic arthritis).

Clinical assessment

Demographic characteristics were collected by standardised questionnaires at baseline and follow-up. Global hand pain was assessed by a 100 mm visual analogue scale (VAS).

No analgesics were allowed during 72 h preceding the clinical and ultrasound assessment.

Ultrasound procedure

Ultrasound was performed on the same day as the clinical assessment by one experienced ultrasonographer (MCK), scoring together in consensus in the presence of a second ultrasonographer (WYK) at all visits, always using the same machine: a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear array transducer. Both ultrasonographers were blinded to clinical findings. Ultrasound assessment was performed of all distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), 1st interphalangeal joints (IPJs), 1st carpometacarpal joints (CMCJs) and metacarpal phalangeal joints (MCPJs); 30 joints in total.

Power Doppler signal (PDS) was assessed with a pulse repetition frequency (PRF) of 13.2 kHz and a medium wall filter. Gain was adjusted until background signal was removed. Settings were optimised by an application specialist of the manufacturer of the machine.

Hand joints were scanned on the dorsal side in longitudinal and transverse planes. Features had to be present in both planes. Each joint was scored for PDS, synovial thickening and effusion as described before. All ultrasound features were scored using a semi-quantitative scale: 0=none, 1=mild, 2=moderate and 3=severe.[3] For the progression analyses, due to low numbers of joints with ultrasound features grade 2 and 3, these grades were analysed together (grade 2+3).

Intraobserver reliability was tested by performing a second ultrasound in 10% (randomly chosen) of patients on the same day after at least 5 h. In between, at least one other ultrasound assessment was performed.

The intraobserver reliability, taking in account the severity of the score, depicted by the intraclass correlation coefficient (ICC), was 0.62 for PDS, 0.93 for synovial thickening, and 0.84 for effusion.

We defined joints with fluctuating and persistent inflammation as follows: reference joints that showed no inflammatory features at baseline nor at follow-up, joints that showed inflammatory features either at baseline or follow-up (fluctuating inflammation), and joints with inflammatory features at both time points (persistent inflammation).

Radiographs

Dorso-volar radiographs of both hands were obtained at baseline and follow-up. The 30 hand joints (being DIPJs, PIPJs, 1st IPJs, 1st CMCJs, MCPJs) were scored for joint space narrowing (JSN) and osteophytes following the OARSI atlas; per joint a grade of 0 to 3 was given.[7] Baseline and follow-up radiographs were scored paired in known order by MCK. Films were blinded for patients' characteristics and clinical data.

The intrareader reliability based on randomly selected radiographs from 10 (18%) patients depicted by the ICC was 0.86 for osteophytes and 0.76 for JSN.

Progression of osteophytes and JSN for each joint was defined as an increase of at least 1 grade of the OARSI score at follow-up.

Statistical analysis

Data were summarised using the mean (SD) for normally distributed, continuous variables, and the median (range) for non-normally distributed or ordinal variables. Differences between ultrasound inflammatory and structural features at baseline and follow-up were analysed using the Wilcoxon signed rank test.

The association between inflammatory ultrasound features and radiographic progression in separate hand joints was studied using generalised estimating equations (GEE), where radiographic progression was the outcome and inflammatory ultrasound features were the determinant. Since a joint with an osteophyte or JSN score of grade 3 cannot further progress, these joints were not included in the analyses for the radiographic feature under study.

Relative risks were presented as OR with 95% CIs. In the present analyses, ORs approximate relative risks since the presence of the outcome (progressive structural damage) was rare (around 6%). Adjustments were made for patient effects, age, gender, Body Mass Index, baseline JSN and osteophytes scores, and the other inflammatory ultrasound features.

Data were analysed using SPSS for Windows, V.20.0 (IBM SPSS statistics, New York, USA).

RESULTS

Study population

Sixty-three patients were included in the study and 56 completed the follow-up (89%). Baseline patient characteristics are depicted in table 6.1. Seven patients discontinued the study: five patients lost interest in the study, one moved away without leaving an address, and one patient was excluded because she was diagnosed with polymyalgia rheumatica for which she was treated with prednisolone. The mean (SD) follow-up duration was 28 (2.7) months.

At follow-up, eight joints of the left hand of one patient were impossible to score on the radiograph due to a positioning problem. Also, four 1st CMCJs were excluded at follow-up due to the fact that prostheses were placed in these joints.

All 56 patients had hand joints with osteophytes. Only one patient had no joints with JSN. All other patients had JSN in at least four joints.

There were no statistically significant differences between baseline characteristics of the studied patient group and the total patient group.

Table 6.1 Baseline characteristics of 56 patients with hand osteoarthritis.

Baseline characteristics	Number=56 patients
Women; number (%)	48 (85.7)
Age; mean, years (SD)	61.2 (8.9)
BMI; mean, kg/m^2 (SD)	27.6 (4.6)
VAS; median, mm (range)	49 (0-99)
Median number of involved joints per patient (range)	
- Nodes	10 (1-22)
- Soft tissue swelling	2 (0-15)
- Osteophytes	14 (3-29)
- JSN	16 (0-27)

BMI, body mass index; VAS, visual analogue scale; JSN, joint space narrowing

Prevalence of inflammatory ultrasound and radiological features at baseline and follow-up.

At baseline and follow-up, the majority of the patients had hand joints with inflammatory ultrasound features. At baseline, 49 patients had joints with PDS, 41 with synovial thickening and 51 with effusion. At follow-up, 49 patients had joints with PDS, and all had synovial thickening and effusion.

The number of joints that showed inflammatory ultrasound signs increased between baseline and follow-up, especially for synovial thickening and effusion. At baseline PDS, synovial thickening and effusion were found in 146 (8.7%), 141 (8.4%) and 332 (19.8%) of 1680 joints, respectively. At follow-up 177 (10.5%), 736 (43.8%) and 768 (45.7%) of 1676 joints showed PDS, synovial thickening and effusion, respectively. These differences were statistically significant ($p=0.006$, $p<0.001$, $p<0.001$).

Osteophytes and JSN were seen at baseline in 890 (53%) and 762 (45%) joints, and at follow-up in 941 (56%) and 798 (48%) joints, respectively. At baseline, 108 joints had an osteophyte score of grade 3, and 88 joints a JSN score grade 3; these joints were omitted in the progression analysis. Radiological progression was seen in 120 (7.1%) joints in 42 patients for osteophytes and in 96 (5.7%) joints in 22 patients for JSN.

Association between baseline inflammatory ultrasound features and radiological progression

Strong associations were found between inflammatory US features at baseline and progression of osteophytes and JSN, as depicted in table 6.2. PDS was dose-dependently and independently of baseline radiological features and other inflammatory features associated with radiological progression.

Synovial thickening was independently associated with radiological progression, but only the association between synovial thickening and JSN progression showed a clear dose-response relationship. Effusion grade 2+3 was associated with radiological

progression, independently from baseline radiological features and other inflammatory features, whereas grade 1 showed no association.

Association between fluctuating and persistent inflammatory ultrasound features and radiological progression

At baseline and follow-up, PDS, synovial thickening and effusion were present at both time points in 40 (2%), 118 (7%) and 232 (14%) joints respectively. Features were present either at baseline or follow-up in 243 (14%), 641 (38%) and 636 (38%) joints, respectively.

The persistent presence, hence present at baseline and follow-up, of all inflammatory ultrasound features was strongly associated with progression of both osteophytes and JSN (table 6.3), even independently of the presence of other inflammatory features at baseline. Only the fluctuating presence, hence the presence at only one time point, of PDS was associated with radiological progression. Synovial thickening and effusion were not. The fluctuating presence of PDS was also associated with osteophytes progression independent of the presence of synovial thickening and effusion at baseline.

Table 6.2 Association of inflammatory US features at baseline and progression of osteophytes and joint space narrowing in hand joints at risk for progression (max. 30 joints per patient) in 56 hand osteoarthritis patients over 2.3 years of follow-up

Ultrasound feature	Number of joints with/without progression	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
		Osteophyte progression		
PDS				
Grade 2+3	13/13	14.8 (5.7-38.8)	11.6 (4.1-32.6)	5.7 (1.5-21.1)
Grade 1	16/81	2.9 (1.7-5.0)	3.4 (2.0-5.9)	2.4 (1.3-4.7)
Grade 0	91/1348	1	1	1
Synovial thickening				
Grade 2+3	15/30	8.1 (4.3-15.1)	6.1 (2.9-12.7)	2.6 (1.02-6.5)
Grade 1	21/56	6.0 (3.1-11.8)	9.1 (4.3-18.9)	5.5 (2.5-12.2)
Grade 0	84/1356	1	1	1
Effusion				
Grade 2+3	24/47	8.3 (4.7-14.8)	7.0 (3.5-14.3)	3.5 (1.7-7.4)
Grade 1	22/188	1.9 (1.09-3.3)	1.5 (0.8-3.0)	0.9 (0.4-1.9)
Grade 0	74/1207	1	1	1
		Joint space narrowing progression		
PDS				
Grade 2+3	8/16	11.1 (4.1-29.8)	6.3 (2.1-19.0)	3.1 (1.01-9.2)
Grade 1	14/90	3.0 (1.6-5.8)	2.4 (1.3-4.3)	2.0 (1.1-3.7)
Grade 0	74/1378	1	1	1
Synovial thickening				
Grade 2+3	12/27	9.5 (3.9-23.1)	6.9 (2.8-17.3)	3.4 (1.3-8.4)
Grade 1	10/69	3.0 (1.4-6.4)	2.3 (1.03-5.4)	1.2 (0.5-3.2)
Grade 0	74/1388	1	1	1
Effusion				
Grade 2+3	16/52	7.5 (3.6-15.6)	4.3 (2.0-9.6)	3.3 (1.5-7.6)
Grade 1	25/193	2.9 (1.6-5.4)	1.9 (0.98-3.5)	1.4 (0.7-2.9)
Grade 0	55/1239	1	1	1

*Model adjusted for age, gender, Body Mass Index (BMI), baseline joint space narrowing score and baseline osteophyte score.

**Model adjusted for age, gender, BMI, baseline osteophyte and baseline joint space narrowing score, and other baseline inflammatory features.

PDS, power Doppler signal

Table 6.3 The natural course of inflammatory ultrasound features and its association with progression of osteophytes and joint space narrowing in hand joints at risk for progression (max. 30 joints per patient) in 56 hand osteoarthritis patients over 2.3 years of follow-up.

US feature	Number of joints with/without progression	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
		Osteophyte progression		
PDS				
Persistent§	14/19	16.4 (7.9-34.0)	13.6 (6.0-30.7)	4.6 (1.8-12.0)
Fluctuating§	33/177	3.2 (2.0-5.2)	3.0 (1.8-5.1)	2.2 (1.3-3.7)
Absent	73/1246	1	1	1
Synovial thickening				
Persistent	34/68	11.8 (6.5-21.4)	11.3 (5.5-23.0)	4.6 (2.0-10.3)
Fluctuating	45/559	1.6 (1.01-2.4)	1.3 (0.8-2.3)	NP
Absent	41/815	1	1	1
Effusion				
Persistent	40/165	5.7 (3.6-9.1)	4.6 (2.7-7.9)	2.2 (1.1-4.5)
Fluctuating	44/538	1.7 (1.05-2.8)	1.3 (0.8-2.2)	NP
Absent	36/739	1	1	1
		Joint space narrowing progression		
PDS				
Persistent	10/21	11.7 (5.1-27.0)	6.6 (2.5-17.8)	3.1 (1.2-8.0)
Fluctuating	24/198	2.6 (1.6-4.0)	1.7 (1.09-2.8)	1.3 (0.8-2.3)
Absent	62/1265	1	1	1
Synovial thickening				
Persistent	21/77	8.2 (4.0-17.0)	5.6 (2.6-12.1)	2.7 (1.1-6.3)
Fluctuating	44/570	2.2 (1.2-3.9)	1.5 (0.8-2.8)	NP
Absent	31/837	1	1	1
Effusion				
Persistent	36/172	6.9 (3.9-12.1)	3.6 (2.0-6.5)	2.3 (1.1-4.5)
Fluctuating	35/555	2.0 (1.2-3.3)	1.3 (0.8-2.1)	NP
Absent	25/757	1	1	1

*Model adjusted for age, gender, Body Mass Index (BMI), baseline joint space narrowing score and baseline osteophyte score.

**Model adjusted for age, gender, BMI, baseline osteophyte and baseline joint space narrowing score, and other baseline inflammatory ultrasound features.

§ Persistent = present both at baseline and follow-up, fluctuating = present either at baseline or at follow-up

PDS, power Doppler signal; NP, not performed.

DISCUSSION

In the present prospective 2.3-year follow-up study in patients with OA of the hand, it was shown that inflammatory ultrasound features, such as PDS, synovial thickening and effusion, are frequently seen in hand joints. Baseline inflammatory ultrasound features in hand joints are strongly associated with radiological progression in these joints, independently of each other and also independent of baseline radiological features. Repeated measurements of inflammatory ultrasound features revealed that the prevalence of joints with synovial thickening and effusion increased with 35 and 26%, respectively, after 2.3 years, while only a slight increase (2%) of joints with PDS was seen. The minority of joints showed persistent inflammatory ultrasound features at baseline and follow-up -2, 7 and 14% respectively for PDS, synovial thickening and effusion- while 14, 38 and 38% of joints showed fluctuating features. Especially persistent inflammatory ultrasound features were associated with radiological progression after 2.3 years. Joints with persistent and fluctuating PDS had an increased risk to progress radiologically over 2.3 years.

This is the first prospective longitudinal study that investigated whether inflammatory ultrasound features associate with structural damage in OA of the hand over time. Earlier, cross-sectional studies have been done showing associations between inflammatory features as assessed by ultrasound or MRI and structural damage[8,2] which support the observations of this study. Risk factors for structural damage have been more widely investigated in patients with OA of the knee. Although, only a few longitudinal studies in OA of the knee have been performed that studied the relationship of inflammatory features and structural damage, using MRI and ultrasound. Three studies with a follow-up duration of 30 months showed that baseline synovitis/ effusion were associated with incident and progressive cartilage loss.[9,10,11] Two longitudinal studies found only an association of effusion with structural damage, but not with synovial thickening.[5,12] One of these studies used ultrasonography to assess inflammation. Visualisation of the whole knee joint could be more difficult using ultrasonography due to the presence of the patella in front of the tibio-femoral joint. Therefore, synovial thickening might be more difficult to capture. The second study used MRI to assess inflammation, but the follow-up period was only 6 months and, therefore, structural progression was only limited. This might explain why no association with synovial thickening in these studies was found. Another possibility is that aetiology of cartilage loss in OA of the knee is different from that in OA of the hand. In OA of the knee, local mechanical forces are thought to be of great importance in the development and progression of OA.[13,14,15] In OA of the hand, systemic factors seem to be involved.[16,17] This might implicate that different underlying pathogenic processes are present and, therefore, that different risk factors for progression are of importance at different OA joint sites.

In the present study, the presence of PDS appears to be a strong predictor of radiological progression. Synovial thickening, and to a lesser extent effusion, are also of importance, but these features are especially associated with radiological progression when they persist over time. In our earlier study, where patients with OA of the hand were followed for 3 months, we already showed that in some joints inflammatory ultrasound features are variable and persistent in others.[4] Further studies are warranted in order to confirm these findings, as well as further elucidating the aetiology and implication of fluctuating and persistent inflammatory features.

After 2.3 years, a large increase of inflammatory features was seen for effusion and synovial thickening. It is possible that this is the natural course of the disease. Since OA of the hand has not been studied longitudinal with ultrasound or MRI up till now, the natural course on the long term of inflammatory features is not known. The study population consisted of patients with severe OA of the hand, as supported by the presence of 18 patients with erosive OA of the hand at baseline, and with a fairly high VAS hand pain. More longitudinal studies in different patient populations are warranted to understand the natural course of these inflammatory features. We do not expect that the increase in inflammatory ultrasound features is an artifact. The ultrasonographers were the same during the whole study period, as was the ultrasound machine, the machine settings and the scoring method.

In an earlier study, performed by the same ultrasonographers and using the same ultrasound machine, we followed patients for 3 months. In this study we did not see an increase in the total amount of inflammatory ultrasound features,[4] which support the truth of our observations.

In conclusion, the present study shows that inflammatory features are strongly and independently associated with radiological progression after 2.3 years in patients with OA of the hand. These findings are of importance to understand the underlying pathogenic processes in radiological progression in OA of the hand. Further research is warranted to confirm these findings.

