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Inflammation as a target for treatment in hand osteoarthritis

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INFLAMMATION AS A TARGET FOR TREATMENT
IN HAND OSTEOARTHRITIS

Féline Pascale Bernadette Kroon

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INFLAMMATION AS A TARGET FOR TREATMENT
IN HAND OSTEOARTHRITIS

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op
dinsdag 3 november 2020
klokke 15:00 uur

door

Féline Pascale Bernadette Kroon

geboren te Nijmegen
in 1992

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Voor bomma

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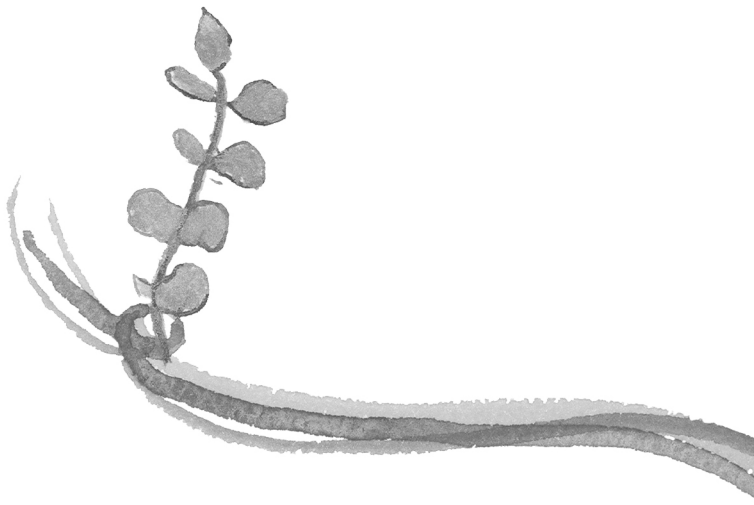
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CHAPTER 1

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.

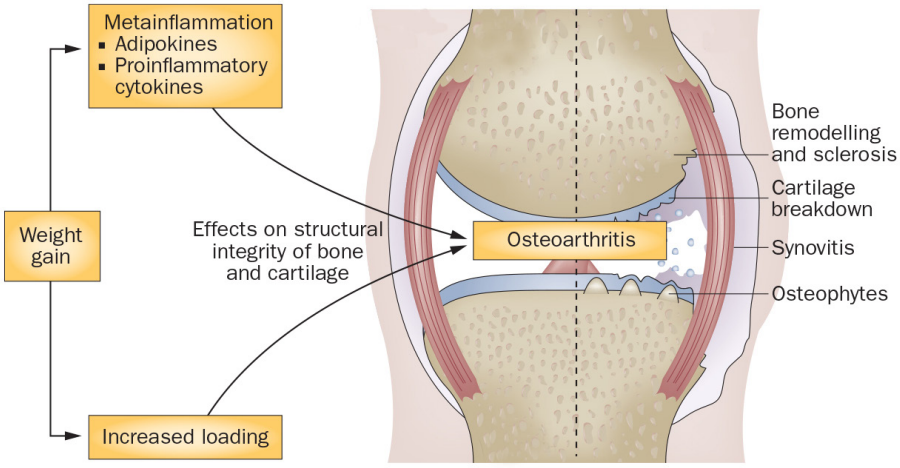


Figure 1. Mechanisms relating obesity to osteoarthritis. Obesity leads to increased joint loading, as well as increased fat mass, the latter creating an environment of low-grade inflammation, so-called *metaflammation*. The combined effect of mechanic and systemic effects can facilitate the pathogenesis 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]

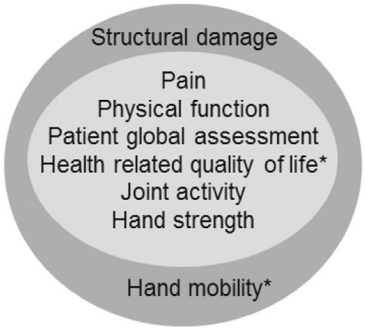


Figure 2. Core domain set for hand osteoarthritis studies. Inner circle: Domains for all settings (clinical trials of symptom modification or structure modification, and observational studies. Outer circle: Domains for some settings (clinical trials of structure modification and observational studies). *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**.

