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Lessons learnt about two-year follow-up in hand osteoarthritis: the HOSTAS study.

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GENERAL INTRODUCTION AND OUTLINE

Osteoarthritis

Osteoarthritis (OA) is a common joint disease leading to pain, disability and joint destruction[1]. The Osteoarthritis Research Society International (OARSI) defined it as: 'Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness'[2].

Epidemiology

The prevalence and burden of OA increase with age. With an ageing population, including an ageing work population, OA results in large health and economic burden[3]. The World Health Organisation described it to be in the top ten of most debilitating diseases in developed countries, affecting 18% of women and 10% of men above 60 years of age[4]. Also in the Dutch population OA is in the top ten of diseases with highest disease burden as expressed in Disability Adjusted Life Years[5]. In 2016 1.25 million persons (7% of the Dutch population) were suffering from OA, of whom 40% (0.5 million) had peripheral OA including hand OA[6,7].

Predilection sites of OA are the knees, hips, spine and hands. Although the hand is one of the most prevalent locations of OA and the relevance of hand OA is more and more recognized, it remains a less studied subtype of OA.

When the prevalence of hand OA is estimated, a distinction is made between symptomatic hand OA and radiographic hand OA. In the elderly population symptomatic hand OA is seen in up to 26% of women[8]. Radiographic hand OA is more prevalent; the large majority of elderly people have radiographic signs of hand OA[9,10]. Although joint pain is associated with radiographic damage, not all joints with radiographic abnormalities are painful and vice versa[11].

Hand osteoarthritis

Pathophysiology and risk factors

Hand OA is a multifactorial whole-joint disease of which the pathogenesis is not fully understood. Pathogenic pathways are described in the definition of the OARSI. Where OA

was formerly considered a wear-and-tear disease, the new consensus is that OA is a low-grade inflammatory disease with inflammatory mediators released by cartilage, bone, and synovium[12].

Several systemic and local biomechanical risk factors for the emerge of hand OA have been recognized. The most important systemic factor is age: hand OA is seldom seen under 40 years. Another important factor is female sex; a meta-analysis showed that the relative risk for men was 0.81 (95% confidence interval [CI] 0.7-0.9) compared with women[13]. Obesity is also associated with hand OA[14]; the risk is twice as high in overweight individuals as in those with normal weight[15]. Since hand joints are non-weight bearing joints, this is thought to be due to metabolic activity of the fat tissue through hormones, growth factors and adipokines[16]. Other risk factors include family history, bone mineral density and (occupational) mechanical stress[17].

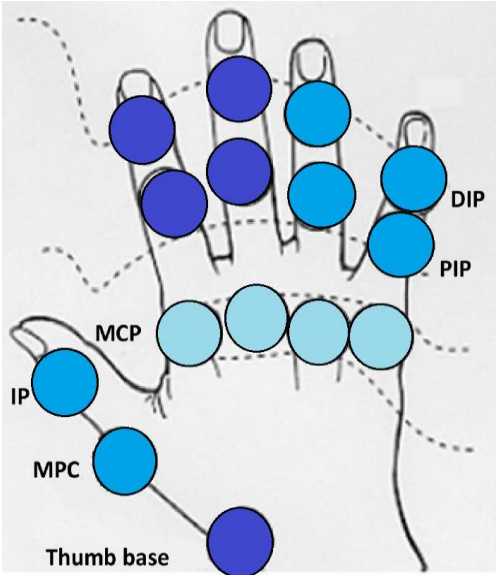

Figure 1. Affected hand joints, from most to least affected (dark to light blue). DIP: distal interphalangeal; PIP: proximal interphalangeal; IP: interphalangeal; MCP: metacarpophalangeal.