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7

In erosive hand osteoarthritis more inflammatory signs on ultrasound are found than in the rest of hand osteoarthritis

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ABSTRACT

Objective

To compare inflammation as assessed by ultrasound between patients with the subset erosive osteoarthritis (EOA) versus non-EOA.

Methods

Consecutive hand osteoarthritis (HOA) patients (fulfilling ACR criteria) were included. Eighteen interphalangeal joints were scored on radiographs using the Verbruggen-Veys anatomical phase score; E and R-phases were defined as erosive. Patients were assigned to EOA when at least one joint was erosive. Effusion, synovial thickening, and power Doppler signal (PDS) were scored with ultrasound on a 4-point scale. Generalized estimating equation analyses were used to compare ultrasound features between EOA and HOA, and to associate ultrasound features with anatomical phases; OR with 95% confidence intervals were calculated with adjustments for patient effects and confounders.

Results

Of 55 HOA patients (mean age 61 years, 86% women) 51% had EOA. In 94 erosive joints synovial thickening, effusion and PDS were found in 13%, 50% and 15%, respectively; in 896 non-erosive joints in 10%, 26% and 8%, respectively. Summated scores of PDS and effusion were higher in EOA than in non-EOA. Effusion and synovial thickening were more frequent in S, J, E and R-phases compared to N-phases. PDS was only associated with E-phase (OR 5.3, 95% CI 1.3 to 20.5) not with other phases. Non-erosive joints in EOA demonstrated more PDS (OR 3.2, 95% CI 1.6 to 6.4) and effusion (OR 2.2, 95% CI 1.2 to 3.8) in comparison to joints in non-EOA.

Conclusions

Inflammatory signs are more frequent in EOA than in non-EOA, not only in erosive joints but also in non-erosive joints, suggesting an underlying systemic cause for erosive evolution.

INTRODUCTION

Erosive hand osteoarthritis (EOA) is considered a subset of hand osteoarthritis (HOA) associated with a higher clinical burden than non-erosive disease.[1,2] Whether EOA is a separate disease entity or a severe stage of HOA has been unclear until now. The diagnosis of EOA is based on subchondral erosions on radiographs in interphalangeal joints (IPJ). Unfortunately, the processes that lead to erosive evolution are still unknown. In an earlier study we showed that erosive evolution in EOA is clustered in certain patients and in certain families, suggesting that underlying systemic processes are involved.[3]

The clinical course of EOA is characterised by episodes of inflammatory symptoms and signs, as assessed during physical examination.[4] Due to these frequent inflammatory signs EOA is sometimes referred to as inflammatory HOA.[5] Recent studies using ultrasound demonstrated that inflammatory signs, such as power Doppler signal (PDS), greyscale (GS) synovitis, synovial thickening and effusion, are frequently seen in both HOA and EOA.[6-10] Two studies, examining the frequency of inflammatory ultrasound signs in patients with EOA compared to HOA, showed a trend toward more inflammatory signs in EOA, but were not conclusive.[9,10]

Based on the observations that underlying systemic processes may be involved in EOA and that during the clinical course inflammatory signs are often seen in EOA, we hypothesised that inflammatory signs are implicated in erosive evolution. We therefore investigated the presence of inflammatory signs assessed by ultrasound in erosive and non-erosive IPJ in patients with EOA in comparison to IPJ from patients with non-EOA.

Patients and methods

Patient population and osteoarthritis diagnosis

Consecutive patients with HOA consulting the rheumatology outpatient clinic of the Leiden University Medical Centre in Leiden, The Netherlands, were recruited from May 2008 until February 2010. For HOA this centre serves as a secondary consultation centre for the region.

Approval for this study was obtained from the local medical ethics committee.

Patients could participate when they met the American College of Rheumatology (ACR) criteria for HOA and were at least 45 years of age.[11] Exclusion criteria were trauma or operation on the hands 6 months before inclusion, positive rheumatoid factor, intra-articular injection within 3 months, or oral corticosteroids within 1 month before inclusion. Other inflammatory joint diseases or disorders such as carpal tunnel syndrome were not allowed. All patients gave informed consent.

Radiographic assessment and definition of EOA

Dorsal-volar radiographs of both hands were obtained within at most 16 weeks from the ultrasound assessment. All IPJ were scored by one experienced reader (MCK) following the anatomical phase score developed by Verbruggen and Veys.[12] This score consists of five phases representing the evolution of HOA: N, normal joint; S, stationary osteoarthritis with osteophytes and joint space narrowing; J, complete loss of joint space in the whole or part of the joint; E, subchondral erosion and R, remodelling of the subchondral plate. EOA was defined by the presence of at least one joint in the E or R phase. Films were blinded for patient characteristics and ultrasound outcomes. The intrareader variability for the assessment of radiographic severity depicted by the intraclass coefficient was 0.80 for the anatomical phases. The intrareader variability was based on the re-examination of 10 (20%) randomly selected radiographs.

Ultrasound procedure

US was performed on the same day as the clinical assessment by one ultrasonographer (MCK) and scored together with a second ultrasonographer (WYK) in consensus using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear array transducer. PDS was assessed with a pulse repetition frequency of 13.2 KHz and a medium wall filter. Gain was adjusted until background signal was removed.

All 18 IPJ were scanned from the dorsal and lateral side only in longitudinal and transverse planes, in accordance with a workshop held by a group of experts in order to develop a scoring system for ultrasound for HOA.[13] Features had to be present in both planes.

Each joint was scored for PDS, effusion and synovial thickening and osteophytes. Synovial thickening and effusion were scored in accordance with the scoring system for inflammatory signs in rheumatoid arthritis described by Szkudlarek et al.[14] The definition of synovial thickening and effusion followed the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions.[15]

All ultrasound features were scored on a four-point scale (0, none; 1, mild; 2, moderate; 3, severe). Summated scores could range from 0 to 54.

Intra-observer variability was tested by performing a second ultrasound in 10% (five) of all patients on the same day after at least 5 h. Between the first and the second ultrasound at least one other ultrasound assessment was performed. These patients were randomly selected throughout the study.

The ultrasonographers were blinded to clinical findings and hand radiographs.

The intra-observer variability, taking in account the severity of the score, depicted by the intra-class coefficient (ICC) was 0.71 for osteophytes 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Clinical assessment

Demographic characteristics were collected by standardised questionnaires. All patients filled in a 100-mm visual analogue scale (VAS) to assess hand pain over the last 48 h. In addition, hand pain and function were assessed over the last 48 h by the subscales of the Australian Canadian osteoarthritis hand index (AUSCAN).[16] AUSCAN responses are rated on a five-point Likert scale (0, none to 4, extreme). Scores ranged from 0 to 20 for pain and 0 to 36 for function.

During physical examination 1st IPJ, proximal IPJ and distal IPJ from both hands were examined for pain upon lateral pressure (0, none; 1, tender; 2, wincing; 3, withdrawal) using the Doyle Index for the hands and for soft tissue swelling (present/absent).[17]

No analgesics were allowed 72 h before the clinical and ultrasound assessments.

Statistical analysis

Data were summarised using the mean SD for normally distributed, continuous variables, and the median (range) for non-normally distributed or ordinal variables. Differences in demographics, self-reported pain or function, and summated ultrasound features between patients with and without erosive joints were calculated using Mann-Whitney U test. The distribution in the grades of inflammatory ultrasound signs in erosive joints was compared with the frequencies in non-erosive joints using the X^2 test.

Generalised estimating equation analyses were performed to study the association between ultrasound inflammatory signs as independent variables and the presence or absence of erosive disease as a dependent variable in individual joints. Relative risks were presented as OR with CI (95% CI). In multivariate analyses adjustments were made for confounders (age, gender and body mass index).

Generalised estimating equation analysis was also performed to study the association between the N, S, J, E and R phases according to the Verbruggen-Veys score (dependent variable) and ultrasound inflammatory features (independent variable).

Data were analysed using SPSS for Windows, V.17.0.

RESULTS

Study population

Sixty-four patients were recruited consecutively. One patient received an intra-articular injection in a finger joint between screening and the ultrasound, and in eight patients the time between ultrasound and radiographs was more than 16 weeks. So, finally 55 patients were studied (table 7.1). Their mean age was 61 years, 86% were women. Median symptom duration was 5 years. Median VAS and AUSCAN pain were 51 and 9.1, respectively. Patients that were excluded did not differ significantly from patients who were included (data not shown).

In 28 patients (51%) at least one IPJ was erosive. In 18 patients (33%) more than one IPJ was erosive. Of the 94 erosive joints, 12 joints were in E phase and 82 joints were in R phase.

Patients with EOA, as defined by at least one erosive IPJ, were significantly older ($p<0.004$) and experienced more pain in comparison to patients with non-EOA ($p<0.04$ for AUSCAN pain and $p<0.01$ for VAS pain)(table 7.1).

Table 7.1 Demography of 55 patients with osteoarthritis of the hands and separately for patients with EOA and non-EOA

	All patients	**EOA[a] patients (n=28)**	**Non-EOA patients (n=27)**
Age, yrs; mean (SD)	61.4 (9.3)	65 (8.5)	58 (8.9)
Female, %	47 (85.5)	89.3	81.5
BMI, kg/m^2; median (range)	27.3 (19.7-39.5)	27.6 (21.5-39.5)	26.9 (19.7-38.7)
AUSCAN pain, median (range)	9.5 (0-19)	12 (1-19)	8 (0-15)
AUSCAN function, median (range)	17 (0-33)	19 (5-33)	12 (0-30)
VAS pain, mm; median (range)	51.0 (0-99)	54 (22-99)	47 (0-79)
Tender joints[b]			
Summated score, median (range)	8.0 (0-31)	12 (0-31)	5 (0-18)
No. of joints, median (range)	6.0 (0-13)	8 (0-18)	4 (0-12)
Soft tissue swelling, no.; median (range)	1 (0-9)	2 (0-9)	0 (0-5)

[a]EOA defined as at least one interphalangeal joint with erosion

[b]Tender joints at physical examination as assessed by the Doyle index for hands

EOA, erosive hand osteoarthritis; BMI, body mass index; AUSCAN, Australian Canadian osteoarthritis hand index ; VAS = visual analogue scale

Also IPJ were significantly more painful on palpation ($p<0.02$ for summated score and for number of tender joints) and more often showed soft tissue swelling ($p<0.02$) in patients with EOA when compared to patients with non-EOA.

When EOA was defined as the presence of more than one erosive IPJ the results remained statistically significant (data not shown).

Inflammatory signs as assessed by ultrasound in EOA and non-EOA

The 94 erosive joints in particular showed inflammation. Ultrasound inflammatory signs in erosive and non-erosive joints are depicted in table 7.2.

Table 7.2 Ultrasound inflammatory signs in erosive and non-erosive joints of 28 patients with EOA and 27 patients with non-EOA

	Erosive joints (n=94)	Non-erosive joints (n=896)	p Value (X^2 test)
PDS			
No. of affected joints (%)	14 (15)	72 (8)	0.02
Distribution of grades, no. (%)			
0	80 (85)	824 (92)	
1	10 (11)	56 (6)	
2	4 (4)	13 (2)	
3	0 (0)	3 (0.3)	0.07*
Synovial thickening			
No. of affected joints (%)	12 (13)	92 (10)	0.45
Distribution of grades, no. (%)			
0	82 (87)	804 (90)	
1	3 (3)	55 (6)	
2	7 (7)	30 (3)	
3	2 (2)	7 (1)	0.08*
Effusion			
No. of affected joints (%)	47 (50)	230 (26)	<0.001
Distribution of grades, no. (%)			
0	47 (50)	666 (74)	
1	32 (34)	174 (19)	
2	13 (14)	42 (5)	
3	2 (2)	14 (2)	<0.001*

*p Value for comparison of the distributions.
EOA, erosive hand osteoarthritis; PDS, power Doppler signal.

In patients with EOA, as defined by at least one erosive IPJ, the summated score as well as the number of affected joints per patient of PDS and effusion were significantly higher than in patients with non-EOA (table 7.3). Only summated scores for synovial thickening were significantly higher in patients with EOA, the number of joints with synovial thickening was not.

The summated scores for osteophytes were higher in EOA patients. The number of joints with osteophytes in patients with EOA did not differ from patients with non-EOA.

When EOA was defined as the presence of at least two erosive joints the results were similar for PDS, effusion and osteophytes; there was no difference in synovial thickening between patients with erosive versus non-erosive disease (data not shown).

Table 7.3 Signs of inflammation and osteophytes as assessed by ultrasound in IPJ of patients with EOA[a] and non-EOA.

	EOA patients (n=28)[b]	Non-EOA patients (n=27)[b]	p-Value
PDS			
Summated score	3.0 (0-9)	1.0 (0-3)	<0.001
No. of joints affected	2.0 (0-5)	1.0 (0-3)	<0.001
Syn thickening			
Summated score	2.5 (0-19)	0 (0-14)	0.05
No. of joints affected	1.5 (0-10)	0 (0-8)	0.09
Effusion			
Summated score	9.0 (0-16)	4.0 (0-17)	0.02
No. of joints affected	7.0 (0-12)	3.0 (0-10)	0.007
Osteophytes			
Summated score	41.5 (20-49)	37.0 (9-47)	0.009
No. of joints affected	18.0 (9-18)	17.0 (9-18)	0.45

[a]EOA, defined as at least one IPJ with erosion
[b]Depicted are median (range), comparison analysis by Mann-Whitney U test.
EOA, erosive hand osteoarthritis; IPJ, interphalangeal joints; PDS, power Doppler signal

Association of inflammatory signs and the anatomical phases of the Verbruggen-Veys score

Synovial thickening was significantly more frequent in S, J, E and R phases when compared to the N phase (table 7.4). Synovial thickening showed the highest association with J phase. Effusion was demonstrated significantly more often in the S, J and R phases, but not in the E phase. Effusion showed the highest association with R phase. PDS was more frequent in the J phase and significantly more often found in E phase; the highest association was seen with the E phase.

Table 7.4 Association analysed by generalized estimating equations of Verbruggen-Veijs anatomical phases and ultrasound inflammatory signs in IPJ of 55 patients with HOA.

	Synovial thickening[a]	Effusion	PDS
N	1	1	1
S	4.7 (2.5 to 8.8)	3.7 (2.3 to 5.8)	1.4 (0.7 to 2.8)
J	10.6 (4.2 to 26.8)	5.9 (2.7 to 12.7)	3.1 (1.0 to 9.6)
E	7.1 (1.5 to 34.1)	2.8 (0.8 to 9.7)	5.3 (1.3 to 20.5)
R	4.6 (1.8 to 11.9)	8.8 (4.4 to 17.6)	2.1 (0.8 to 6.1)

[a]Depicted are OR (95% CI), adjusted for age, gender and body mass index.
HOA, hand osteoarthritis; IPJ, interphalangeal joints; PDS, power Doppler signal

Inflammatory signs as assessed by ultrasound in non-erosive joints: comparison of patients with EOA to patients with non-EOA

After the exclusion of joints with erosions, the IPJ without erosions of patients with EOA demonstrated more PDS (OR 3.2, 95% CI 1.6 to 6.4) and effusion (OR 2.2, 95% CI 1.2 to 3.8) compared to the IPJ of patients with non-EOA (table 7.5).

Therefore, we concluded that effusion and PDS are independently more frequent in IPJ of patients with EOA, although these joints themselves were not erosive.

No increased frequency was seen for synovial thickening or osteophytes in non-erosive joints of patients with EOA.

Table 7.5 Comparison between ultrasound features in non-erosive IPJ in 28 patients with EOA versus 27 patients with non-EOA analysed by generalised estimating equations.

Ultrasound features	Adjusted OR (95% CI)[a]
PDS	3.2 (1.6 to 6.4)
Synovial thickening	1.3 (1.0 to 5.5)
Effusion	2.2 (1.2 to 3.8)
Osteophytes	0.7 (0.3 to 1.8)

[a]Adjusted for age, gender and body mass index.
EOA, erosive hand osteoarthritis; IPJ, interphalangeal joints; PDS = power Doppler signal.

DISCUSSION

The present study showed that IPJ of patients with EOA demonstrate more PDS and effusion, but not more synovial thickening, in comparison to IPJ from patients with non-EOA. Further detailed investigation revealed that especially erosive IPJ show inflammatory signs. Remarkably, also IPJ without erosions in patients with EOA demonstrated more inflammatory ultrasound signs in comparison to IPJ of patients with non-EOA. The anatomical phases S, J, E and R showed more signs of inflammation compared to IPJ in N phase, but PDS was only significantly associated to the E phase.