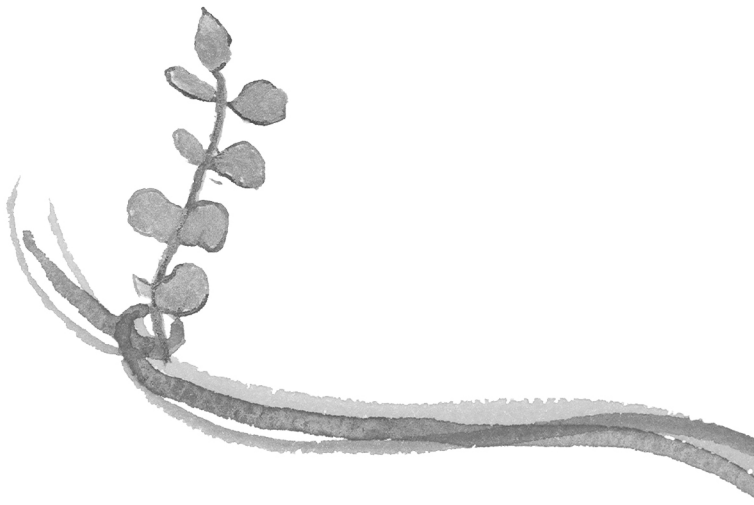
REFERENCES

1. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1603-58.
2. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437-41.
3. Bijlsma J, Berenbaum F, Lafeber F. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115-26.
4. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
5. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
6. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
7. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
8. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
9. Zhang Y, Xu L, Nevitt MC, et al. Lower prevalence of hand osteoarthritis among Chinese subjects in Beijing compared with white subjects in the United States: the Beijing Osteoarthritis Study. *Arthritis Rheum* 2003;48:1034-40.
10. Dillon CF, Hirsch R, Rasch EK, et al. Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991-1994. *Am J Phys Med Rehabil* 2007;86:12-21.
11. Andrianakos AA, Kontelis LK, Karamitsos DG, et al. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. *J Rheumatol* 2006;33:2507-13.
12. Carmona L, Ballina J, Gabriel R, et al. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 2001;60:1040-5.
13. Grotle M, Hagen KB, Natvig B, et al. Prevalence and burden of osteoarthritis: results from a population survey in Norway. *J Rheumatol* 2008;35:677-84.
14. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
15. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
16. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012;64:465-74.
17. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242-51.
18. Keen HI, Wakefield RJ, Grainger AJ, et al. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum* 2008;59:1756-63.
19. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
20. Kortekaas MC, Kwok WY, Reijnierse M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367-9.
21. Liu R, Damman W, Reijnierse M, et al. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. *Osteoarthritis Cartilage* 2017;25:1093-99.
22. Kortekaas MC, Kwok WY, Reijnierse M, Kloppenburg M. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. *Ann Rheum Dis* 2015;74:1720-4.
23. Mancarella L, Addimanda O, Pelotti P, et al. Ultrasound detected inflammation is associated with the development of new bone erosions in hand osteoarthritis: a longitudinal study over 3.9 years. *Osteoarthritis Cartilage* 2015;23:1925-32.
24. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. *Ann Rheum Dis* 2016;75:117-23.

