Inflammation as a target for treatment in hand osteoarthritis

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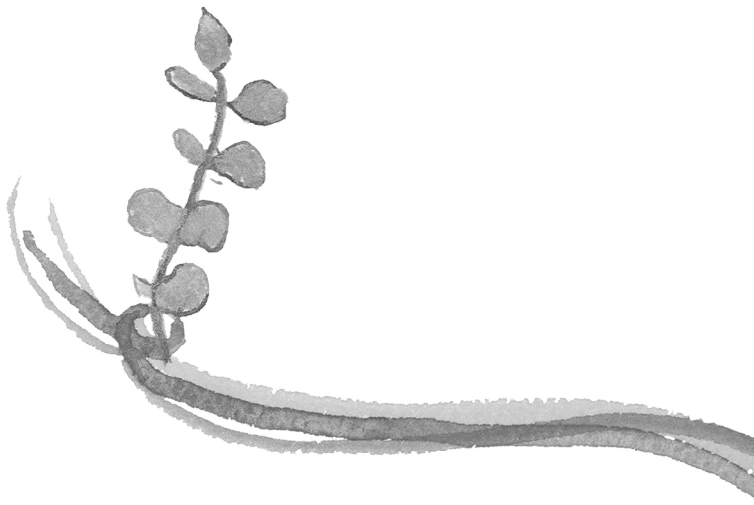
CHAPTER 1

General introduction



GENERAL INTRODUCTION

Osteoarthritis is a chronic rheumatic disease often occurring in knee, hip or hand joints. It is one of the most common rheumatic musculoskeletal disorders in the developed world, and a leading cause of disability among elderly.[1] The disease is not only associated with a substantial individual disease burden, but also with a significant socioeconomic burden.[2] The prevalence of osteoarthritis is high, and with age being an important risk factor, it is expected to rise with the aging population.[3] Hand osteoarthritis is among the most common osteoarthritis phenotypes.

Clinical presentation

Hand osteoarthritis is clinically characterized by bony enlargements and deformities of the hand joints, at times accompanied by soft tissue swelling.[4] It leads to pain, stiffness, reduced grip strength, loss of hand mobility, functional disability and aesthetic damage, resulting in a considerable disease burden with diminished quality of life.[5] The most commonly affected hand joints are the distal interphalangeal (DIP), proximal interphalangeal (PIP) and first carpometacarpal (CMC-1) joints.[5] The most commonly used classification criteria for hand osteoarthritis, which are based on a combination of clinical signs and symptoms, are those of the American College of Rheumatology (ACR, table).[6]

Though not included in current classification criteria, structural abnormalities that can be seen on radiographs are a hallmark of the disease. These include osteophytes, joint space narrowing and subchondral sclerosis.[7] In some patients, large subchondral erosions are present.

Within the disease, different subsets are recognised, based on distinct risk factor profiles and disease outcomes. Recognised subsets include interphalangeal osteoarthritis (with or without nodes), thumb base osteoarthritis and erosive osteoarthritis.[4] The presence of different subsets, as well as the simultaneous involvement of multiple hand joints, make hand osteoarthritis a disease that is complex to study.

Table. American College of Rheumatology classification criteria for hand osteoarthritis.[6]

Hand pain, aching or stiffness and at least 3 of the following:
• Hard tissue enlargement of at least 2 of 10 selected joints*
• Hard tissue enlargement of at least 2 DIP joints
• Less than 3 swollen MCP joints
• Deformity of at least 1 of 10 selected joints*

*Selected joints: DIP-2, DIP-3, PIP-2, PIP-3 and CMC-1 joints of both hands. CMC-1, first carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal

Prevalence

Hand osteoarthritis is highly prevalent, though estimates vary. Important determinants of prevalence estimates are the definitions used for the disease (most importantly radiographic versus symptomatic osteoarthritis), as well as population characteristics such as age (a steep increase of prevalence is seen with increasing age) and sex (women are more often affected than men).

Radiographic signs of hand osteoarthritis have been reported in up to 81% of the elderly population.[8,9] In a population-based study from the United States amongst individuals aged 60 and over, clinical signs of hand osteoarthritis in the form of bony enlargement of the DIP and PIP joints – termed Heberden's and Bouchard's nodes, respectively – were found in 58% and 30%, and deformities of the CMC-1 joint in 18% of the participants.[10] Symptomatic hand osteoarthritis however, is less often present. Age- and sex-adjusted prevalence estimates of symptomatic hand osteoarthritis vary between 2.0% and 6.2%.[10-13] However, in women over 70 years of age, the prevalence of symptomatic hand osteoarthritis is reported to be as high as 26%.[14]

Challenges in treatment

The first set of European League of Against Rheumatology (EULAR) recommendations for the treatment of hand osteoarthritis were published in 2007, and the ACR issued combined management recommendations for hand, hip and knee osteoarthritis in 2012.[15,16] Since then, however, many trials had been published, and it was timely to update the management recommendations.