Clinical presentation and diagnosis

In hand OA all hand joints could be involved, but they are not equally affected. The most affected joints are the distal interphalangeal (DIP) joints, followed by the first carpometacarpal, proximal interphalangeal (PIP) and interphalangeal joints (Figure 1)[8]. Rarely, the metacarpophalangeal or other hand joints are involved. Hand OA comprises several recognized subsets, such as interphalangeal OA, thumb base OA and erosive

OA[17,18]. Clinical hallmarks are Heberden's nodes in the DIP joints and Bouchard's nodes in the PIP joints, which are associated with, but not the same as, underlying structural abnormalities[19,20]. The most important symptoms in hand OA are pain, aching, stiffness and functional impairment. Disability and pain are associated with reduced health-related quality of life (HRQoL)[17,21]. The impact of the disease can be profound; clinical burden can be as severe as in rheumatoid arthritis[22].

Hand OA is a clinical diagnosis according to the judgement of a physician, which is usually based on patient's history, risk factor assessment and physical examination. Additional tests such as blood tests for inflammatory markers are used only to exclude other diagnoses. X-rays are not necessary for the diagnosis, but can help in assessing disease severity. Other imaging modalities like magnetic resonance (MR) imaging have no place in the diagnostic process. The European League Against Rheumatism (EULAR) endorsed recommendations for the diagnosis which are a composite of several factors in a diagnostic ladder[18].

Patients who consult a physician with hand OA are heterogeneous in their presentation. Many patients with hand OA stay in primary care or do not even consult a doctor for their hand symptoms. The proportion of individuals with symptomatic hand OA not consulting a physician is unknown. Patients are referred to secondary care when the diagnosis is unclear or when symptoms such as pain and disability are therapy resistant. When patients are referred to secondary care, this could be to a rheumatologist, orthopedic surgeon, plastic surgeon or rehabilitation specialist, depending on the problem. The research in this thesis concerns patients who were referred to a rheumatology outpatient clinic.

Clinical management: treatment of hand OA

Treatment is multidisciplinary, involving non-pharmacological, pharmacological and surgical options[23]. Until now, no treatment to halt or reverse the disease exists for hand OA. Hence, the aim of treatment is to reduce symptoms and therewith maintain independence and quality of life. Education is a key component of disease management. Patients should receive information about the etiology, risk factors, disease course, self-help and treatment options, dealing with chronic pain and the principles of joint protection. Non-pharmacological treatment modalities consist of occupational therapy, physiotherapy, assistive devices and self-management education. Pharmacological treatment is only symptomatic, mostly with painkillers. These can be systemic painkillers with acetaminophen as a first choice, supplemented with non-steroidal anti-inflammatory drugs (NSAIDs) or cox-inhibitors on demand. Topical NSAIDs are as effective as systemic NSAIDs in relieving pain but do not have an increased risk of systemic side effects and are

therefore preferred as initial treatment[24]. The role of other anti-inflammatory medication such as corticosteroids or biologics is still undetermined. When non-pharmacological and pharmacological options are insufficient, hand surgery can be performed; this could be arthrodesis in the DIP joints or arthroplasty in the PIP joints. For the thumb base, several surgical options exist, of which trapeziectomy with ligament reconstruction and tendon interposition is the most commonly performed[25]. Procedures for early-stage disease include volar ligament reconstruction and dorsal wedge extension osteotomy and for later stages trapeziectomies, arthrodesis and joint replacement.

Disease course and risk factors for progression

The disease course of hand OA varies and is slowly progressive, taking years before structural damage develops[26,27]. Symptoms fluctuate over time and can both deteriorate and improve. This was illustrated in a follow-up study over a period of six years, which showed that clinical change and radiographic progression where not related[28]. Another follow-up study showed that already after a - for hand OA relatively short - period of two years, pain and function worsened and radiographic damage progressed[29]. Also in that study radiographic progression and changes in self-reported pain and function were not associated.

Risk factors that contribute to progression are largely unknown. A systematic review from 2013 found only limited evidence for a positive association between an abnormal scintigraphic scan and radiographic progression[30]. Other risk factors for clinical or radiographic progression that were evaluated were age, female sex, subset of hand OA, number and group of OA joints affected, painful joints, self-reported symptoms, radiographic OA, family effect, hormonal factors and body mass index and bony mineral density loss; all showing limited or inconclusive evidence. The authors concluded that studies on risk factors, especially for clinical progression, are warranted in order to identify modifiable factors in symptomatic patients with hand OA[30].

