1

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]

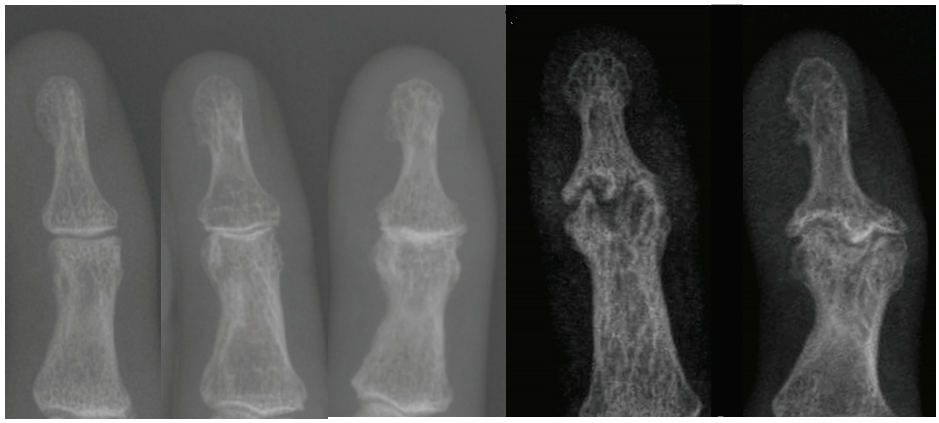
Imaging

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.

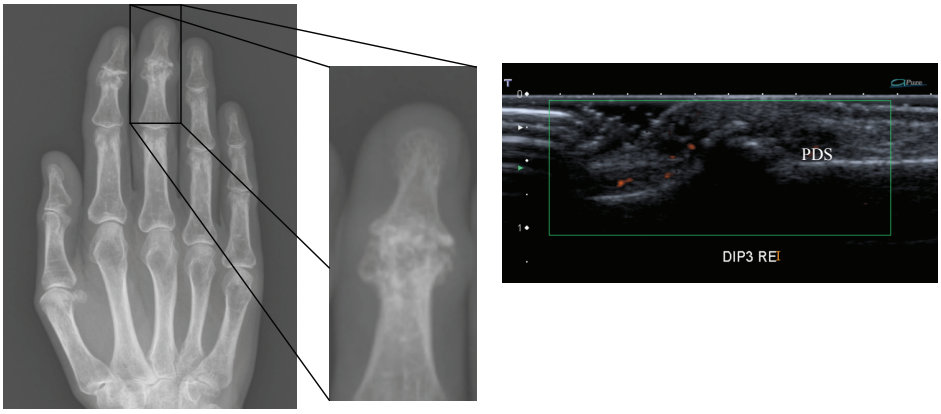


Figure 1.2 Images of erosive distal interphalangeal joint of the right hand. On the right the radiograph with in the window the affected joint, on the left the US image. Synovial thickening with power Doppler signal, and osteophytes grade 3 are depicted.

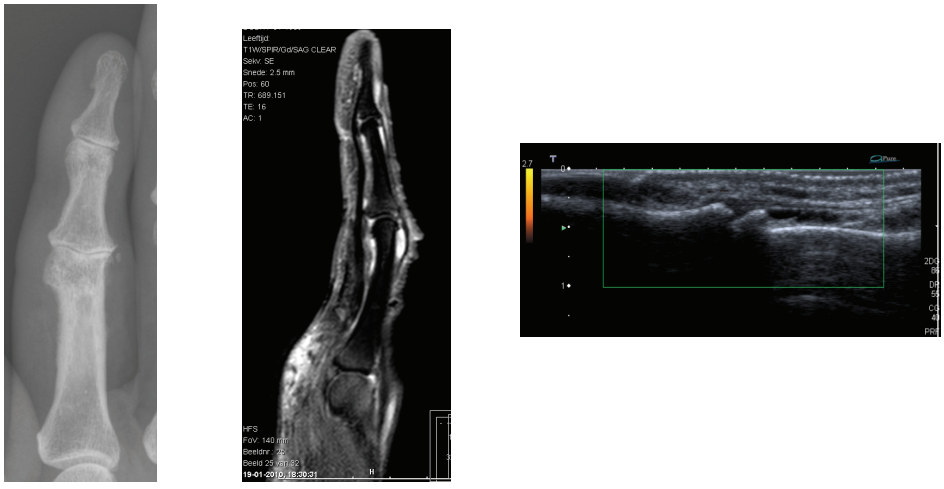


Figure 1.3 Images of the second finger of the right hand of an OA patient. On the left the radiograph of the same finger. In the middle a T1 weighted sagittal MRI image with gadolinium enhancement showing synovitis and on the right the ultrasound image of the DIP joint showing an osteophyte, effusion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