Currently, disease-modifying treatments are not available. Treatment for hand osteoarthritis mainly targets symptom alleviation, though with limited efficacy.[17] The combination of a high disease-burden, high prevalence and limited (efficacy of) therapeutic options, results in an unmet need for novel therapies. However, the development of disease-modifying treatments is not without difficulties. A main reason for this, is that the aetiology of the disease is still largely unexplained, hampering identification of the most important tissue to target by treatment. Another important reason are shortcomings in outcome measurement in studies.

Inflammation in osteoarthritis

Classically, osteoarthritis has been viewed as a degenerative disease, mainly affecting the cartilage. In recent years, however, it has become clear that osteoarthritis is a disease affecting all joint compartments, including the synovium and subchondral bone.[3] At the start of this thesis, ultrasonography (US) and magnetic resonance imaging (MRI) studies had shown that synovial inflammation is frequently present in hand joints with osteoarthritis, especially the DIP and PIP joints.[18-20] It was also shown that synovial inflammation is associated with clinical outcomes, in particular pain,[18-21] and with increased radiographic damage over time.[22-26] Subsequently, longitudinal studies showed that an increase in inflammatory signs on MRI was associated with the development of joint tenderness, independent of structural progression.[27,28] The opposite was also found: decreasing synovial inflammation was associated with less joint tenderness.[28]

Another argument to support a role of inflammation in osteoarthritis comes from evidence that obesity is a risk factor for osteoarthritis in weight-bearing, but also in non-weight-bearing joints.[29,30] While the association between obesity and osteoarthritis in weight-bearing joints is likely primarily caused by the increased loading and mechanical stress on the joint, the association with osteoarthritis in non-weight-bearing joints is thought to be an indication of systemic effects of adiposity on joints.[31] It has been hypothesised that obesity, specifically the abundance of adipose tissue, creates an environment of systemic low-grade inflammation, sometimes referred to as *metaflammation*, with detrimental effects on the joints (figure 1).[32]

Even though at the start of this thesis several arguments existed for a role of inflammation in osteoarthritis, especially in non-weight-bearing joints such as the hand joints, it remained to be seen whether inflammation could subsequently also serve as a treatment target.

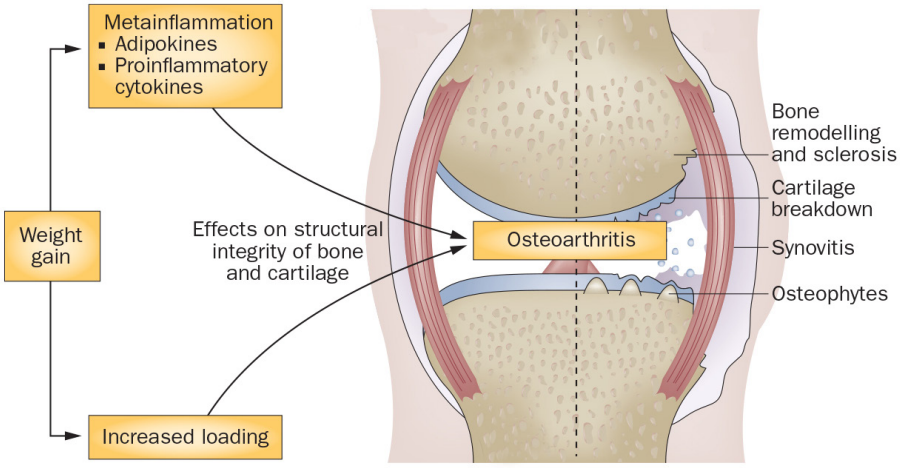


Figure 1. Mechanisms relating obesity to osteoarthritis. Obesity leads to increased joint loading, as well as increased fat mass, the latter creating an environment of low-grade inflammation, so-called *metaflammation*. The combined effect of mechanic and systemic effects can facilitate the pathogenesis of osteoarthritis, affecting bone, cartilage and synovial tissue. [*Figure adapted from Wluka AE, et al. Nat Rev Rheum 2013;9:225-35.*]