The discrepancy between progression of structural damage and course of symptoms might be explained by the contribution of psychosocial factors such as depression, illness perceptions, coping styles and anxiety[31–33]. These factors are promising candidates for intervention. For example, trials in other chronic conditions such as diabetes, heart disease and back pain, showed that illness perceptions can change and that this has positive effects on health outcomes[34–36]. Data on the role of psychosocial factors in hand OA is limited.

Research in hand osteoarthritis

Classification criteria and outcome measures

Although for the diagnosis of hand OA no fulfilment of diagnostic criteria is required, for research purposes classification criteria are often used. Although they have similar underlying algorithms, it should be noted that a clinical diagnosis and fulfilment of classification criteria are not the same. Amongst the most widely used classification criteria are the American College of Rheumatology (ACR) criteria (Table 1)[37].

For research it is crucial to define standardized outcome measures. Therefore, the Outcome MEasures in Rheumatology (OMERACT) hand OA working group has endorsed core outcome domains for symptom-modifying and structure-modifying clinical trials and observational studies (Figure 2)[38]. These are pain, physical function, patient global assessment, HRQoL, joint activity, hand strength and for structure-modifying trials and observational studies also structural damage and hand mobility. They also defined a core set of contextual factors for the same settings and a preliminary set of instruments for each core domain. For several domains, including joint activity, and contextual factors, including comorbidities, further research is necessary and a future research agenda was formulated.

In measuring disease status, a distinction is made between patient-reported outcome measures (PROMs) and other measures such as structural damage. Visser et al. provided an overview of instruments measuring the PROMs pain, physical function or patient's global assessment[39]. Amongst the most used questionnaires with good metric properties were the Australian/Canadian hand OA index and the Functional Index for Hand OsteoArthritis[40,41], which measure hand-specific pain and function.

Table 1. American College of Rheumatology classification criteria for osteoarthritis of the hand.

Hand pain, aching or stiffness AND 3 or 4 of the following features:

- Hard tissue enlargement of 2 or more of 10 selected 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 10 selected joints are the second and third distal interphalangeal (DIP), the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands (dark blue joints in Figure 1). MCP: metacarpophalangeal. References: Altman R et al. *Arthritis Rheum.* 1990;33:1601–10.

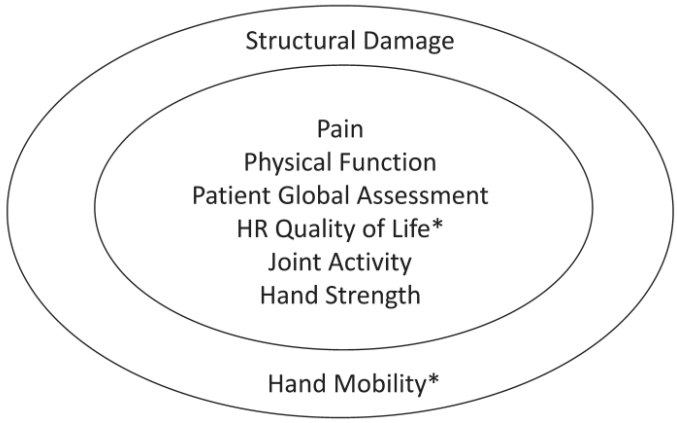

Figure 2. Preliminary set of endorsed core domains for hand osteoarthritis studies. Inner circle: Domains for all settings, i.e., clinical trials of symptom modification, clinical trials of structure modification, and observational studies. Outer circle: Domains for some settings, i.e., clinical trials of structure modification and observational studies. *Domains not mandatory as long as no disease-specific instruments are available. HR: health-related. Reference: Kloppenburg et al. *J Rheumatol.* 2015;42:2190–7.

Imaging

Radiographs

Although imaging is not essential for diagnosing hand OA, it is important for morphological assessment, for research and for assessment of progression over time. There are several imaging modalities to visualize hand OA. The most widely used imaging modality is radiography, which can be used to assess structural abnormalities[42]. A widely used semi-quantitative visual grading method is the Kellgren-Lawrence OA scoring system[43]. This is a general score on joint level from 0 (normal) to 4 (severely affected) taking into account all signs of OA; osteophytes, joint space narrowing (JSN), subchondral sclerosis and cysts. In Figure 3 scores are specified.