This study demonstrates for the first time that non-erosive IPJ of patients with EOA have more inflammation, as reflected by PDS and effusion, than IPJ in patients with non-EOA. These findings confirm our hypothesis that inflammatory signs might be implicated in erosive evolution. The present study suggests that EOA is a phenotype affecting all IPJ in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions.[3] Whether it means that non-erosive joints with inflammatory signs in EOA patients are at an increased risk to develop erosions in the future can not be answered in the present cross-sectional study. To answer that question longitudinal studies are necessary.

The present study showed that signs of inflammation were frequent in HOA, but significantly more frequent in EOA. Further investigation revealed that especially the E phases were associated with active synovitis as reflected by positive PDS. Inflammation was also more frequently seen in EOA at physical examination, since soft tissue swelling was present during physical examination in EOA. These results underscore the earlier observations of EOA as inflammatory HOA.[4,5] In contrast, synovial thickening, which is frequently found in HOA,[6-10] does not distinguish between the different HOA subsets. The non-discriminating nature of synovial thickening was also described in an ultrasound study evaluating the effect of methylprednisolone in hand OA; in the latter study no effect of methylprednisolone on synovial thickening was seen.[18] So whether synovial thickening reflects any inflammation in HOA is not clear and should be studied further. The latter can be done by performing MRI studies with contrast enhancement.

The prevalence of EOA was estimated to be 2.8% in the general population, rising to 15.5% in those with symptomatic HOA.[19] In the present study in consecutive patients with HOA, a high prevalence (51%) of EOA was found, which is in accordance with prevalences of EOA in other rheumatology clinics.[20] An explanation for this high prevalence could be the source of patients, being a rheumatology outpatient clinic. Often patients were referred by their general practitioner because of suspicion of an inflammatory rheumatic disease. This might have caused a selection of patients with more severe HOA. To make sure that the included patients had HOA and not an inflammatory rheumatic disease, patients were carefully examined for rheumatic diseases and psoriasis. Patients with presence of rheumatoid factor or anticyclic citrullinated peptide antibodies could not participate from the study. Another explanation for the high prevalence of EOA in the present study population could be the use of the ACR criteria for HOA requesting signs of OA in multiple hand joints.

The diagnosis of EOA is based on subchondral erosions on radiographs in IPJ [21] The number of erosive IPJ necessary to diagnose EOA is not clear. Often it is stated that more than one erosive interphalangeal joint is needed,[21] but we showed earlier that already one erosive IPJ increases the clinical burden of HOA.[19] Therefore in the present study we investigated both EOA as defined by at least one or by more than one erosive IPJ. The results were the same for both definitions, confirming that one erosive IPJ is enough to define a patient as having EOA.

The present study has limitations. Erosive features were not studied by ultrasound but only by radiography. In earlier articles it was found that erosions are better detected by radiography, because the ultrasone beam is unable to penetrate the cortex and visualise structures beneath it.[22] Bony abnormalities such as osteophytes can overly erosions, which can therefore be undetected on ultrasound. However, recent studies performed on ultrasound showed good detection of erosions using ultrasound.[10,2]

Also, in the present study the pulse repetition frequency was 13.2 kHz. The machine was tested for optimal settings by a technical engineer from the manufacturer of the machine before the study was started and this was the lowest available PRF at that time. We do not know what the optimal values for PRF are. Lower values give higher sensitivity, but on the other hand, it is not known whether such low PRF values still give clinically relevant information.

In the present study, an age difference between patients with and without EOA was present. For this reason all analyses were adjusted for age.

In conclusion, this study shows that EOA demonstrates more inflammatory signs compared to non-EOA, even in IPJ that are not erosive. This is already true when EOA is defined as the presence of one erosive IPJ. Whether inflammation in EOA are a cause of erosive evolution or a result of extensive destruction in particular joints is not known; the finding that inflammatory signs are also demonstrated more often in non-erosive joints in EOA suggests that inflammation is a cause. Further longitudinal studies are needed to elucidate the role of inflammation in the development of erosiveness. In case inflammation is a cause of erosive evolution inflammation could be a therapeutic target.

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Inflammation is associated with erosive development in patients with hand osteoarthritis: a prospective ultrasonography study

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ABSTRACT

Objective

To study associations between inflammatory ultrasound (US) features and erosive development over 2.3 years follow-up in hand osteoarthritis (OA).

Methods

In 56 consecutive hand OA patients (mean age 61 years, 86% female), fulfilling ACR criteria, effusion, synovial thickening and Power Doppler signal (PDS) were assessed in all interphalangeal joints (IPJs) with US using standardized methods at baseline and follow-up. Radiographs were scored at both time-points for osteophytes/JSN (OARSI method) and for erosive disease, defined as E- and R-phase (Verbruggen-Veys method). Erosive development was defined as a non-erosive joint becoming erosive. E- and R-phases at baseline were excluded. Associations were analysed using GEE logistic regression, adjusting for age, gender, BMI and baseline structural abnormalities.

Results

At baseline 51 IPJs (18 patients) and at follow-up 89 IPJs (26 patients) were erosive, hence 38 IPJs showed erosive development. Moderate/severe synovial thickening and PDS at baseline were associated with erosive development: adjusted odds ratio (95% confidence interval) 8.8 (2.4-32.3) and 7.1 (1.9-26.9), respectively. Especially persistent inflammation was associated with the development of erosions.

Conclusions

Inflammatory US features are associated with the development of erosions in hand OA, implicating that inflammation plays a role in its pathogenesis and could be a therapeutic target.

INTRODUCTION

Erosive hand osteoarthritis (OA) is a subset of hand OA, defined radiographically by subchondral central erosions, cortical destruction and subsequent reparative change, which may include bony ankylosis.[1] Currently, its pathogenesis is not understood and it is unclear whether it is a separate disease entity or reflects a severe disease stage. What we do know is that erosive OA has a high clinical burden and can progress relatively fast[2]. Few studies looked into underlying mechanisms or risk factors that associate with development of erosions. A sib-pair study in hand OA patients reported that erosive development clusters in patients and families.[3] Especially, painful joints, that have soft tissue swelling or joint space narrowing (JSN) on radiographs, seem to be at risk.[3,4] These findings suggest that underlying systemic processes, such as inflammation, play a role in erosive development. Inflammation is often seen in erosive OA.[5,6] An earlier study showed that inflammatory features are more frequently present in erosive OA as compared to non-erosive hand OA,[6,7] not only in joints with erosions, but also in joints without.[7]

Therefore, the objective of the present study is to investigate the association of erosive development with inflammatory US features in patients with hand OA.

Patients and methods

Patient population and OA diagnosis

Consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre from May 2008 until January 2010. Follow-up visits took place between January 2011 and April 2012. Patients were included after informed consent; the local medical ethics committee gave approval.

Patients with primary hand OA following the American College of Rheumatology criteria and ≥ 45 years were included.[8] Exclusion criteria were: trauma/operation of the hands, treatment with corticosteroids or the presence of another inflammatory joint disease, as described in more detail elsewhere.[7]

Clinical assessment

Demographic characteristics as assessed by standardized questionnaires, and 100 mm visual analogue scale were obtained at baseline and follow-up. Patients were not allowed to use any analgesics during 72 hours preceding the assessments.

Ultrasound procedure

US was performed on the same day as the clinical assessment at baseline and follow-up by one experienced ultrasonographer (MCK) in the presence of a second ultrasonographer (WYK) scoring together in consensus, always using the same Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear

array transducer. Settings were optimized. Both ultrasonographers were blinded to clinical findings.

All 1st interphalangeal joints (1st IPJs), distal IPJs (DIPJs), proximal IPJs (PIPJs), (total 18 joints) were scored for power Doppler signal (PDS), synovial thickening and effusion with US as described[9], using a semi-quantitative scale: 0=none, 1=mild, 2=moderate and 3=severe[9]. Due to the limited amount of joints with grade 2 /3, these were combined in generalized estimating equations (GEE) analyses.

To study associations between the course of inflammatory US features and development of erosions, inflammatory US features were defined as "persistent" (present both at baseline and follow-up), "fluctuating" (present only at baseline or follow-up), or "absent" (absent at both time-points).

Intra-observer reliability was good, as reported elsewhere[7].

Radiographs

Radiographs were obtained at baseline and follow-up and scored paired in known order by MCK. IPJs of both hands were scored for JSN (grade 0-3) and osteophytes (grade 0-3) using the OARSI atlas.[10] Films were blinded for patient characteristics and clinical data.

Erosions were scored in the IPJs using the Verbruggen-Veys method[11], which comprises of five anatomical phases: normal (N), stationary (S), joint space loss (J), erosive (E) and remodeled (R) phase. The sequence of evolution from N to S to J to E to R phases is presumed to reflect the natural history of erosive OA. A joint in E- or R-phase has been defined as erosive. Erosive OA has been defined as having at least one erosive joint. Erosive development has been defined as transition of N-, S- or J-phase into E- or R-phase. Since joints in E- and R-phase at baseline were not at risk to develop into an erosive joint anymore during follow-up, these joints were removed from the analyses.

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Intra-reader reliability based on 18% randomly selected radiographs depicted by the ICC was 0.86 for osteophytes and 0.76 for JSN, and 0.80 for the anatomical phases.

Statistical analysis

Differences between the original population, and the study population were calculated using Mann-Whitney U test.

Reliability was determined by estimating intra-class correlation coefficients (ICC) using generalizability theory, a random factor model ANOVA approach that estimates the components of variance within each model. Using this method is more suitable compared to traditional ICC analyses or kappa analyses due to the separate outcomes on joint level, with unique joints clustered within a patient. Interpretation of the correlations is: 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 excellent.

Associations between inflammatory US features and erosive development were estimated using logistic regression. To correct for within patient correlations between joints, GEE approach was followed with an exchangeable working correlation model. Associations were presented as odds ratios (OR) with 95% confidence intervals (CI). OR can be interpreted as relative risks since the outcome (erosive development) was rare (4%). Adjustments were made for age, gender, body mass index and structural abnormalities at baseline.

Structural abnormalities were assessed in this study by individual features (osteophytes and JSN) as well as anatomical phases. We aimed to adjust for all possible structural features at baseline, and therefore wanted to include all assessments, but we expected overlap between the scoring of the individual features and the anatomical phases. Therefore, the frequency of anatomical phases and osteophytes/JSN was evaluated using cross tables. Osteophyte scores did not overlap with the anatomical phases and therefore adjustments were performed for both variables separately. JSN and the anatomical phases did overlap, except for the S-phase. (supplementary table S8.1). Therefore, no adjustments were made for JSN, but in order to include the variance of JSN in the S-phase, structural abnormalities at baseline were defined by a variable consisting of 6 categories, being the anatomical phases N, J, E and R, and in addition the categories “S-phase-JSN grade 0/1” and “S-phase-JSN grade 2/3”. No joints at baseline in N-phase showed erosive development. Therefore, N- and S-phase-JSN0/1 were combined in the analyses. Data were analysed using SPSS 20 for Windows/Apple, version 20.0 (IBM SPSS).

RESULTS

Study population:

Sixty-three patients were included, 56 completed follow-up (89%). Five patients lost interest in the study, one moved away without leaving an address and one patient developed polymyalgia rheumatica and was excluded. At follow-up radiographic scoring of 8 joints of a patient’s left hand was impossible due to a positioning problem, and were therefore excluded.

The follow-up duration was 2.3 years (mean (SD): 28 (2.7) months).

There were no statistical differences between baseline characteristics of the studied patient group and the original patient group.

Table 8.1 Baseline characteristics of 56 hand osteoarthritis patients.

Baseline characteristics	**N=56**
Age, yrs; mean (SD)	61.2 (8.9)
Female; %	48 (85.7)
BMI, kg/m^2; median (range)	27.6 (4.6)
VAS, mm; median (range)	49 (0-99)
Imaging features, no. of joints per patient (0-18); median (range)	
Ultrasonography:	
- Synovial thickening	1 (0-10)
- Effusion	5 (0-12)
- PDS	1 (0-5)
Radiography	13 (3-18)
- Osteophytes	12 (0-18)
- JSN	

yrs=years, SD=standard deviation, BMI=body mass index, VAS= visual analogue scale, mm=millimeter, no.=number, PDS = power Doppler signal, JSN= joint space narrowing.

Table 8.2 Evolution of anatomical phases of 1008 joints in 56 hand osteoarthritis patients over 2.3 years follow-up.

Anatomical phases	**Baseline; no. of joints (%)**	**Transition from baseline to follow-up; no. of joints***		**Follow up; no. of joints (%)**
N-phase;	158 (15%)	N-N =147 N-S =8	Missing: 3	148 (15%)
S-phase	773 (77%)	S-N =1 S-S =733 S-J =15 **S-E =17** **S-R =2**	Missing: 5	741 (74%)
J-phase	J =26 (3%)	J-J =7 **J-E =15** **J-R =4**		22 (2%)
E-phase	E =26 (3%)	E-E =15 E-R =11		47 (5%)
R-phase	R =25 (3%)	R-R=25		42 (4%)

*Numbers displayed in bold were joints that developed an erosion at follow-up.

Erosive development

Of 56 hand OA patients, 18 (32%) were erosive at baseline. During follow-up 8 patients developed erosions, hence 26 patients were erosive (47%). 51 (5%) of 1008 joints at baseline, and 89 (9%) of 1000 joints (8 missing joints) at follow-up showed erosive disease; thus 38 (4%) joints developed an erosion.

Table 8.2 shows the evolution of the anatomical phases during follow-up. No joints in N-phase progressed to E- or R-phase. Of 51 erosive joints at baseline, 25 were in the R-phase and 26 joints in the E-phase. The baseline joints in the E-phase were potentially at risk to progress to an R-phase: 11 of 26 joints (42%) progressed.

Association of inflammatory US features and erosive development.

Table 8.3 shows the association of inflammatory US features at baseline and erosive development on joint level. Synovial thickening, effusion and PDS were associated with erosive development, however after adjustment for baseline structural abnormalities only synovial thickening and PDS remained associated.

All inflammatory US features -synovial thickening, effusion and PDS- were strongly associated with erosive development when persistently present both at baseline and follow-up.

Inflammatory features also seem to play a role in baseline joints that progress from E- to R-phase. Since just 26 joints were in E phase at baseline of which 11 progressed to follow up, only descriptive analyses were performed. Of the joints that progressed to R-phase after 2.3 years of follow up, synovitis, effusion and PDS was seen in 3 (27%), 6 (55%) and 1 (9%) joints respectively versus 2 (13%), 3 (20%) and 3 (20%) joints that remained in E-phase. The joint with PDS in the group of joints that progressed to R phase had a PDS score of 3. The joints with PDS in the group of joints that remained in E phase, all had a PDS score of 1.

Table 8.3 Association of inflammatory US features at baseline, and in addition the course of inflammatory US features, and erosive development in 949 interphalangeal joints in 56 hand osteoarthritis patients at approximately 2.3 years of follow-up analysed using generalized estimating equations.

Imaging feature (grades)	Total joints* (No. of joints without / with development of erosion)	Adjusted OR (95% CI)**	Adjusted OR (95% CI)***
Syn. thick.			
2+3	38 (27/11)	14.5 (5.4-39.1)	8.8 (2.4-32.3)
1	60 (56/4)	2.7 (0.8-9.3)	4.1 (0.7-23.7)
0	851 (828/23)	1	1
Effusion			
2+3	69 (57/12)	7.3 (2.9-18.2)	2.5 (0.7-9.1)
1	191 (182/9)	1.6 (0.8-3.6)	0.7 (0.3-1.9)
0	644 (627/17)	1	1
PDS			
2+3	20 (13/7)	13.1 (3.5-48.5)	7.1 (1.9-26.9)
1	61 (57/4)	2.1 (0.6-7.0)	1.4 (0.2-9.9)
0	868 (841/27)	1	1
Imaging feature course**	**Total joints* (No. of joints without / with development of erosion)**	**Adjusted OR (95% CI)****	**Adjusted OR (95% CI)*****
Syn. thick.			
Persistent	88 (73/15)	10.7 (3.6-31.5)	9.6 (3.2-29.2)
Fluctuating	502 (486/16)	1.7 (0.6-4.4)	1.5 (0.5-4.5)
Absent	359 (352/7)	1	1
Effusion			
Persistent	188 (171/17)	4.6 (1.6-13.2)	3.7 (1.1-12.0)
Fluctuating	476 (460/16)	1.8 (0.7-4.4)	2.3 (0.8-6.7)
Absent	279 (274/5)	1	1
PDS			
Persistent	22 (16/6)	13.5 (4.6-40.0)	11.4 (2.7-49.1)
Fluctuating	136 (119/17)	5.7 (2.7-12.1)	4.9 (2.1-11.6)
Absent	791 (776/15)	1	1

Abbreviations: US=ultrasound, OR=odds ratio, CI= confidence interval, syn. thick.=synovial thickening, PDS= power Doppler signal.
*Joints that could not progress at baseline (E- and R-phase, being 51 joints) were excluded.
**Adjusted for age, gender and body mass index.
*** Adjusted for age, gender, body mass index and baseline structural abnormalities (osteophytes and joint space narrowing/anatomical phases).
**** Persistent defined as: feature present at baseline and follow-up, fluctuating: feature present at baseline or follow-up and absent: features absent both at baseline and follow-up.