Outcome measurement

Another important factor in the limited insight in underlying pathophysiology and treatment options in hand osteoarthritis are shortcomings in outcome measurement in studies. High-quality outcome measurement in well-designed observational studies and clinical trials is warranted to advance our understanding of this complex disease. Measurement of relevant outcomes for different stakeholders (e.g., patients, clinicians, policymakers) is essential for research to influence clinical practice. Another important step involves standardisation of outcome measurement. Development of so-called 'core outcome sets' increases the number of studies that measure the same outcomes, which is needed to be able to combine data from different studies, allowing evidence synthesis and comparison of data sets.[33]

In the case of hand osteoarthritis, specific aspects of the disease that further complicate outcome measurement include the simultaneous involvement of multiple joints and the presence of multiple disease subsets or phenotypes. The first core outcome set in osteoarthritis was developed for knee, hip and hand osteoarthritis as one disease, though it is now recognised that hand osteoarthritis has several unique characteristics that sets it apart from knee and hip osteoarthritis, not in the least in its involvement of non-weight-bearing joints.[34]

In 2010, the Outcome Measures in Rheumatology (OMERACT) Hand Osteoarthritis Working Group was established to advance standardisation of outcome measurement in hand osteoarthritis. This working group agreed on a core domain set for clinical trials of symptom and structure modification and observational studies in hand osteoarthritis in 2014 (figure 2).[35]

Following the development of a core domain set, it should be decided how to measure these core domains, finally resulting in the definition of a 'core instrument set'. Before a measurement instrument can be endorsed as a core instrument, its metric properties should be rigorously investigated.[36] Awaiting more studies on the metric properties of many instruments used in hand osteoarthritis research, a core instrument set for hand osteoarthritis was still under development while writing this thesis.[35]

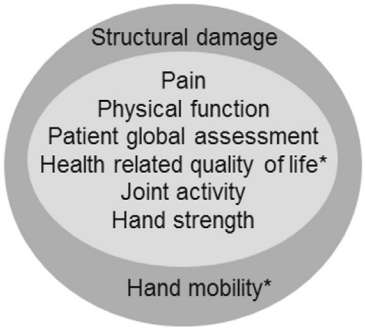


Figure 2. Core domain set for hand osteoarthritis studies. Inner circle: Domains for all settings (clinical trials of symptom modification or structure modification, and observational studies. Outer circle: Domains for some settings (clinical trials of structure modification and observational studies). *Domains not mandatory as long as no disease-specific instruments are available.
[*Figure from Kloppenburg M, et al. Osteoarthritis Cartilage 2015;23:772-86.*]

Aims of this thesis

This thesis had the following three aims:

1) To evaluate the current state of treatment options in hand osteoarthritis;
2) To investigate the role of inflammation as a treatment target in hand osteoarthritis; and
3) To facilitate development of new treatment options by improving outcome measurement in hand osteoarthritis.

THESIS OUTLINE

Current treatment options in hand osteoarthritis

This thesis was divided into three parts to address the three aims. Before we set out to investigate inflammation as a new treatment target in hand osteoarthritis, we wanted to gain better insight in currently available treatment options for hand osteoarthritis. These efforts are described in **Part I** of this thesis.

In **chapter 2** a narrative review of current treatment options in daily clinical practice for hand osteoarthritis is presented. In **chapter 3** the efficacy and safety of all therapeutic options for hand osteoarthritis was more thoroughly investigated in a systematic literature review and meta-analysis. Based upon this work, the EULAR recommendations for the management of hand osteoarthritis were revised and updated (**chapter 4**).

Inflammation as a treatment target

As became clear from studies described in **part I**, no disease-modifying therapies were available at time of conducting studies for this thesis, and effect sizes of available therapies for symptom relief were disappointing. It was evident that new treatment options were needed in the field of hand osteoarthritis. As mentioned before, previous research led us to believe that inflammation plays an important role and could serve as a new treatment target in hand osteoarthritis. In **part II** we used data from a clinical trial and several cohort studies to investigate whether inflammation could serve as a treatment target in hand osteoarthritis.

In **chapter 5** we describe the results of a fourteen-week placebo-controlled randomised clinical trial of low-dose oral prednisolone in hand osteoarthritis patients, the HOPE study. The rationale behind this proof-of-concept study was based on prednisolone's well-known potent anti-inflammatory characteristics, providing us with the opportunity to investigate whether inflammatory signs seen in hand osteoarthritis patients can be modulated, and whether this consequently has beneficial effects on patients' signs and symptoms.