To enable quantification of separate features other methods are available. The OARSI atlas depicts scores for osteophytes and JSN separately[44]. This score is 0 (no osteophytes/no JSN) to 3 (large osteophytes/no joint space left). Since bone can be visualized on radiographs but cartilage cannot, the joint space is used as a surrogate marker to measure thickness of cartilage and cartilage loss. The Verbruggen-Veys score is used to score erosions, where the anatomical phase is scored from N = normal, S = stationary (osteophytes or little JSN), J = JSN, E = erosions to R = remodeled[45].

Signs of OA on radiographs reflect changes in the bone and cartilage. These features are progressive, irreversible and are markers of later stages of the disease. On the contrary, visualization of the disease in an earlier stage will aid understanding of which processes are involved and could facilitate identification of treatment targets.

Ultrasound and MRI

In recent years other imaging modalities such as ultrasound and MR imaging (MRI) have become available. These modalities are not only able to visualize structural abnormalities, but also soft tissue and subchondral bone and inflammation in these tissues. A 2014 review concluded that ultrasound and MRI seem to be the most promising imaging modalities to detect early-stage hand OA and for use in clinical trials, but more research on the value of these techniques is necessary[46]. Up till now, research on the role of inflammatory features is limited in hand OA[47].

Ultrasound enables visualization of soft tissue such as synovium[48]. Inflammatory ultrasound features (grey-scale synovitis and power doppler signal) are shown to be clinically important for their association with pain and radiographic progression[49–51]. Ultrasound is unable to visualize the subchondral bone.

Subchondral bone processes and synovial inflammation can also be visualized with scintigraphy, although this technique is non-specific and not easy in clinical practice since

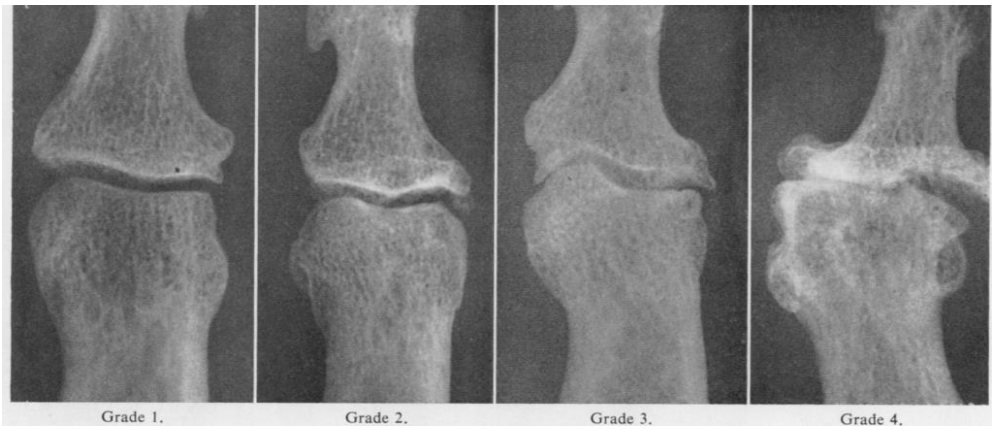

Figure 3. Grades in distal interphalangeal joints following Kellgren-Lawrence grading score.
Grade 0: No features of osteoarthritis; Grade 1: doubtful OA, small osteophyte; Grade 2: mild OA, definite osteophyte(s), unimpaired joint space; Grade 3: moderate OA, definite multiple or moderate osteophytes, diminution of joint space; Grade 4: severe OA, large osteophytes, joint space greatly impaired with sclerosis of sub-chondral bone. Reference: Kellgren JH and Lawrence JS. *Ann Rheum Dis.* 1957;16:494–502.

radiation is used. There is limited evidence for an association between an abnormal scintigram and radiographic progression based on studies done in the 1980s-1990s[30], supporting the hypothesis that synovial inflammation and bone processes play a role.