DISCUSSION

In this longitudinal US study in patients with hand OA the association of inflammatory US features and erosive development was investigated. It shows that non-erosive hand joints have an increased risk to develop erosions when moderate to severe synovial thickening or PDS is present at baseline in the same joints, independent of cartilage and bone abnormalities at baseline. No statistical significantly association was seen between moderate to severe effusion at baseline and erosive development. All inflammatory US features were associated with erosive development when the inflammatory feature was present both at baseline and follow-up. These observations implicate a role for inflammation in the pathogenesis of erosive OA and it might render new therapeutic options that can halt erosive development.

Few studies investigated risk factors associated with erosive development. In an earlier randomized control trial of 12 months in 60 erosive OA patients,[4] an association of soft tissue swelling and erosive development on joint level was found, suggesting that inflammation might be of importance. However, no adjustments for confounders were made. In an observational study in 236 hand OA patients erosive development after 6 years was associated with self-reported pain at baseline, but also with JSN at baseline.[3] The latter observation stresses the need for adjustment for structural abnormalities at baseline. Inflammation was not assessed, but possibly self-reported pain could reflect signs of inflammation.

Recently, Haugen and colleagues examined associations of baseline MRI features and erosive development after 5 years.[12] Of 209 recruited patients with hand OA eventually 74 were included in the study. Of these only joints of female participants were included in the analyses concerning erosive development. Associations adjusted for age, BMI and duration of follow-up, were found between erosive development and moderate/severe synovitis. No adjustments were made for structural abnormalities at baseline in this study. The authors comment that synovitis could be an intermediate variable in between structural damage and the development of erosions. This could be the case. However, some pathways have been described that could induce synovitis of the joints independent of structural damage, such as aging, presence of crystals and adipokines, whereas via other pathways inflammation could induce structural damage by itself.[13] In order to investigate whether synovitis could be an independent risk factor, we performed additional adjustments for structural damage at baseline as well. When synovitis would have been only an intermediate variable, it is expected that the association would disappear after adjustment. In the present analyses, the strength of the association weakened but remained statistically significant, suggesting that synovitis is independently associated with erosive development.

The present study confirms the hypothesis that inflammation plays a role in the pathogenesis of erosive OA, suggesting a systemic process. Earlier studies in erosive OA patients observed higher CRP levels than in non-erosive hand OA, and synovitis indistinguishable from rheumatoid arthritis in biopsies from erosive IPJs.[2,14]
Studies aiming at suppression of inflammation in erosive OA, however, have shown inconclusive results.[15] Further research is warranted to investigate the efficacy of an anti-inflammatory drug, such as prednisolone, in erosive OA to understand more of the role of inflammation.

In the present study, 4% of IPJs showed erosive development, which is in line with an earlier study reporting 5.7% progression after 3 years,[11] and the study by Haugen et al. reporting 9% progression after 5 years. Bijsterbosch et al. found progression in only 4.4% of IPJs after 6 years.[3,12] This difference could be explained by the more severely affected patients in the present study. No joints with N-phase at baseline showed erosive development, whereas only a limited number of joints in S-phase did (2.5%). Joints in J-phase progressed in 73%; E-phase progressed to R-phase in 40%. This is in line with earlier results[3,11].

The present study has limitations. Patients were selected from a rheumatology outpatient clinic and were severely affected, as reflected by the high percentage of erosive OA at baseline. Further studies are warranted to investigate whether these results are reproducible in other hand OA populations.

Contributor statement

Substantial contributions to the conception or design of the work (MCK, MK), or the acquisition (MCK, WYK, MR), analysis or interpretation of data. MCK, MK, TS

Drafting the work or revising it critically for important intellectual content. MCK, MR, WYK, TS, MK

Final approval of the version published. MCK, MK

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MCK, MK

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Supplement

Table S8.1 Crosstabulation comparing the anatomical phases of the Verbruggen-Veys score with joints space narrowing, and with osteophytes.

Anatomical phases		**Baseline JSN score**				**Total**
		none	**mild**	**moderate**	**severe**	
	N fase	156	1	1	0	158
	S fase	209	409	137	18	773
	J fase	0	0	2	24	26
	E fase	0	0	1	25	26
Total		365	410	141	67	983
		Baseline osteophytes score				**Total**
		none	**mild**	**moderate**	**severe**	
	N fase	157	0	1	0	158
	S fase	162	453	121	37	773
	J fase	2	5	6	13	26
	E fase	0	1	5	20	26
Total		321	459	133	70	983

Abbreviations: JSN=joint space narrowing

9

MRI in hand osteoarthritis: validity for osteoarthritis clinical and structural characteristics

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ABSTRACT

Objective

To investigate criterion validity and intraobserver reliability of MRI in hand osteoarthritis (HOA).

Methods

In sixteen HOA patients (median age 57 years, 62% female, 13 with erosive OA) 3 Tesla MR scans with gadolinum-chelate administration of 2nd–5th DIPJs/PIPJs of the right hand were obtained and scored according to the Oslo HOA scoring method for synovial thickening, bone marrow lesions (BMLs), osteophytes, joint space narrowing (JSN) and erosions (grade 0-3). Ultrasound was scored for synovial thickening and osteophytes, radiographs for osteophytes and JSN (OARSI score) and anatomical phases (Verbruggen-Veys score). Pain was assessed during physical examination. Correlations of MRI with US and radiographic features were assessed with generalizability theory. With Generalized Estimating Equations MRI features were associated with pain, adjusting for within-patient effects, age, sex and BMI.

Results

Forty-three percent, 27%, 77% and 61% of joints had synovial thickening (moderate/severe), BML, osteophytes and erosions, on MRI respectively. Intra-observer reliability, assessed in 6 patients, was good (ICCs 0.77-1.00). Correlations between osteophytes, JSN and erosions on radiographs and MRI were moderate, substantial and fair (ICC 0.53,0.68 and 0.32 respectively), with MRI showing more lesions than radiography. Correlation between synovial thickening and osteophytes on MRI and US was moderate (ICC 0.43 and 0.49 respectively). MRI was more sensitive for synovial thickening, US for osteophytes. Pain was associated with the presence of moderate/severe synovial thickening (adjusted OR 2.4 (95%CI 1.06-5.5)), collateral ligaments (4.2 (2.2-8.3), BMLs (3.5 (1.6-7.7)) , erosions (4.5 (1.7-12.2)) and osteophytes (2.4 (1.1-5.2).

Conclusions

MRI is a reliable and valid method to assess inflammatory and structural features in HOA. It gives additional information over radiographs and US.

INTRODUCTION

Hand osteoarthritis (HOA) is a prevalent musculoskeletal disease that can lead to pain or functional limitations.[1,2] The osteoarthritis (OA) process results in structural involvement of all compartments of the joint, including cartilage, subchondral bone, synovium, capsule and ligaments.[3] In HOA of several subsets can be distinguished, of which nodal and erosive OA preferentially involve the interphalangeal joints (IPJs).[1,4]

Patients with nodal OA in the IPJs present with bony enlargements, deformities and loss of range of motion.[4] These classical structural hallmarks of HOA can be visualized on conventional radiographs as osteophytes, malalignment and joint space narrowing (JSN).[5] In addition in erosive OA, subchondral erosions with widening can be seen.[4] However, radiography is an insensitive imaging modality and a more sensitive method visualizing not only structural changes but also soft tissues is needed. More recently, ultrasound (US) has been introduced to visualize osteophytes and soft tissues in HOA. It has been shown that US is more sensitive than radiography to detect osteophytes, and, moreover, that synovitis is frequently seen in HOA.[1,6-8]

In knee OA, magnetic resonance imaging (MRI) sems to be a valid imaging modality which enables visualization of the subchondral bone, including bone marrow lesions (BMLs) and soft tissues.[9,10] For HOA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone.[4,11,12,13] Recently, a MRI scoring method supported by an atlas was proposed, which facilitates research with MRI in HOA. The Oslo Hand OA MRI score (OHOA-MRI score) was developed as a reliable method to assess key features in HOA.[14] To be able to use MRI and a scoring system for HOA, it is however necessary to proof validity, reliability and feasibility.

The purpose of the present study is therefore to test the intraobserver reliability and criterion validity of the MRI in a severe HOA population.

PATIENTS AND METHODS

Patient population

Sixteen HOA patients, fulfilling American College of Rheumatology criteria,[15] were recruited from the Rheumatology outpatient clinic from July 2008-October 2010. The patients were all participants of an international placebo-controlled medication study (Clinical Trial Governance reference is: EudraCT 2007-003, 994-18). For this study, baseline data of the participants in the Netherlands were used. Participants had at least one (pre)erosive joint (defined below) in the IPJs on conventional radiographs and pain ≥ 30 mm on the visual analogue scale (VAS). Patients were excluded if they suffered from chronic inflammatory rheumatic diseases (e.g. rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, haemochromatosis, gout or chondrocalcinosis).

Approval of the study by the medical ethical committee of the Leiden University Medical hospital and signed informed consent were obtained.

Clinical assessment

Demographic characteristics were collected by standardized questionnaires. All patients completed a 100-mm VAS to assess hand pain over the past 48 hours. Usage of analgesics was allowed during the study. Pain upon palpation, bony and/or soft swelling ('absence'/'presence') for each distal and proximal IPJ (DIPJ, PIPJ) was assessed by a single observer (WYK) during physical examination using the Doyle Index, which has been validated for HOA.[16]

MRI examinations

The 2nd-5th DIPJs and PIPJs of the right hand were imaged in a 4-channel wrist coil using a 3T MRI Unit (Achieva 3T; Philips Medical Systems), with the patient positioned supine with the arm in neutral position parallel to the body. In all patients, the following sequences were obtained: coronal turbo spin echo (TSE, slice thickness (ST) 2 mm, repetition time/echo time (TR/TE) 1139/20 ms), coronal frequency selective fat-suppressed T2-weighted images (ST 3 mm, TR/TE 4013/60 ms), sagittal T1-TSE (ST 3 mm, TR/TE 450/20 ms), sagittal frequency selective fat-suppressed T2-weighted images (ST 3.5 mm, TR/TE 7768/60 ms), coronal post-gadolinum-chelate (Gd)-DOTA fat-suppressed images (ST 2 mm, TR/TE 1138/20 ms), sagittal post-Gd-DOTA fat-suppressed images (ST 3 mm, TR/TE 995/20 ms) (0.1 mmol/kg, Dotarem, Guerbet, Netherlands). In 4 patients, additional images were obtained with the following sequences: axial native T1-weighted images (ST 3 mm, TR/TE 633/20 ms) and post-Gd-DOTA frequency selective fat-suppressed T1- (ST 3 mm, TR/TE 570/20 ms) and axial frequency selective fat-suppressed T2-weighted images (ST 3 mm, TR/TE 4490/60 ms). MRI-examinations were obtained on the same day as clinical assessments and radiographs.

MRI features were scored by a single reader (WYK), after a training session of one week with the developers of the OHOA-MRI score. MRI-features were scored using T1-weighted fat suppressed Gd images for synovial thickening (grade 0-3), flexor tenosynovitis (grade 0-3) and bone cysts (grade 0-1, proximal and distal), using T1 weighted images for collateral ligaments (present or absence: the absence of the collateral ligament was defined as a non-visible or non-continuous collateral ligament) (grade 0-1, radial and ulnar), bone erosions (grade 0-3, proximal and distal), osteophytes (grade 0-3, proximal and distal), JSN (grade 0-3) and malalignment (grade 0-1, sagittal and frontal plane) and using T2 weighted fat suppressed images to detect BMLs at insertion sites of collateral ligaments (grade 0-1, radial, ulnar, proximal and distal), and BMLs (grade 0-3, proximal and distal). For the analyses, collateral ligaments, cysts and erosions were dichotomized as present/ absent. To be able to compare osteophytes on MRI with osteophytes on radiographs and US, the highest score given to either the

distal or proximal part of the joint on MRI images was used. So for instance when a joint had a score 1 at the distal part and score 3 at the proximal part of the joint, score 3 was assigned to that joint.

MRI sequences were adopted according to the original article of the OHOA-MRI score, with the exception of the T1 weighted fat suppressed images, which are normally not used in MR imaging. Instead T1 weighted images without fat suppression were acquired.

Since the study was designed before the OHOA-MRI was published, and the axial planes were not included in the original protocol but sagittal planes were, only the last 4 patients had additional axial planes.

MR images of six patients (three with coronal and sagittal planes only, three with coronal, sagittal and axial planes) were scored twice with an interval of 5 weeks to determine intraobserver reliability.

US assessment

US was performed by one experienced ultrasonographer (WYK) always in the presence of a second ultrasonographer (MCK) scoring together in consensus, using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear array transducer. Settings were optimized by the application specialist of the manufacturer of the machine.

US was performed 3-19 weeks in advance of the MRI and clinical assessment (median 6 weeks) due to logistic/practical reasons.

All hand joints were scanned from the dorsal side only in longitudinal and transverse planes. Features had to be present in both planes. Each joint was scored for osteophytes, power Doppler signal (PDS) and synovial thickening.[7,17] All US-features were scored on a four-point scale (0=none, 1=mild, 2=moderate, 3=severe). The intra-observer reliability was good to excellent (ICC= 0.62-0.91).[7]

Conventional radiographs

Radiographs (dorso-volar) of the right hand, using a standardized protocol, were read by WYK, and scored for osteophytes (grade 0-3) , JSN (grade 0-3) and cysts (grade 0-1) using the OARSI-atlas.[18] Erosions were scored according to the Verbruggen-Veys scoring method, defined as an erosive (E-phase) or remodelled phase (R-phase).[19] A pre-erosive joint was defined as a joint with complete joint space loss in part or the whole joint (J-phase). The intraobserver reliability was good to excellent (ICC 0.62-0.94) for all radiographic features.

Statistical analysis

Data were analyzed using SPSS, version 20.0 (IBM SPSS statistics, New York, USA).

Reliability was determined by estimating intra-class correlation coefficients (ICC) using generalizability theory, a random factor model ANOVA approach that estimates the components of variance within each model. Using this method was more suitable compared to the traditional ICC analyses due to the separate outcomes on joint level, with unique joints clustered within a patient. The ICC calculated in this study is not similar to the classical definition of ICC, and are called G-coefficients as defined by Streiner and Norman.[20] We retained the term ICC to indicate that the results are comparable to the classical ICC. Interpretation of the correlations are: 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 almost perfect.

Elementary sources of variance in data are called facets in generalizability theory. For intra-observer reliability relevant facets in this study are: patients (0-16) and hand joints (0-8). Dependent variables were the separate features of each imaging modality.

In generalizability theory, a distinction is made between fixed and random facets. The facets `patient' and `hand joints' were defined as random facets. The facet `hand joints' was nested within the facet `patient' since each patient has a unique set of hand joints.

In order to study criterion validity of MRI features, concurrent validity was evaluated by comparing MRI with radiograph and US features in the 2nd-5th DIPJs/PIPJs of the right hand only (128 joints). Subsequently, generalizability theory was used to determine correlations between MRI and US or radiographic features, since for these analyses separate outcome per joint are of relevance, in a situation where in a patient 8 unique joints are clustered. Generalizability theory is a statistical method that is capable of analyzing this nested model.

For the different imaging modalities the facets were defined as 'patient' (0-16), 'hand joints' (0–8) and 'method' (MRI, US, CR). The dependent variables being imaging features. The facets `patient' and `hand joints' were defined as random facets, the imaging modality as fixed facet. The facet `hand joints' was again nested within the facet `patient'.

Since we expected, based on results from earlier studies,[21-23] that radiographs are less sensitive in detecting features compared to MRI, we expected to find correlations between the imaging modalities, but these correlations were expected not to be 1, but ranging between about 0.4 and 0.8.

We expected to find higher correlations between MRI and US since they are both considered to be more sensitive imaging modalities when compared to radiographs.

Mann-Whitney U test was used to compare affected joints between the different imaging modalities. P<0.05 was considered significant.