So far, studies of the role of inflammation in hand osteoarthritis had mainly focused on hand osteoarthritis as a whole, or specifically on the DIP and PIP joints. The thumb base, however, is also often involved in hand osteoarthritis, and osteoarthritis at this site has been recognised as a distinct hand osteoarthritis subset.[4] The thumb base complex includes the CMC-1 and scaphotrapeziotrapzoid (STT) joints. It has certain unique qualities, such as a high range of motion and bearing of high loads, setting it apart from other hand joints.[37] Mechanical loading seems to play a crucial role in thumb base osteoarthritis development, in contrast to finger osteoarthritis. This led to the hypothesis that inflammation may play a different role in finger and thumb base osteoarthritis. In **chapter 6** we summarised the efficacy and safety of different intra-articular therapies, including intra-articular glucocorticoid injections, in thumb base and finger osteoarthritis in a systematic literature review and meta-analysis. Making use of observational data from three cohorts of hand osteoarthritis patients from the LUMC, we assessed the relative contribution of osteophytes and synovitis to pain in thumb base osteoarthritis in **chapter 7**. In **chapter 8** we describe the course of inflammation in relation to clinical signs and symptoms in the thumb base of hand osteoarthritis patients over two years.

To conclude **part II** of this thesis, we viewed the role of inflammation in osteoarthritis from a broader perspective, taking the known association between obesity and osteoarthritis as a starting point. As noted before, it has been suggested that obesity not only leads to increased mechanical stress across weight-bearing joints, but that it also has systemic metabolic effects which may induce joint damage. In fact, adipose tissue is known to be a source of several bioactive factors, including adipokines, cytokines, chemokines and complement factors.[38] Of these, adipokines have been postulated as a potential link between obesity and osteoarthritis.[39,40] In

chapter 9 we used data from the NEO study, a large population-based cohort study including 6671 individuals to investigate whether adipokines are mediators in the relationship between obesity and osteoarthritis.[41]

Outcome measurement

The studies described in **part I** did not only shed light on the available evidence for different therapeutic options in hand osteoarthritis, it also made clear that outcome measurement in trials is still very diverse and of variable quality. **Part III** of this thesis focusses on our efforts to improve outcome measurement in hand osteoarthritis research. It is a compilation of studies of several measurement instruments, guided by the research agenda developed by the OMERACT Hand Osteoarthritis Working Group in 2014.[35]

Homogenising the use of outcome measures is important to progress hand osteoarthritis research. To support the choice of one instrument over another, in-depth assessment of available instruments is warranted. The visual analogue scale (VAS) and numerical rating scale (NRS) are widespread instruments to assess pain and patient global assessment. Besides, several hand-specific pain and function questionnaires are in use, most importantly the Australian/Canadian Hand Osteoarthritis Index (AUSCAN), Functional Index in Hand Osteoarthritis (FIHOA) and Michigan Hand Outcomes Questionnaire (MHQ). No consensus has yet been reached as to which of these questionnaires should preferentially be used in hand osteoarthritis research. For other core domains, such as hand mobility and health-related quality of life, no disease-specific instruments are available yet.

In **chapter 10**, we describe the development of reference curves, analogous to children's growth curves, of the AUSCAN to better interpret AUSCAN scores in future studies. In **chapter 11**, the clinimetric properties of the MHQ were assessed and compared to the more often used AUSCAN, FIHOA and VAS pain. In **chapter 12** we aimed to identify an appropriate instrument to measure hand mobility in hand osteoarthritis patients, since no disease-specific instrument to measure this outcome had been available thus far. In **chapter 13** we present a report of the discussions of the OMERACT Hand Osteoarthritis Working Group at the 2018 OMERACT meeting, including a review of the measurement properties of VAS and NRS to measure pain and patient global assessment in hand osteoarthritis. In this report, an updated research agenda is also presented to guide future outcome research in hand osteoarthritis, with the ultimate goal of developing a standardised core instrument set to be used in all hand osteoarthritis studies.

To gain more insight into the thumb base osteoarthritis phenotype specifically, we present the development of the first magnetic resonance imaging (MRI) scoring system for the thumb base and its cross-sectional reliability in **chapter 14**. An atlas to facilitate scoring with this scoring system is presented in **chapter 15**. In order to be able to use the scoring system in follow-up studies, its longitudinal reliability was investigated in **chapter 16**.

To conclude, **chapter 17** presents a summary and general discussion of the findings of this thesis, as well as the future perspectives resulting from our conclusions. A summary of this thesis in Dutch is provided in **chapter 18**.

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