MR imaging has an advantage over ultrasound or radiographs because it enables visualization of all joint structures including the subchondral bone, where abnormalities are scored as bone marrow lesions (BMLs)[52,53]. These are lesions seen as high water signal in the subchondral bone. A recent review concluded that subchondral bone abnormalities correlate to a variety of histological features including fibrosis, cell death, inflammation and bone remodelling[54].Other than in rheumatoid arthritis, BMLs in osteoarthritic knees seem to represent areas of bone remodelling and fibrosis rather than inflammation (osteitis)[55,56]. In knees with OA, BMLs are thought to be the structural equivalent for malalignment, which is a major determinant for OA progression[57]. It is possible that this also applies for hand OA, since Tan et al. found BMLs at the insertion sites of collateral ligaments in hands, possibly representing 'bone trauma' or increased loading like in malalignment[58]. Nevertheless, BMLs are usually regarded as an inflammatory feature in hand OA. Other MRI-defined inflammatory features are synovitis and effusion. Using contrast-enhancement, synovitis can be seen as enhanced synovial thickening. One MR study in late-stage hand OA showed that BMLs and synovitis are of clinical importance for their association with pain and radiographic progression[59,60]. Effusion, i.e., excess fluid in the joint, is another inflammatory feature that is often seen with synovitis, but it is not included in hand OA MR scoring[52,53]. The few studies that studied effusion suggested that it is of clinical importance[49,50,61].

Challenges in hand osteoarthritis research

Hand OA is a variable disease regarding to joints, risk factors and symptoms involved but also in its disease course. This makes it difficult to define hand OA and to measure disease status and progression over time, lacking standardized outcome measures.

In order to develop new and better treatments and to enable identification of patients who will benefit from certain treatments it is pivotal to identify modifiable factors in disease status and progression. Such factors are not yet widely available for hand OA. It is also important to be able to measure disease status and to measure change or progression.

Therefore, in this thesis several factors were evaluated for their association with disease status and progression of hand OA. We studied progression over a follow-up period of two

years, for this could be the term of a clinical trial. Furthermore, clinimetric properties of outcome measure were assessed.

Aim of this thesis

1. To evaluate non-OA-related and OA-related factors that associate with disease status and progression of hand OA.
2. To investigate the role of MRI-defined inflammatory features in hand OA.
3. To evaluate clinimetric properties of outcome measures in hand OA.

Outline of this thesis

The research described in this thesis was mainly performed in the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort. The HOSTAS is an ongoing observational cohort study aimed at investigating determinants of outcome, utility of clinimetric instruments and the role of MRI-defined inflammation in primary hand OA. Between June 2009 and October 2015, 538 consecutive patients from the Leiden University Medical Center (LUMC) outpatient clinic were included. Primary hand OA was diagnosed according to the clinical judgement of the treating rheumatologist. Secondary hand OA (e.g., due to trauma) and hand symptoms which could be explained by another diagnosis were excluded. The LUMC serves both as secondary and tertiary referral center for rheumatic diseases, which allowed the inclusion of patients with primary hand OA in all disease stages. From January 2011 onwards, a number of extended questionnaires was added to the study protocol and from March 2011 to October 2012 eligible patients received contrast-enhanced hand MR imaging at baseline. Analyses in these subgroups with extra data are part of this thesis. Patients underwent a study visit (including physical examination, radiographs and MR imaging) every two years and filled out questionnaires yearly. Baseline and follow-up data are used to study progression.

Data from another hand OA cohort, the ECHO study, are also used in this thesis. The ECHO study is a longitudinal observational study in which consecutive patients with hand OA - fulfilling the ACR criteria - from the rheumatology outpatient clinic of the LUMC were enrolled between May 2008 and January 2010. Follow-up visits were performed between January 2011 and April 2012. Details of this study have been described by Kortekaas[50].

Part I: Factors associated with hand OA disease state and progression of hand OA.