To study the relationship between MRI features (as independent variables) and pain on the individual joint level, we associated MRI features with pain upon palpation in hand joints using Generalized Estimating Equations (GEE) with robust variance estimators to account for the correlation of observations within the same person. Adjustments were made for age, sex and BMI. Results were presented as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Study population

Sixteen patients (median (range) age 56.7 (42.0-70.7) years, 62% female, median (range) BMI 25.7 (20.2-32.4) kg/m^2) were included. The median symptom duration was 6.5 years. Erosive OA was found in 13 patients and median (range) VAS pain was 70 (35-93) mm. The median (range) number of swollen and tender joints was 2.5 (1-6) and 5 (1-12), respectively. Bony swelling was present in 61% and soft swelling in 18% of the joints palpable during clinical assessment.

In one patient, the contrast arrived subcutaneously instead of intravenously. Therefore (teno)synovitis could not be assessed in 8 joints and consequently the number of joints assessed by MRI for the presence of synovial thickening and structural changes varied. In two DIPJs, correct scoring was not possible for some features due to incorrect positioning of the joint in the coil.

MRI detected synovial thickening was present in 117 joints (98%). If the cut-off for MRI synovitis is set on grade ≥2 (moderate to severe), 51 joints (43%) had synovial thickening. Flexor tenosynovitis was seen in 36 (30%), erosions in 77 (61%), bone cysts in 16 (13%) and BMLs in 36 (27%) joints on MRI. Collateral ligaments were present in 84 (66%) joints and BMLs at the insertion sites of collateral ligaments in 17 (13%) joints. Osteophytes and JSN were seen in 98 (77%) and 116 (91%) joints on MRI, respectively. Malalignment was only seen in the 2 DIPJs on MRI. Table 9.1 shows the distribution of these features stratified for DIPJs/PIPJs.

Table 9.1 Findings on MRI in the examined right hand in 16 patients with hand osteoarthritis (total 128 joints), stratified for DIPJs and PIPJs

Feature (range of scores)	DIPJs, affected/total no. joints (%)	PIPJs, affected/total no. joints (%)
Synovial thickening (grade ≥1)	58/60 (97)	59/60 (98)
Synovial thickening (grade ≥2)	22/60 (37)	29/60 (48)
Flexor tenosynovitis (grade ≥1)	15/60 (25)	21/60 (35)
Collateral ligaments (normal)	34/63 (54)	50/64 (78)
BML at insertion sites (present)	8/64 (13)	9/64 (14)
Bone erosions (grade ≥1)	45/62 (73)	32/64 (50)
Bone cysts (present)	8/63 (13)	8/64 (13)
Osteophytes (grade ≥1)	54/63 (86)	44/64 (69)
JSN (grade ≥1)	62/63 (98)	54/64 (84)
Malalignment (present)	2/63 (3)	0/64 (0)
BML (grade ≥1)	22/64 (34)	12/64 (19)

DIPJs = Distal interphalangeal joints
PIPJs = Proximal interphalangeal joints
BML = Bone marrow lesions
JSN = Joint space narrowing

Table 9.2 Intra-observer reliability depicted by intraclass correlation coefficient for MRI features of 48 joints of erosive hand osteoarthritis patients.

MRI feature	ICC
Synovial thickening	0.94
Flexor tenosynovitis	0.77
Collateral ligaments	0.79
Bone marrow lesions at insertion site	0.72
Bone erosions	
Distal	0.91
Proximal	0.87
Bone cysts	0.93
Osteophytes	
Distal	0.92
Proximal	0.86
Joint space narrowing	0.88
Malalignment	1
Bone marrow lesions	
Distal	0.89
Proximal	0.87

MRI=magnetic resonance imaging, ICC= intraclass correlation coefficient, estimated using generalizability theory.

Reliability

The intra-observer reliability of MRI features as determined in 6 patients with 48 hand joints was substantial to almost perfect, as depicted in table 9.2.

Validity of MRI versus ultrasound

US detected synovial thickenings (grade ≥1) in 54 (42%) of 128 joints (20 DIPJs, 34 PIPJs), PDS in 29 joints (23%) (13 DIPJs, 16 in PIPJs), and osteophytes in 127 joints (64 in DIPJs, 63 in PIPJs). MRI was significantly more sensitive for the detection of synovial thickening compared to US ($p < 0.0001$), while MRI was less sensitive for osteophytes ($p < 0.0001$).

A moderate correlation coefficient of 0.43 was found between synovial thickening on MRI (graded 0-3) and on US (graded 0-3). When presence of MRI synovial thickening was defined as grade >1, an ICC of 0.54 was found.

Correlation coefficient between osteophytes on US (grade 0-3) and MRI (grade 0-3) was 0.49.

Validity of MRI versus radiography

Radiographic osteophytes (grade ≥1) were present in 53 (41%) and JSN (grade ≥1) in 97 (76%) joints, significantly less than on MRI (77% ($p<0.001$) and 91% ($p=0.001$), respectively). Radiographic erosions were detected in 23 (18%) joints, significantly less than on MRI (61%), ($p<0.001$). Twenty-two joints with radiographic erosions were erosive on MRI as well. Radiographic bone cysts were seen in 25 (20%) joints, significantly more than on MRI (12%, $p<0.001$)(table 9.3).

Table 9.3 Overview of MRI, ultrasonographic and radiographic features in distal and proximal interphalangeal joints (total 128 joints, but 1 missing) of the right hand of 16 patients with hand osteoarthritis.

Feature	MRI	Ultrasound	Radiographs
Synovial thickening	117 (98)*	49 (38)	NA
Synovial thickening**	51 (43)	48 (38)	NA
Osteophytes	98 (77)	127 (99)	52 (41)
Joint space narrowing	116 (91)	NA	97 (76)
Erosions	76 (60)	NA	23 (18)
Cysts	16 (12)	NA	25 (20)

* Depicted are numbers (%) **Synovial thickening in MRI defined as ≥grade 2.
NA= not applicable

The correlation coefficient for osteophytes (0-3), JSN (0-3) erosions (0-1), and cysts (0-1) were 0.53, 0.68, 0.32 and 0.43, respectively, indicating fair to substantial correlations between the MRI versus radiographic features.

Validity of MRI features with pain upon palpation at joint level

We hypothesized that joints with osteoarthritic MRI features would be painful more often. Therefore, associations between pain upon palpation and synovial thickening were calculated.

Only 3 joints were classified as grade 0 for synovial thickening and could not be used as reference category. Therefore synovial thickening was dichotomized into no/mild (grade 0/1) versus moderate/severe (grade 2/3) for the analyses. All other features were dichotomized as presence (grade 1-3) or absence (grade 0).

Pain upon palpation was significantly associated with the presence of moderate/severe synovial thickening, BMLs, erosions, and abnormal collateral ligaments after adjustments for age, sex, and BMI (table 9.4). A positive trend was seen with BMLs at the insertion sites of collateral ligaments and JSN.

Table 9.4 Association of MRI features and pain upon palpation in distal and proximal interphalangeal joints of the right hand in 16 patients (total 128 joints) with hand osteoarthritis

MRI feature score	No. of normal joints without feature		No. of abnormal joints with feauture		Adjusted OR* (95%CI)
	DIPJs	PIPJs	DIPJs	PIPJs	
Syn. thick (grade 2-3)	38	31	22	29	2.4 (1.06-5.5)
Collateral ligaments	34	50	29	14	4.2 (2.2-8.3)
BML at insertion sites	56	55	8	9	3. 1 (0.95-10.1)
Bone erosions	17	32	45	32	4.5 (1.7-12.2)
Bone cysts	55	56	8	8	2.0 (0.6-7.1)
Osteophytes	9	20	54	44	2.4 (1.1-5. 2)
Joint space narrowing	1	10	62	54	5.6 (0.8-41.4)
Malalignment	61	64	2	0	2.2 (0.2-26.2)
Bone marrow lesions	42	52	22	12	3.5 (1.6-7.7)

No.=number, DIPJs= distal interphalangeal joints, PIPJs=proximal interphalangeal joints, OR=odds ratio, 95%CI = 95% confidence interval, syn. thick= synovial thickening, BML=bone marrow lesion

*= Adjustments for age, sex, body mass index and within patient effects.

8 joints not available for (teno)synovitis

1 DIPJ not available for collateral ligaments, bone cysts, osteophytes, JSN, malalignment

2 DIPJs not available for bone erosions

DISCUSSION

In this severe, (pre)erosive, HOA population MRI was found to be a reliable method to investigate OA characteristics in HOA, as shown by substantial to almost perfect intraobserver reliability of all MRI features.

MRI criterion validaty was confirmed by comparing MRI with ultrasonography, radiography and clinical features showing substantial correlations.

Comparison with physical examination showed that MRI abnormalities such as synovial thickening, osteophytes, but also abnormal collateral ligaments, BMLs, and bone erosions, were associated with pain upon palpation in individual joints.

Up till now, radiographs are used as golden standard for detection of HOA features for diagnosis and research purposes. Unfortunately, this imaging modality has limitations since it is unable to show soft tissue. Recently, US has been used not only for visualization of structural, but also inflammatory features. A drawback of this imaging modality is however the inability of the US beam to penetrate through bone, making it more difficult to visualize subchondral abnormalities, such as BMLs. MRI has the possibility to identify both soft tissue, structural abnormalities and abnormalities in subchondral bone, and is therefore potentially a better alternative to radiographs as golden standard.

In order to test this hypothesis, concurrent validity was assessed by comparing features detected on radiographs and US with those found on MRI. As expected correlations found were between 0.40 and 0.80 for all features, except for erosions. MRI is therefore a valid method.

Erosions detected on MRI versus radiographs showed a lower correlation than expected (0.32). This might be explained by the fact that erosions on MRI were not always identified as erosions on radiographs, but were classified as cysts. The latter became obvious when comparing the presence of cysts and/or erosions on MRI and radiographs on joint level. The observation that cysts found on radiographs appear to be erosions on MRI was also made by Haugen et al.[21]

In the present study, MRI showed far more joints with synovial thickening compared to US. Only few studies compared synovial thickening on MRI and US earlier.

Vlychou et al studied MCP, PIP and DIP joints of one hand of erosive HOA (N=13) and non-erosive HOA (N=7) patients. In this study population, means of affected joints appeared higher in US compared to MRI, but results have to be interpreted with caution due to the small sample sizes since analyses were done on patient level.[22]

Wittoek et al[8] studied 8 interphalangeal joints of 14 patients (9 erosive HOA, 5 non-erosive HOA) and found more synovitis using 3 Tesla MRI (20% of all joints) compared to US (15% of joints) with a percentage exact agreement of 87%. The authors used recommendations for hand joint pathology in RA. In these recommendations synovitis on contrast enhanced MRI is defined as an area in the synovial compartment that shows above normal post-gadolinium enhancement of a thickness greater than the width of the normal synovium.

After contrast administration, normal synovial tissue enhances as well as abnormal and thickened synovial tissue. The treshold for abnormal synovial thickening is most likely set too low in the present study. A reason for this might that more detail could be visualized on the high resolution images of the 3 Tesla MRI machine. Thin synovial tissue is seen in these images while this is less visible on the the atlas used as a reference, which is based on images derived from a 1 Tesla MRI machine. Moreover, sequences used were not obtained directly but were constructed afterwards, which results in a lower resolution of images.

When in the present study MRI synovial thickening score 0 and 1 were considered both within the normal limits, MRI and US demonstrated synovial thickening in 43 and 42% of hand joints respectively, and correlation between the two modalities increased.

It was expected that US and MRI showed more osteophytes compared to radiographs, since these two imaging modalities are capable of scanning in different planes enabling osteophytes on locations other then on the sides to be detected. US however detected more osteophytes compared to MRI. This is in concordance with earlier studies.[8, 21] The reason for this higher sensitivity might be the ability to scan around the joint in a continuum using ultrasound, while MRI is performed in coronal and sagittal slices. Maybe this is making it more difficult to discern osteophytes that are for instance in between two images.

MRI features of OA were frequently seen in the hand joints of our HOA population. The prevalence of MRI-abnormalities are comparable with those described earlier. In the present study 61% erosions, 77% osteophytes and 27% BMLs were found. Wittoek et al.[8] studied 9 erosive HOA patients using 3.0T MRI and found 63% erosions, 57% osteophytes and 52% BMLs. In another study in HOA patients, done by the developers of the OHOA-MRI score,[11] osteophytes were found in 89%, erosions in 51% and BML in 13% of joints.

The association between MRI features with pain was also investigated to increase the understanding of causes of pain in HOA and validate MRI with clinical features. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause of pain in

HOA. This is in line with an earlier study in HOA,[11] and an US study in HOA showing that synovial thickening and PDS are associated with more pain per joint.[7]

The MRI images were scored by the recently developed OHOA-MRI score.[14] Our 3.0T MRI-images (supplementary figure S9.1-9.4) were of good quality with higher spacial resolution compared to the 1.0T images of the atlas that was made by the developers of the OHOA-MRI score.

After implementing and using the scoring method, we experienced some items that need consideration.

First of al, it is not common practice to use T1 weighted fat suppressed images as the OHOA-MRI developers recommend. In T1 sequences all water containing structures appear black in the image, leaving good visualisation of fat containing structures. After suppression of the latter, it is difficult to descern any structure. Therefore, T1 weighted images were used instead.

Also, the present scoring method scores collateral ligaments as 'absence' or 'presence', suggesting that the absence of collateral ligaments is a rupture of these ligaments. However, if abnormalities around collateral ligaments are present, more signal will be visualized on MRI, mimicking the 'absence' of the ligament as illustrated in the MRI-atlas and therefore we suggest scoring collateral ligaments as 'normal'/'abnormal'.

Although the objective of this study didn't allow investigation of feasability, it was noticed during scoring of MRI-images that a considerable amount of time was needed for the assessment of one patient (approximately 75-90 minutes). This should be an objective for further studies.

Several limitations can be addressed in this study. MR-images were obtained in a highly selected population with severe complaints. The sample size was small. This could influence the results especially on patient level. All analyses were however performed on joint level, taking into account patient effect. Therefore, we believe that results are of importance.

No finger joints of a control group were imaged with MRI, since this study focusses on the validity of MRI in patients with HOA.

Due to logistical reasons, US was performed some weeks before the MRI. This might have influenced the results on the correlation between MR and US detected synovial thickening, since synovial thickening can fluctuate over time.[24] Therefore, it is possible that the correlation is underestimated.

Since the OHOA-MRI scoring method was published during the course of the present study, axial sequences were not performed by all patients. Therefore, features

such as synovitis could not be scored optimally in the patients where these sequences were lacking. This might have underestimated correlations.

Regarding the scoring of MRI, only one observer reviewed all MRI-images since the scoring was time consuming. However, the intraobserver reliability is substantial to almost perfect and the reader was trained by the developers of the OHOA-MRI scoring method. In the future, MRI-studies in less selected HOA population with follow-up data are needed to confirm these findings. In addition, further investigation in a longitudinal study is recommended to study other metric properties of the scoring method, being longitudinal inter and intraobserver reliability and sensitivity to change. In addition, also the influence of variation in the acquisition of the MR images should be studied.

Acknowlegdements
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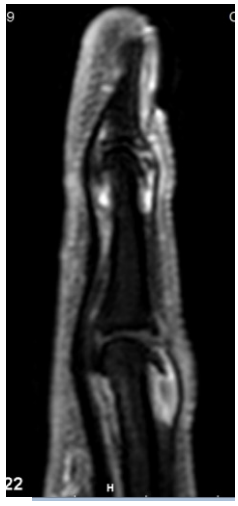
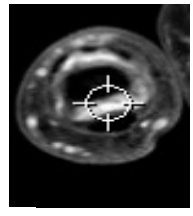
Supplement: Images of 3T MRI of osteoarthritis features in interphalangeal joints.

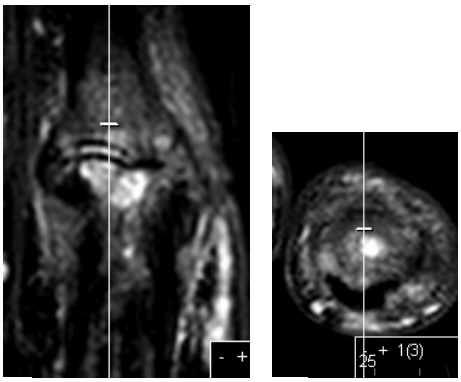


A



B

Figure S9.1 A: Sagital and B: post-gd-DOTA fat suppressed image. 2th DIP and PIP joint of the right hand showing synovitial thickening. B: Axial post-gd-DOTA fat suppressed image. 5th PIP joint of the right hand showing synovitial thickening.



A B

Figure S9.2 A: Coronal and B: axial frequency selective fat suppressed T2 weighted image. Second PIP joint of the right hand with bone marrow lesions.