In **chapter 2** we describe the clinical burden of hand OA in our HOSTAS cohort. Recent studies in many chronic (musculoskeletal) diseases suggest that the presence of non-disease-related factors such as comorbidities is associated with increased clinical burden. However, the role of comorbidities in hand OA disease burden remains unclear. Therefore, we study the association, and its clinical relevance, between comorbidities and general burden (HRQoL), as well as disease-specific burden (hand function and hand pain) in primary hand OA. We also use this chapter to describe the baseline clinical characteristics as well as the prevalent comorbidities in the complete HOSTAS cohort.

Not only patient-specific factors such as comorbidities, but also psychosocial factors like illness perceptions could play a role in PROMs such as disability. Knowledge about these factors could help explain variability in disease course and is of importance to design patient-tailored treatment strategies. Therefore, in **chapter 3** we investigate the association of illness perceptions with disability both cross-sectionally and longitudinally over a – for hand OA - short-term follow-up period of two years. We hypothesize that, like was previously shown in generalized OA and other musculoskeletal and chronic conditions, in hand OA negative illness perceptions associate with poor clinical outcome after two years.

Studies on MRI-defined inflammatory features in hand OA

Hand pain is a major symptom in hand OA and can lead to decreased quality of life. Therefore it is important to understand the underlying mechanisms attributing to pain. Ultrasound studies have shown that synovial inflammation is associated with the presence of hand pain. One MR imaging study in patients with late-stage hand OA showed the same for BMLs. However, no data on MRI-defined inflammatory features in earlier-stage hand OA were available and the relationship between BMLs and synovitis was not elucidated yet. Therefore, we investigate in **chapter 4** the association of MRI-defined BMLs and (teno)synovitis with joint pain in patients from the HOSTAS cohort who received contrast-enhanced MRI. Further, we investigate co-occurrence of BMLs and synovitis and their interaction with respect to pain to be able to determine which target is most promising to alleviate pain. We also investigate whether extensor tendon involvement plays a role.

From the study in **chapter 4** we learn that effusion, i.e., fluid in the joint, often appears to be present. Whether it coincides with synovial thickening or stands on itself is not clear. Furthermore, this is difficult to study, since no specific score for effusion exists. In **chapter**

5 we make an effort to define effusion on MR images and investigate its prevalence and its clinical role, separately from synovial thickening.

We learn in **chapter 4** that synovitis and BMLs are clinically relevant. Therefore, the longitudinal aspect of their relevance is explored in **chapter 6,** where we assess the association between synovitis and BMLs and radiographic progression after two years. Further, we explore the role of MRI-defined inflammatory features in onset and progression of radiographic osteoarthritic damage separately and we investigate progression on patient level.

Since in **chapter 4** and **chapter 6** synovitis and BMLs appear to have a clinically relevant role, predict disease course and are in potential modifiable factors, as a next step we investigate in **chapter 7** longitudinal MRI data over two years. We assess how MRI-defined synovitis develops over this time period and whether a decrease in synovitis is associated with a decrease in pain in the same hand joint.

Part II: clinimetric properties of outcome measures in hand OA

Hand osteoarthritis (OA) research is in need of disease-specific validated instruments to measure patient-reported outcomes. Self-reported painful joint count could be useful to assess pain and joint activity, while being less time-consuming than assessor-reported tender joint count. Therefore, in **chapter 8** we evaluate the metric properties of the self-reported painful joint count compared with assessor-reported tender joint count and evaluate whether the joint counts could be useful as instruments for assessment of joint activity.

Visual grading methods such as the OARSI atlas are considered the 'gold standard' to assess joint space. These methods are reader-dependent and even when the reader is experienced; assigning grades remains a subjective process in which the number of grades is limited from 0 to 3. Cartilage loss in small hand joints is particularly difficult to assess. Therefore, more objective and sensitive methods are preferred. With advancing technology, automated methods to assess joints space on radiographs have become available. In **chapter 9** we explore in the ECHO study whether semi-automatic joint space width measurements are valid and sensitive-to-change for the assessment of progression in hand osteoarthritis.

Finally, in **chapter 10** we summarize and review our findings and discuss future perspectives.

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