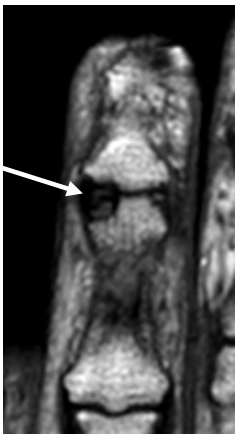


Figure S9.3 Coronal T1 weighted image. 4th DIP joint with erosion (arrow).

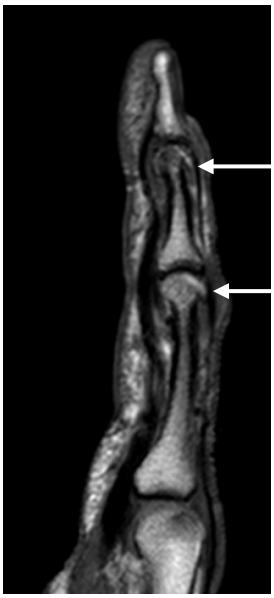


Figure S9.4 Coronal T1 weighted image. Second DIP and PIP joint with osteophyte (arrow)

10

Summary and discussion

Osteoarthritis (OA) is the most common musculoskeletal disorder, characterized by cartilage degradation and changes in subchondral bone. It often leads to pain and disability. It is an increasing burden for society, especially with the aging of the population. The hand is one of the most frequently involved sites.

The etiology of pain and structural progression in hand OA has not been fully understood up till now, and the role of inflammatory features have not been thouroughly investigated.

This thesis presents the results of the ECHO (= ultrasound (US) in hand OA) study. In this study 63 patients with symptomatic hand OA according to the American College of Rheumatology (ACR) criteria were recruited from the rheumatology department of the Leiden University Medical Center and followed for 2.3 years. At baseline, after 3 months and 2.3 years, an US examination, physical examination and global pain score were performed. The baseline and 2.3 year follow-up visits also included radiographs and questionnaires on demographics and selfreported outcome measures. In this cohort we investigated the association between inflammatory US features and clinical outcomes, the evolvement over time, and the association with progression of structural abnormalities, such as osteophytes, joint space narrowing (JSN) and erosions. The association of structural abnormalities and clinical outcomes were also investigated since earlier studies gave conflicting results. In the latter analyses we especially focussed on results on patient level versus joint level. The role of inflammatory features in the subset erosive OA was studied separately cross-sectionally as well as prospectively after 2,3 years of follow-up.

In addition two studies are presented looking into the value of MRI in OA.

The association of OA features with pain

The association of pain and OA features has been studied much more frequently in knee OA than in hand OA. For this reason, a systematic review of 22 studies that associated MRI features and pain in knee OA patients was described in Chapter 2. We identified a moderate level of evidence for a positive association for bone marrow lesions (BMLs) and effusion/synovitis with pain in knee OA. The level of evidence was limited for a positive association for knee ligamentous abnormalities with pain, and limited for no association for osteophytes and subchondral cysts with pain.

In our review, we used an a priori defined qualitative level of evidence to summarize the results. More robust results could have been obtained by performing a meta-analysis, but due to the heterogeneity of the included studies, it was not possible to perform these analyses. The assignment of a level of evidence to studies results in counting positive and negative studies taking in account the design and quality of the study. This has some limitations. First of all, sizes of studies cannot be taken into account, and the cut-off point for the decision of ‘positive or negative’ studies is only

based on statistical significance. Also, the use of a selected quality score set to assess the methodological quality of the studies is a potential limitation. It is possible that when a different quality score set is used, the interpretation of the results could be influenced.

Other limitations of this review mostly reflect the limitations of the studies investigated. First, no publication bias could be investigated due to the limited number of studies that reported their results in relative risks or odds ratio's. Second, the quality of included studies was not excellent.

Thus, additional high-quality research is needed to further explore the associations of BML and effusion/synovitis with pain in knee OA.

In Chapter 3 the first results of the ECHO study were presented. It was demonstrated that the majority of patients had inflammatory US features. In the present study 96% of patients showed grayscale (GS) synovitis (a composite measure of synovial thickening and effusion), 91% effusion, 86% power Doppler signal (PDS) and 73% synovial thickening.

Dose dependent associations of inflammatory US features and pain were found in individual joints taking into account patient effects and confounders. In addition it was shown that these associations were all independent of the other inflammatory features, although the association with PDS did not reach significance, probably due to insufficient power. Associations on patient level were found for GS synovitis with the patient reported outcomes AUSCAN pain and stiffness and the SF-36 physical component scale, and for effusion with AUSCAN pain.

In earlier studies of hand OA[1,2] and in the manuscript by Keen et al.,[3] defining a preliminary scoring system for US, only GS synovitis was investigated. The separate scoring of effusion and synovial thickening was not proposed. The choice for a composite measure GS synovitis is due to the assumption that effusion and synovial thickening are difficult to distinguish separately. In the present study it was demonstrated that it is technically possible and clinically relevant to study effusion and synovial thickening as separate entities, since both effusion and synovial thickening can be scored reliable and it is shown that both features associate independently of each other with pain and progression.

Up till now, structural abnormalities assessed on radiographs, such as osteophytes and JSN, are frequently used as outcome measure in research to study associations with clinical features in hand OA. Using radiography, conflicting results have been reported on these associations. [4] We hypothesized that the lack of association between structural abnormalities and pain in hand OA might be caused by the choice of the imaging modality. A few studies have shown that radiographs are less sensitive in

detecting osteophytes compared to US.[5,6] Therefore, we compared the sensitivity for the detection of osteophytes using radiography and US. In addition, we investigated the association between structural abnormalities and pain using both imaging modalities. In Chapter 4 it is demonstrated that more osteophytes were found using US compared to radiography. Also, it was shown that a strong dose-dependent association between pain and structural abnormalities assessed on joint level is present, taking into account patient effects in patients with symptomatic hand OA. These associations were found when structural abnormalities were assessed using US as well as radiographs. Associations were absent when summated scores of structural abnormalities and global pain scores were analysed. Both osteophytes and JSN are independent of each other associated with pain. Thus, although higher sensitivity of US is found for the detection of osteophytes compared to the detection on radiographs, both imaging modalities show equally strong associations with pain. It is therefore not sure whether the increased sensitivity of US is of clinical relevance. It is possible that the sensitivity is too high in US to reveal bony abnormalities.

The fact that JSN is independently associated with pain is especially interesting, since the cartilage in itself is aneural. Healthy cartilage absorbs mechanical forces that are imposed on the joint. With the thinning of the cartilage, these forces are loaded increasingly on the subchondral bone, which does contain nerve fibres. It is possible that the association found between cartilage loss and pain, is in fact an association between increased loading of the subchondral bone. Further studies are necessary to investigate this hypothesis. Since US is incapable to access subchondral bone, for this research MRI would be the imaging modality of choice.

Results from both Chapter 3 and 4 reveal that analyses on joint level taking in account patient effects, such as genetic and psychosocial factors, are able to show associations between OA features and pain in hand OA, while analyses on patient level without taking these factors into considerations cannot always support these associations.

An explanation for these differences could be that patients' effects in hand OA are predominantly responsible for patients reporting pain. It is possible that hard tissue and to a lesser extent soft tissue abnormalities are not of clinical relevance.

Another hypothesis could be raised by the complex nature of hand OA. Since multiple joints are involved in the hands and OA joint-specific features that showed to be associated with pain on joint level are differentially present within the joints of the hands (for instance structural abnormality in one joint, effusion in the other, JSN in yet another joint) it is much more difficult to show an association with a certain feature on patient level, even taking in account all these different OA joint-specific features in the analyses. Moreover, some joints, such as the 1st CMC joint, attribute more to overall pain and disability than other joints, making it even more difficult to capture the associations on patient level.

Finally, it is of course important to have a large enough patient population. The latter might by a problem in the present study for the analyses on patient level.

Follow-up studies

In Chapter 5 we present results of the 3 months follow-up study. In this study it is shown in hand OA patients, that total inflammatory US features remained stable over time. At joint level 19% of hand joints had persistent inflammatory features, while they fluctuated in 20%. Remarkably, overall pain reduced over time, while the associations of inflammatory features with pain on joint level remained and even tended to grow stronger after three months. This implies that the decrease in overall pain can't be explained by a decrease of inflammation. A possible explanation could be a decrease in psychosocial (i.e. anxiety) and mechanical causes of pain, (i.e. joint protection principles) which is not directly related to inflammation. This observation emphasized the multifactorial origin of pain yet again.

In Chapter 6 the prospective 2.3-year follow-up study in patients with hand OA from the ECHO cohort is described. In this study it was shown that baseline inflammatory US features in hand joints are positively associated with radiological progression in these joints, independently of each other and also independent of baseline radiological features. Repeated measurements of inflammatory US features revealed that the prevalence of joints with synovial thickening and effusion increased with 35 and 26%, respectively, after 2.3 years, while only a slight increase (2%) of joints with PDS was seen. The minority of joints showed persistent inflammatory US features at baseline and follow-up -2, 7 and 14% respectively for PDS, synovial thickening and effusion-while 14, 38 and 38% of joints showed fluctuating features. Especially persistent inflammatory US features were associated with radiological progression after 2.3 years. Joints with both persistent and fluctuating PDS had an increased risk to progress radiologically over 2.3 years.

In the present study, especially the presence of PDS, reflecting active synovitis, appears to be a predictor of radiological progression. Synovial thickening and to a lesser extent effusion are also of importance, but these features are especially associated with radiological progression when they persist over time.

After 2.3 years, a large increase of inflammatory features was seen for effusion and synovial thickening. It is possible that this is the natural course of the disease. Since hand OA has not been studied after long-term follow-up with ultrasound or MRI up till now, the natural course on the long-term of inflammatory features is not known. The study population consisted of severe hand OA patients, as supported by the presence of 18 patients with erosive hand OA at baseline and with a fairly high VAS hand pain. More longitudinal studies in different patient populations are warranted to understand the natural course of these inflammatory features.

Studies in erosive hand OA

Chapter 7 describes that interphalangeal joints of patients with erosive OA demonstrate more PDS, GS synovitis and effusion, but not more synovial thickening, in comparison to interphalangeal joints from patients with non-erosive hand OA. Further detailed investigation revealed that especially erosive interphalangeal joints show inflammatory features. Remarkably, also interphalangeal joints without erosions in patients with erosive OA demonstrated more inflammatory US signs in comparison to interphalangeal joints of patients with non-erosive hand OA. The anatomical phases S, J, E and R showed more signs of inflammation compared to interphalangeal joints in N-phase, but PDS was only significantly associated to the E-phase.

These findings support our hypothesis that inflammatory signs might be implicated in erosive evolution. The present study suggests that erosive OA is a phenotype affecting all interphalangeal joints in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions. To fully understand the role of inflammatory features in erosive evolution longitudinal studies have to be done.

Further investigation revealed that especially the E-phases were associated with active synovitis as reflected by positive PDS. In contrast, synovial thickening, which is frequently found in hand OA, does not distinguish between the different hand OA anatomical phases.

The diagnosis of erosive OA is based on subchondral erosions on radiographs in interphalangeal joints. The number of erosive interphalangeal joints necessary to diagnose erosive OA is not clear. Often it is stated that more than one erosive interphalangeal joint is needed. In this study we investigated both erosive OA as defined by at least one or by more than one erosive interphalangeal joint. The results were the same for both definitions, confirming that one erosive interphalangeal joint is enough to define a patient as erosive OA.

In the present study the clinical burden of patients with erosive OA was compared to patients with non-erosive hand OA. This study confirms the results of earlier studies that patients with erosive OA patients have a higher clinical burden.[7]

In conclusion, this study shows that erosive OA demonstrates more inflammatory features compared to non-erosive hand OA, even in interphalangeal joints that are not erosive. This is already true when erosive OA is defined as the presence of one erosive interphalangeal joint. Whether inflammation in erosive OA is a cause of erosive evolution or a result of extensive destruction in particular joints is not known; the finding that inflammatory features are also demonstrated more often in non-erosive joints in erosive OA suggests that inflammation is a cause.

In Chapter 8 we investigated associations between inflammatory US features and erosive development in hand OA. This study shows that erosive development is associated with moderate/severe synovial thickening, effusion and PDS at baseline in the same joints, however after adjustment for baseline structural abnormalities only synovial thickening and PDS remained associated. In addition, all inflammatory US features were associated with erosive development when present at baseline and follow-up. This implicates a role for inflammation in the pathogenesis of EOA and it might render new therapeutic options that can halt erosive evolution.

Reliability and validity of MRI in hand OA

In Chapter 9 we performed a reliability and validity study of MRI features in a severe hand OA population. In this severe, (pre)erosive, hand OA population MRI was found to be a reliable method to investigate OA characteristics in hand OA, as shown by substantial to almost perfect intra-reader reliability of all MRI features.

MRI was shown to be a valid method: Criterion validaty was tested by comparison with ultrasonography, radiography and clinical features and showed good correlations varying between 0.40 and 0.80 except for erosions.

Erosions detected on MRI versus radiographs showed however a lower correlation then expected (0.32). This might be explained by the fact that erosions on MRI were not identified as such on radiographs, but were classified as cysts, as we observed when the presence of cysts and/or erosions on radiographs and MRI was compared on joint level.

Comparison with physical examination showed that MRI abnormalities such as synovitis, osteophytes, but also abnormal collateral ligaments, BMLs, and bone erosions, were associated with pain upon palpation in individual joints.

The association between MRI features with pain was also investigated to increase the understanding of causes of pain in hand OA and validate MRI with clinical features. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause of pain in hand OA.

Future recommendations

In this thesis the role of inflammatory features in OA has been investigated. Based on the studies described in this thesis, we conclude that inflammatory features appear to be important and of clinical relevance, since they are involved in the perception of symptoms and in progression of structural damage over time.

This conclusion was partly based on the results of the systematic review we performed for the association of pain and inflammatory features in knee OA. However, the level of evidence was only moderate. Therefore, more research is needed in order to further strengthen these findings. High-quality epidemiological studies investigating BML and effusion/synovitis are especially warranted. An ideal epidemiological study design would be a case-crossover study where individual MRI findings in the presence of knee pain at one time point will be compared with MRI findings in the same patient without knee pain at another time point. The ideal data analysis would provide an association size and permit adjustment for confounders, including age, sex and BMI, and also for other MRI features when multiple MRI findings are studied simultaneously.

Since the performance of the review, more studies have been published on this issue and an update of the present review will follow in the near future.

An important conclusion that has implication for future research on pain in hand OA, is the multifactorial nature of pain. Independent associations were found on joint level of both hard tissue and soft tissue abnormalities. However, on patient level these effects are more difficult to discern. Probably this is due to the multiple causes, such as hard and soft tissue abnormalities simultaneaously, but also psychological and genetical factors, that are present within a patient. It is therefore important to study hand OA on joint level taking into account patients effects.

More longitudinal studies investigating inflammatory US features in hand OA are warranted. Because the studied population in the ECHO study appeared to be a rather severe hand OA population, these studies should be repeated, also in different and larger hand OA populations. In addition to the present study, a follow-up cohort study was started in the Leiden University Medical Center in 2009, where all consecuitive patients who were diagnosed with hand osteoarthritis by their rheumatologist are included. In this study MR images and radiographs of the hands are obtained. To understand more fully the role of soft tissue abnormalities it would be recommended to incorporate US as well. This would give the opportunity to investigate inflammatory features in a larger, less severe hand OA population.

In our studies we found that at follow-up some inflammatory US features are persistent, whereas others are fluctuating. Recently, several clinical trials have been performed with a follow-up duration of around 3 months including inflammatory features as outcomes.[8,9] It is important to realize when performing such trials that inflammatory features fluctuate due to their natural course of disease. These fluctuations should not be mistaken for a possible treatment effect. Therefore, we recommend, first, to undertake large observational studies in hand OA populations to acquire detailed knowledge on the natural course of hand OA. Second, to perform a randomized trial with a placebo group as control .

This thesis shows that US has contributed greatly in our search after the pathogenesis of hand OA and has increased our knowledge on the etiology of pain and structural progression in hand OA. An important task for the future is yet to define more exact criteria for OA features in imaging modalities. In several studies it was shown that the features described as “slight” were not clinically relevant. Also, we have shown that although US descerned far more osteophytes then radiographs, association with pain were found with both modalities, thereby questioning the relevance of the increased sensitivity of US for osteophytes. Also, recently it has become clear that in the knee using MRI in normal subject an astonishing amount of abnormalities can be found that are considered to be OA abnormalities. It has high priority therefore to develop good definitions what is considered to be normal and what abnormal using imaging modalities. The same is true for the definition of what is considered hand OA, since no satisfactory definition is present at this time. In 2010 we started a working group within the OMERACT (Outcome Measures in Rheumatology) with these themes amoung it’s objectives. Within this working group definitions for MRI and US are being defined and validity and reliability exercizes performed. This work is still ongoing.

In the subset erosive hand OA, more inflammatory features were found, not only in the erosive joints, but also in the non-erosive joints of erosive patients. Moreover, strong associations were found between inflammatory US features and erosive development. These findings suggest that in erosive OA systemic underlying mechanisms are implicated.

Finally, to understand the clinical relevance of inflammatory features in hand OA, a proof-of-concept study with an anti-inflammatory drug in patient with hand OA could be very helpful.

There have been three studies that have investigated the effect of corticosteroids in hand OA. These studies did not came to equivocal results.[8,10,11] However, these studies had limitations. One study did not investigate inflammatory features by imaging modalities as US or MRI making it difficult to evaluate the effect on inflammation.[10] Two studies included small patient populations and analyses were done on patient level only, not taking into account patient effects.[8,11] One study had an open study design and lacked a placebo group,[8] the other did only perform 0.2 Tesla MRI without contrast enhencement at baseline and at 4 weeks in the most painfull hand.[11] An ideal proof-of-concept study would be a randomized trial comparing placebo with oral prednisolon during at least one year with evaluation of both clinical outcomes and inflammatory signs. Osteophytes, JSN and erosions should be evaluated as well by radiography and MRI or US.

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11

Nederlandse samenvatting

Artrose is één van de meest voorkomende aandoeningen van het bewegingsapparaat. Het wordt gekenmerkt door de afbraak van kraakbeen en veranderingen in het bot dat net onder het kraakbeen gelegen is: het subchondrale bot. Artrose lijdt vaak tot pijn en beperkingen. Het is een toenemend probleem voor de gemeenschap, vooral vanwege het steeds ouder worden van de populatie. Eén van de meest frequent aangetaste gewrichten zijn die van de hand.

De mechanismen die leiden tot pijn en structurele progressie bij hand artrose zijn nog grotendeels onbekend. De rol die ontsteking daarbij eventueel zou kunnen spelen is nauwelijks onderzocht.

In dit proefschrift worden de resultaten gepresenteerd van de ECHO (EChografie bij Hand Osteoartrose) studie. Aan deze studie namen in totaal 63 patiënten met symptomatische hand artrose, volgens de American College of Rheumatology (ACR) criteria, deel, allen afkomstig van de polikliniek reumatologie van het Leids Universitair Medisch Centrum. De patiënten werden gedurende gemiddeld 2.3 jaar gevolgd.

Bij het eerste bezoek, na 3 maanden en na 2.3 jaar, werd een echo onderzoek en lichamelijk onderzoek verricht en globale pijnscores afgenomen. Bij het eerste bezoek en na 2.3 jaar werden bovendien vragenlijsten afgenomen over demografische gegevens en zelf-gerapporteerde klinische uitkomsten en werd een röntgenfoto van de beide handen gemaakt. In deze patiëntengroep hebben we de associatie tussen echografische ontstekingskenmerken en klinische uitkomsten onderzocht, de ontwikkeling van ontstekingskenmerken over de tijd en de associatie tussen ontstekingskenmerken en de progressie van structurele afwijkingen zoals osteofyten, gewrichtsspleetversmalling en erosies. De associatie tussen structurele afwijkingen en klinische uitkomsten werd eveneens onderzocht omdat eerdere studies tegenstrijdige resultaten lieten zien. Bij deze laatste analyses hebben wij ons met name gericht op resultaten op patiënt niveau versus resultaten op gewrichtsniveau.

De rol van ontsteking in de subgroep erosieve artrose werd apart bestudeerd zowel cross-sectioneel als prospectief na 2.3 jaar follow-up.

Daarnaast worden twee studies gepresenteerd die de waarde van MRI bij artrose bestuderen.

De associatie van artrose kenmerken met pijn

De associatie tussen pijn en artrose kenmerken zijn vaker onderzocht bij knieartrose dan bij handartrose. Om deze reden verrichtten wij een systematische review waarbij 22 studies geïdentificeerd werden, die de associatie van MRI kenmerken en pijn in knieartrose onderzochten. De resultaten worden beschreven in hoofdstuk 2. Een positieve matige associatie met pijn in knieartrose werd gevonden voor beenmerg laesies (BML) en effusie/synoviale zwelling. Het niveau van evidentie was zwak voor een positieve associatie van pijn en ligament afwijkingen, en zwak voor de afwezigheid van een associatie tussen pijn en osteofyten en subchondrale cysten.

In onze review hebben we een van tevoren gedefinieerd kwaliteitsniveau gebruikt om de resultaten samen te vatten. Preciezere resultaten zouden verkregen kunnen worden wanneer we een meta-analyse hadden kunnen doen, maar dit was helaas niet mogelijk vanwege de heterogeniteit van de studies. Het toekennen van niveaus van bewijs aan studies betekende dat de positieve en negatieve studies geteld werden, waarbij rekening werd gehouden met het studie design en de kwaliteit van de studie. Dit heeft enkele nadelen. Ten eerste kon de omvang van de studie niet meegenomen worden, en het afkappunt voor de beslissing van "positief" of "negatief" was alleen gebaseerd op statistische significantie.

Verder was het gebruik van een geselecteerde kwaliteitsscore set om de methodologische kwaliteit van studies in kaart te brengen een mogelijke beperking. Het is mogelijk dat de gebruikte kwaliteitsscore de interpretatie van de resultaten beïnvloed heeft.

Andere beperkingen van deze review betreffen vooral de beperkingen van de onderzochte studies. Ten eerste kon publicatie bias niet onderzocht worden vanwege het beperkte aantal studies dat resultaten in relatieve risico's of odd ratio's presenteerde. Ten tweede was de kwaliteit van de geïncludeerde studies niet geweldig.

Aanvullend onderzoek van hoge kwaliteit is nodig om de associaties tussen BML en effusie/synoviale zwelling en pijn in knieartrose verder te onderzoeken.

In hoofdstuk 3 worden de eerste resultaten van de ECHO studie gepresenteerd. In deze studie werd gevonden dat bij de meerderheid van de patiënten echografisch ontstekingskenmerken aanwezig zijn. In deze studie werd bij 96% van de patiënten synovitis (een samengestelde maat bestaande uit synoviale zwelling en effusie), bij 91% effusie alleen, bij 86% power Doppler signaal (PDS) en bij 73% synoviale zwelling gevonden.

Dosis afhankelijke associaties tussen echografische ontstekingskenmerken en pijn werden gevonden in individuele gewrichten waarbij gecorrigeerd werd voor patiënteffecten (zoals genetisch, psychosociaal) en verstorende factoren. Daarnaast bleek dat deze associaties allen onafhankelijk waren van de overige ontstekingskenmerken, alhoewel de associatie met PDS niet significant was, waarschijnlijk ten gevolge van onvoldoende grote groepsgrootte. Associaties op patiëntniveau werden gevonden tussen synovitis en de zelf gerapporteerde uitkomsten AUSCAN pijn en stijfheid en de SF-36 fysische component schaal. Tevens werd een associatie gevonden tussen effusie en AUSCAN pijn.

In eerdere handartrose studies, en in het voorlopige scoringssysteem van Keen et al., werd alleen synovitis gescoord. Het scoren van zowel effusie als synoviale zwelling apart werd eerder niet voorgesteld, omdat gedacht werd dat het onderscheid tussen de beide kenmerken moeilijk kon worden gemaakt. In dit hoofdstuk wordt aangetoond dat het niet alleen technisch mogelijk is om effusie en synoviale zwelling

apart te onderscheiden, maar ook dat dit klinisch relevant is. Beide kenmerken kunnen betrouwbaar worden gescoord en zijn beide onafhankelijk van elkaar geassocieerd met pijn en progressie.

Structurele radiologische afwijkingen zoals osteofyten en gewrichtsspleetversmalling, worden vaak gebruikt als uitkomstmaat bij onderzoek naar associaties met klinische kenmerken bij handartrose. Tot nu toe werden tegenstrijdige resultaten gevonden bij het bestuderen van deze associaties. Een mogelijke hypothese voor het ontbreken van een associatie tussen structurele afwijkingen en pijn bij handartrose zou de gebruikte beeldvormende techniek kunnen zijn. Enkele studies hebben namelijk aangetoond dat röntgenfoto's minder sensitief zijn in het detecteren van osteofyten in vergelijking met echografie. Om deze reden onderzochten we de sensitiviteit van de detectie van osteofyten middels röntgenfoto's en vergeleken beide methoden met elkaar. Tegelijkertijd werd de associatie bestudeerd tussen structurele afwijkingen, gescoord met behulp van röntgenfoto's of echografie, en pijn bij handartrose. Hoofdstuk 4 laat zien dat er meer osteofyten gevonden worden met echografie in vergelijking met röntgenfoto's. Tevens werd een sterke dosis respons relatie gevonden op gewrichtsniveau tussen pijn en structurele afwijkingen, gecorrigeerd voor patiënteffecten, bij patiënten met symptomatische handartrose. Deze associaties waren aanwezig zowel wanneer de structurele afwijkingen gescoord waren met behulp van röntgenfoto's als wanneer dit gebeurde middels echografie. Er werd geen associatie gevonden wanneer analyses op patiëntniveau werd gedaan met behulp van gesommeerde scores voor structurele afwijkingen en globale pijnscores. Zowel osteofyten als gewrichtsspleetversmalling waren onafhankelijk van elkaar geassocieerd met pijn. Dus, alhoewel echografie gevoeliger was dan radiografie in het detecteren van osteofyten, werden voor beiden sterke associaties gevonden met pijn. Het is daarom niet zeker of de verhoogde sensitiviteit van echografie voor osteofyten klinisch relevant is. Het is mogelijk dat de sensitiviteit van echografie om structurele afwijkingen te meten, te hoog is.

Het feit dat gewrichtsspleetversmalling onafhankelijk is geassocieerd met pijn is vooral interessant omdat het kraakbeen zelf geen zenuwen bevat. Gezond kraakbeen absorbeert mechanische krachten waar het gewricht aan bloot gesteld wordt. Wanneer het kraakbeen dunner wordt, zullen deze krachten in toenemende mate uitgeoefend worden op het subchondrale bot. Het subchondrale bot bevat zenuwuiteinden. Het is mogelijk dat de associatie die gevonden werd tussen gewrichtsspleetversmalling en pijn, in feite de associatie is tussen toenemende belasting van het subchondrale bot. Verdere studies zijn nodig om deze hypothese te onderzoeken. Omdat echografie niet in staat is om het subchondrale bot in beeld te brengen, heeft het de voorkeur om MRI te gebruiken voor dit onderzoek.

Resultaten van zowel hoofdstuk 3 als hoofdstuk 4 laten zien dat analyses op gewrichtsniveau, waarbij rekening wordt gehouden met het patiënteffect, zoals genetische en psychosociale factoren, associaties kan aantonen tussen artrosekenmerken en pijn, terwijl deze relaties niet altijd kunnen worden ondersteund door analyses op patiëntniveau waarbij geen rekening wordt gehouden met deze factoren.

Een verklaring voor deze verschillen zou kunnen zijn dat pijn bij handartrose voornamelijk wordt bepaald door patiënteffecten. Het is mogelijk dat benige en in mindere mate weke delen afwijkingen niet klinisch relevant zijn.

Een andere verklaring zou de complexiteit van handartrose kunnen zijn. Omdat meerdere gewrichten betrokken zijn in de hand en verschillende artrosekenmerken die geassocieerd zijn met pijn in verschillende gewrichten aanwezig kunnen zijn (bijvoorbeeld structurele afwijkingen in het ene gewricht, effusie in een ander en gewrichtsspleetversmalling in weer een ander gewricht), wordt het moeilijker om een associatie aan te tonen van een specifiek kenmerk op patiëntniveau, zelfs wanneer al deze verschillende artrosekenmerken in de analyse worden meegenomen. Daarbij dragen sommige gewrichten, zoals het duimbasis gewricht, meer bij aan globale pijn en functieverlies, wat het nog moeilijker maakt om associaties op patiëntniveau te laten zien.

Tot slot is het uiteraard belangrijk om een patiënten populatie te hebben die groot genoeg is. Dit laatste zou een probleem kunnen zijn in de ECHO studie voor de analyses op patiëntniveau.

Vervolgstudies

In hoofdstuk 5 worden de resultaten weergegeven van de 3 maanden vervolgstudie. In deze studie wordt aangetoond dat bij handartrose de totaal gevonden hoeveelheid ontsteking stabiel blijft over de tijd. Op gewricht niveau had 19% persisterende ontstekingskenmerken, terwijl ze fluctueerden in 20% van de gewrichten. Opmerkelijk genoeg verminderde de globale pijn na drie maanden, terwijl de associatie van ontstekingskenmerken met pijn op gewrichtsniveau aanwezig bleef en zelfs sterker leek te zijn. Dit impliceert dat de vermindering van handpijn niet kan worden verklaard door vermindering van ontsteking. Een mogelijke verklaring zou kunnen zijn dat er een daling was van psychosociale (bv angst) en mechanische oorzaken van pijn (bv toepassing van gewrichtsbeschermende principes), wat niet direct gerelateerd is aan ontsteking. Deze observatie benadrukt wederom de multifactoriële oorzaak van pijn.

In hoofdstuk 6 wordt de prospectieve 2.3 jaar vervolgstudie van handartrose patiënten uit het ECHO cohort beschreven. Hierbij werd gevonden dat echografische ontstekingskenmerken in handgewrichten bij het eerste bezoek positief geassocieerd zijn met radiologische achteruitgang in deze gewrichten na 2.3 jaar, onafhankelijk van elkaar en ook onafhankelijk van de radiologische kenmerken bij het eerste bezoek.

Herhaalde metingen van echografische ontstekingskenmerken lieten een toename van synoviale zwelling en effusie in de gewrichten zien van respectievelijk 35 en 26% na 2.3 jaar, terwijl er slechts een geringe toename van PDS werd gezien in de gewrichten (2%). De minderheid van de gewrichten had echografische ontstekingskenmerken bij zowel het eerste bezoek als na 2.3 jaar - 2, 7 en 14% voor PDS, synoviale zwelling en effusie- terwijl 14, 38 en 38% van de gewrichten alleen bij het eerste bezoek of na 2.3 jaar deze kenmerken had. Vooral in gewrichten waarbij de ontstekingskenmerken persisteerden werd een associatie gevonden met radiologische achteruitgang na 2.3 jaar. Alle gewrichten met PDS, zowel persisterend als fluctuerend, toonden een associatie met een verhoogd risico op radiologische achteruitgang na 2.3 jaar.

In de huidige studie, lijkt vooral de aanwezigheid van PDS, wat actieve synovitis reflecteert, een voorspeller te zijn voor radiologische progressie. Synoviale zwelling en in mindere mate effusie zijn eveneens belangrijk, maar deze kenmerken zijn vooral geassocieerd wanneer ze over de tijd aanwezig blijven.

Het aantal gewrichten met echografische ontstekingskenmerken was na 2.3 jaar evident toegenomen. Het is mogelijk dat dit het natuurlijk beloop van de ziekte is. Omdat handartrose nog niet is bestudeerd in longitudinale studies over langere termijn met behulp van MRI of echografie, is het natuurlijk beloop van ontstekingskenmerken niet bekend. De studie populatie bestaat uit patiënten met ernstige handartrose, wat blijkt uit de aanwezigheid van 18 (32%) patiënten met erosieve handartrose bij het eerste bezoek en de redelijk hoge score op de visuele analoge schaal betreffende handpijn. Meer longitudinale studies in verschillende patiënten populaties zijn nodig om het natuurlijk beloop van deze kenmerken te begrijpen.

Studies in erosieve handartrose

Hoofdstuk 7 beschrijft dat vingergewrichten van patiënten met erosieve handartrose meer PDS, synovitis en effusie wordt gevonden, maar niet meer synoviale zwelling, in vergelijking met vingergewrichten van patiënten met niet-erosieve handartrose. Verder gedetailleerd onderzoek maakt duidelijk dat vooral erosieve vingergewrichten meer ontstekingskenmerken hebben. Opmerkelijk genoeg zijn er in vergelijking met gewrichten van patiënten met niet-erosieve handartrose, ook in gewrichten zonder erosies van patiënten met erosieve handartrose meer echografische ontstekingskenmerken te vinden. De anatomische fases S (stationair gewricht), J (volledige gewrichtsspleetversmalling in het gewricht), E (erosief gewricht) en R (geremodelleerd gewricht) bevatten meer ontstekingskenmerken in vergelijking met vingergewrichten in N- (normaal gewricht) fase, maar PDS was vooral significant geassocieerd met E-fase.

Deze bevindingen ondersteunen onze hypothese dat ontsteking betrokken kunnen zijn bij de ontwikkeling van erosies. Deze studie suggereert dat erosieve artrose een fenotype is dat invloed heeft op alle vingergewrichten, niet alleen op de gewrichten

met erosies, en dit zou kunnen verklaren waarom de ontwikkeling van nieuwe erosies vaker gezien wordt bij patiënten die al een gewricht met een erosie hebben. Om de rol van ontsteking volledig te begrijpen bij de ontwikkeling van erosies zullen longitudinale studies moeten worden gedaan.

Nader onderzoek liet zien dat vooral de E-fases geassocieerd waren met actieve synovitis, weergegeven door positieve PDS. Dit in tegenstelling tot synoviale verdikking, wat vaak wordt gevonden bij handartrose, wat niet onderscheidt tussen de verschillende anatomische fasen van handartrose.

De diagnose van erosieve artrose is gebaseerd op subchondrale erosies in vingergewrichten op röntgenfoto's. Het is niet duidelijk hoeveel erosieve vingergewrichten nodig zijn om de diagnose erosieve artrose te stellen. Vaak wordt gesteld dat er meer dan één erosief gewricht aanwezig moet zijn. In deze studie hebben we de analyses gedaan met twee verschillende definities van erosieve artrose . De eerste definitie was de aanwezigheid van één of meer erosieve gewrichten bij een patiënt. De andere definitie was de aanwezigheid meer dan één erosieve vingergewrichten bij een patiënt. De resultaten van de analyses waren hetzelfde zowel wanneer de eerste, als de tweede definitie werd gebruikt. Dit bevestigt dat reeds één erosief vingergewricht bij een patiënt voldoende is om de diagnose erosieve artrose te stellen.

In de huidige studie werd de ziektelast van patiënten met en zonder erosieve artrose met elkaar vergeleken. Deze studie bevestigt de resultaten van eerdere studies dat patiënten met erosieve artrose een hogere ziektelast hebben.

Concluderend laat deze studie zien dat bij erosieve artrose meer ontsteking gevonden worden in vergelijking met niet-erosieve handartrose, zelfs in de vingergewrichten zonder erosies. Dit is al zo wanneer erosieve artrose wordt gedefinieerd als de aanwezigheid van één erosief vingergewricht. Of ontsteking bij erosieve artrose een oorzaak van het ontstaan van erosies is, of een resultaat van uitgebreide destructie in bepaalde gewrichten is niet uit deze studie af te leiden gezien het dwarsdoorsnede design van de studie; de bevinding dat ontstekingskenmerken ook meer worden gevonden in gewrichten zonder erosies bij erosieve artrose suggereert dat het een oorzaak is.

In hoofdstuk 8 werd de associatie tussen echografische ontstekingskenmerken en de ontwikkeling van erosies in handartrose onderzocht tijdens de follow up studie van 2.3 jaar. Deze studie laat zien dat de ontwikkeling van erosies geassocieerd is met matige tot ernstige synoviale zwelling en PDS op baseline in hetzelfde gewricht, onafhankelijk van structurele afwijkingen bij het eerste bezoek. Daarnaast werden associaties gevonden tussen de ontwikkeling van erosies met alle ontstekingskenmerken wanneer deze bij zowel het eerste bezoek als na 2.3 jaar in een gewricht aanwezig waren. Dit impliceert een rol voor ontsteking in de pathogenese van erosieve artrose en zou aanleiding

kunnen zijn voor de ontwikkeling van nieuwe therapeutische opties om de vorming van erosies een halt toe te roepen.

Betrouwbaarheid en validiteit van MRI bij handartrose
Hoofdstuk 9 beschrijft de bevindingen van een betrouwbaarheid en validiteit studie naar MRI kenmerken bij een populatie met ernstige handartrose. In deze ernstige, (pre)erosieve, handartrose populatie bleek MRI een betrouwbare methode te zijn om artrose karakteristieken bij handartrose te onderzoeken, zoals blijkt uit de goede tot excellente intra-lezer-betrouwbaarheid van alle MRI kenmerken.

MRI is een valide methode: criterium validiteit werd onderzocht door de vergelijking met echografie, röntgenonderzoek en klinische kenmerken en liet goede correlaties zien van 0.40 tot 0.80, met uitzondering van erosies.

Erosies gevonden bij MRI onderzoek versus erosies gevonden op de röntgenfoto lieten een zwakkere correlatie zien dan verwacht (r=0.32). Dit zou verklaard kunnen worden door het feit dat erosies op de MRI, op de röntgenfoto werden geclassificeerd als cysten, wat inderdaad het geval bleek te zijn wanneer we de aanwezigheid van cysten en/of erosies op röntgenfoto's en MRI vergeleken op gewrichtsniveau.

Bij het vergelijken van lichamelijk onderzoek en MRI afwijkingen bleken MRI afwijkingen zoals synovitis, osteofyten, maar ook abnormale collaterale ligamenten, beenmerg laesies en erosies, geassocieerd te zijn met pijn bij palpatie van individuele gewrichten.

De associatie tussen MRI kenmerken en pijn werd niet alleen onderzocht om de MRI te valideren ten opzichte van klinische kenmerken, maar ook om de oorzaak van pijn bij hand artrose beter te begrijpen. De aanwezigheid van matige/ernstige synovitis en beenmerg laesies bleken positief geassocieerd te zijn met pijn, wat suggereert dat ontsteking een onderliggende oorzaak is voor pijn bij handartrose.

Aanbevelingen voor de toekomst
In dit proefschrift werd de rol van synovitis onderzocht bij artrose. Op basis van de beschreven studies lijkt er een belangrijke rol te zijn weggelegd voor ontstekingskenmerken, omdat ze betrokken zijn bij de perceptie van symptomen en de achteruitgang van structurele schade over de tijd.

Deze conclusie is deels gebaseerd op de resultaten van een systematische review die we uitvoerden betreffende de associatie van pijn en ontstekingskenmerken bij knieartrose. Het bewijs hiervoor was echter slechts matig. Het is daarvoor nodig om meer onderzoek te doen om deze bevindingen te verduidelijken. Epidemiologische studies van goede kwaliteit die beenmerglaesies en effusie/synovitis onderzoeken zijn vooral noodzakelijk. Een ideale epidemiologische studieopzet zou een case cross-over studie zijn waar individuele MRI bevindingen in de aanwezigheid van kniepijn op een bepaald moment vergeleken wordt met MRI bevindingen van dezelfde patiënt zonder

knie pijn op een ander moment. In de ideale analyse van de data zou bovendien de grootte van de associatie worden gegeven en ook gecorrigeerd zijn voor verstorende factoren, zoals onder meer voor leeftijd, geslacht en BMI, en ook voor andere MRI kenmerken wanneer meerdere MRI kenmerken tegelijkertijd worden bestudeerd.

Sinds het voltooien van deze review, zijn meer studies gepubliceerd over dit onderwerp en een update van de huidige review zal in de nabije toekomst volgen.

Een belangrijke constatering die implicaties heeft voor verder onderzoek naar pijn bij handartrose, is dat de oorzaak van pijn multifactorieel is. Onafhankelijke associaties werden gevonden op gewrichtsniveau met zowel structurele afwijkingen als afwijkingen van de weke delen zoals het synovium. Echter op patiënt niveau zijn deze effecten moeilijker te onderscheiden. Dit wordt waarschijnlijk veroorzaakt door multifactoriële origine van pijn bij handartrose, waardoor in een patiënt verschillende factoren aanwezig kunnen zijn die pijn veroorzaken, zoals zowel benige als weke weefsel afwijkingen in de gewrichten, maar ook psychologische en genetische factoren. Het is daarom van belang bij het doen van onderzoek om associaties te analyseren op gewrichtsniveau, rekening houdend met het patiënteffect.

Meer longitudinale studies die echografische ontstekingskenmerken bestuderen bij handartrose zijn noodzakelijk. Omdat de onderzochte populatie van de ECHO studie een nogal ernstige handartrose populatie bleek te zijn, zal dit onderzoek herhaald moeten worden in een grotere handartrose populatie waarbij ook minder ernstige handartrose patiënten zijn betrokken. Aansluitend aan de huidige studie is een vervolgstudie gestart in het Leids Universitair Medisch Centrum in 2009, waar alle patiënten, die gediagnosticeerd werden door hun reumatoloog met handartrose, geïncludeerd zijn. Bij deze studie zijn röntgenfoto's en een MRI scan gemaakt. Om de rol van weke delen afwijkingen volledig te begrijpen is het aan te raden om ook echografie te includeren. Dit zou de mogelijkheid bieden om ontstekingskenmerken in een grotere, minder ernstigere hand artrose populatie te onderzoeken.

In onze studies is gebleken dat sommige echografische ontstekingskenmerken persisteren over de tijd, terwijl andere fluctueren. Recent zijn verschillende klinische trials naar de werkzaamheid van medicatie verricht met een follow-up tijd van ongeveer 3 maanden waarbij ontstekingskenmerken als uitkomst maat zijn meegenomen. Het is belangrijk te realiseren wanneer dergelijke trials worden verricht dat het natuurlijk beloop van een deel van de ontstekingskenmerken is dat zij fluctueren. Deze fluctuaties moeten niet worden gezien als een mogelijk behandeleffect. Daarom bevelen we aan om in eerste instantie grote observationele studies in handartrose populaties te verrichten om gedetailleerde kennis te vergaren over het natuurlijk beloop van ontsteking bij handartrose. Ten tweede bevelen wij aan om gerandomiseerde trials te verrichten met een placebo groep als controle.

Zoals dit proefschrift laat zien heeft echografie veel bijgedragen aan onze zoektocht naar de pathogenese van handartrose en onze kennis betreffende de etiologie van pijn en structurele achteruitgang bij handartrose verdiept. Een belangrijke taak voor de toekomst is om exactere definities te maken om artrosekenmerken te classificeren bij gebruik van moderne beeldvormende technieken. Uit verschillende studies komt naar voren dat de kenmerken die worden aangeduid als “mild” niet klinisch relevant bleken te zijn. We hebben tevens laten zien dat alhoewel echografie meer osteofyten onderscheidde in vergelijking tot röntgenfoto’s, associaties met pijn werden gevonden met beide modaliteiten. De klinische relevatie van de toegenomen sensitiviteit van de echografie betreffende osteofyten is daarom twijfelachtig. Daarnaast is het recent duidelijk geworden dat MRI scans van de knie van gezonde individuen een behoorlijke hoeveelheid afwijkingen kunnen tonen die worden beschouwd als horende bij artrose. Het heeft een hoge prioriteit om goede definities van te stellen wat normaal en wat abnormaal is wanneer men beeldvormende technieken gebruikt. Hetzelfde geldt voor de definitie van de diagnose handartrose, omdat de huidige definitie veel beperkingen kent. Om deze verbetering in definities te bewerkstellingen zijn we is in 2010 zijn we begonnen met een werkgroep binnen de OMERACT (Outcome Measures in Rheumatology). Middels deze werkgroep zullen definities voor MRI en echografie opgesteld worden en zal validiteit- en betrouwbaarheidsonderzoek worden verricht. Dit werk is momenteel gaande.

In het subtype erosieve handartrose werden meer ontstekingskenmerken gevonden, niet alleen in de erosieve gewrichten maar ook in de niet-erosieve gewrichten van patiënten met erosieve artrose. Sterker nog, er werden positieve associaties gevonden tussen echografische ontstekingskenmerken en de ontwikkeling van erosies. Deze bevindingen suggereren dat bij erosieve artrose systemische onderliggende mechanismen een rol spelen.

Tot slot zou een proof-of-concept studie meer inzicht geven in de klinische relevantie van ontsteking bij handartrose. Er zijn drie studies die het effect van corticosteroïden hebben onderzocht bij handartrose. Deze studies hebben echter niet geleid tot eenduidige conclusies. De studies hadden nogal wat beperkingen. Eén studie onderzocht de ontstekingskenmerken niet middels beeldvormende modaliteiten zoals echografie of MRI waardoor het moeilijk is het effect op ontsteking te beoordelen. Twee studies includeerden slechts een klein aantal patiënten en verrichtten analyses alleen op patiëntniveau, zonder rekening te houden met patiënteffecten. In deze twee studies die wel moderne beeldvormende technieken gebruikten, had er één een open studie design zonder placebo groep en de ander verrichtte slechts een 0.2 Tesla MRI zonder contrast. Een ideale proof-of-concept studie zou een gerandomiseerde trial zijn waarbij placebo met orale prednison toediening vergeleken zou worden gedurende minimaal een jaar en waarbij zowel klinische uitkomsten en ontsteking geëvalueerd zou worden. Osteofyten, gewrichtsspleetversmalling en erosies zouden eveneens onderzocht moeten worden middels radiografie en echografie of MRI.

LIST OF PUBLICATONS

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CURRICULUM VITAE

Marion Catharina Kortekaas (1974) werd geboren in Haarlem, alwaar zij de lagere en middelbare school doorliep. In 1993 begon zij met de opleiding geneeskunde aan de Vrije Universiteit in Amsterdam. Uit interesse in de immunologie, deed zij in 1997 haar wetenschappelijke stage aan het Centenary Institute of Cancer Medicine and Celbiology in Sydney, Australie, waar zij middels diermodellen het mechanisme van celdood via het Fas-Fas-ligand in T lymfocyten bestudeerde (hoofd: dr. J. Sedgwick). Na terugkomst in Nederland in 1998, zette zij de wetenschappelijke stage gedurende een jaar voort bij de afdeling Moleculaire celbiologie en immunologie van de Vrije Universiteit onder leiding van prof. dr. C.D. Dijkstra en bestudeerde zij de rol van diverse (auto)antilichamen bij apoptose van myeline. In 2000 werd het artsenexamen behaald en geboeid door de immunologie, startte zij haar opleiding tot reumatoloog in het Leids Universitair Medisch Centrum (opleider prof. dr. F.C. Breedveld, later opgevolgd door prof. dr. T.W.J. Huizinga). De vooropleiding werd gedaan in het Kennemer Gasthuis te Haarlem (opleider prof. dr. R.W. ten Kate).

Tijdens de specialisatie tot reumatoloog werd de interesse voor de musculoskeletale echografie gewekt en werd zij hierin opgeleid door dr. I. Watt, radioloog, tijdens een stage musculoskeletale echografie gedurende 6 maanden. In 2007 was zij betrokken bij de ontwikkeling van een preliminaire score methode voor onder andere inflammatoire echografische kenmerken bij handartrose door de internationale werkgroep DICHOA. Een en ander leidde tot de vraag of ontsteking een rol speelt bij de klinische verschijnselen en radiologische progressie bij handartrose, en onder leiding van prof. dr. G. Kloppenburg werd vervolgens de ECHO (EChografie bij Hand Osteoartrose) studie opgezet. Dit leidde uiteindelijk tot het voorliggende promotie onderzoek. 1 december 2008 rondde zij haar opleiding tot reumatoloog af en startte zij, naast de parttime onderzoekaanstelling in het LUMC, op 1 januari 2009 als reumatoloog in het Flevoziekenhuis te Almere.
Het ECHO onderzoek resulteerde in 2010 in het toekennen van de Young Investigator Award van de OARSI.

Tijdens het promotie traject specialiseerde zij zich verder in de echografie. Na voltooien van de verschillende EULAR sonography cursussen, werd zij in 2013 gecertificeerd als EULAR ultrasound teacher, en sindsdien is zij actief in het onderwijzen van musculoskeletale echografie waarbij ze optreedt als tutor en examinator bij IRON bijeenkomsten, en in 2014 als tutor bij de EULAR sonography course.

Daarnaast is zij verantwoordelijk voor de in 2013 geaccrediteerde verdiepingsstage echografie in het Flevoziekenhuis binnen de regionale opleiding vanuit het AMC te Amsterdam.

Sinds 2009 is zij actief in de speciale werkgroep handartrose binnen de OMERACT (Outcome Measures in Rheumatology) welke als doel heeft om te komen tot goede definities voor handartrose en het doen van onderzoek bij handartrose. Zij is in dit kader onder andere betrokken bij betrouwbaarheidsstudies, welke in samenwerking met de werkgroep Ultrasound van de OMERACT worden verricht.

Marion is getrouwd met Remco en zij hebben samen drie kinderen.

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