25. Mathiessen A, Slatkowsky-Christensen B, Kvien TK, et al. Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years. *Ann Rheum Dis* 2016;75:825-30.
26. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-17.
27. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Ann Rheum Dis* 2016;75:702-8.
28. Van Beest S, Damman W, Liu R, et al. In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study. *Osteoarthritis Cartilage* 2019;27:1048-56.
29. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:507-15.
30. Yusuf E, Nelissen RG, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* 2010;69:761-5.
31. Visser AW, de Mutsert R, le Cessie S, et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Ann Rheum Dis* 2015;74:1842-7.
32. Berenbaum F, Wallace IJ, Lieberman DE, et al. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2018;14:674-81.
33. Williamson PR, Altman D, Blazeby J, et al. Driving up the quality and relevance of research through the use of agreed core outcomes. *J Health Serv Res Policy* 2012;17:1-2.
34. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;24:799-802.
35. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies. *J Rheumatol* 2015;42:2190-7.
36. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
37. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
38. Neumann E, Junker S, Schett G, et al. Adipokines in bone disease. *Nat Rev Rheumatol* 2016;12:296-302.
39. Berry PA, Jones SW, Cicuttini FM, et al. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. *Arthritis Rheum* 2011;63:700-7.
40. Dumond H, Presle N, Terlain B, et al. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 2003;48:3118-29.
41. De Mutsert R, den Heijer M, Rabelink TJ, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol* 2013;28:513-23.

PART I

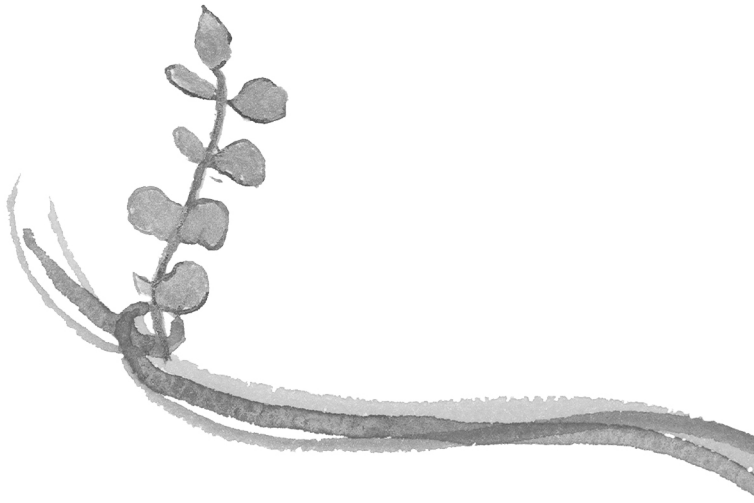
Current treatment





CHAPTER 2

Management of hand osteoarthritis



Féline Kroon*
Margreet Kloppenburg*

*co-first authorship

UpToDate, Curtis MR (Ed). Waltham, MA, 2020 (Version 5.0)

INTRODUCTION

Hand osteoarthritis (OA) is one of the most common OA phenotypes, and it has a high clinical burden. It leads to joint pain, disability, decreased hand strength, and a reduced quality of life. Management strategies target symptom alleviation, involving a combination of non-pharmacologic, pharmacologic and surgical interventions.[1-4] While there is ongoing research to address the need for disease-modifying OA drugs (DMOADs), none have gained regulatory approval.

The management of hand OA will be reviewed here. The history and examination of the adult with hand pain, as well as the diagnosis, clinical manifestations, and management of OA affecting other joints are presented separately. (See "History and examination of the adult with hand pain" and "Clinical manifestations and diagnosis of osteoarthritis", section on 'Hand' and "Overview of the management of osteoarthritis" and "Management of knee osteoarthritis" and "Management of moderate to severe knee osteoarthritis".)

GENERAL PRINCIPLES

In addition to local signs and symptoms, the patient's beliefs, preferences, and expectations should be taken into account when managing hand osteoarthritis (OA). Educating patients about their disease and encouraging self-management are important features of OA treatment. (See "Overview of the management of osteoarthritis", section on 'General principles'.)

Education – The aim of education is to enhance the patient's understanding of their disease. Although the clinical benefits appear to be small, educating patients about the nature and course of the disease and their role in self-management principles and treatment options in hand OA is essential. Focus group interviews have shown that hand OA patients often perceive a lack of support and understanding of the impact of the disease on the individual.[5] Patients also described a lack of available information on how to manage their disease and contradictory advice from different health care professionals about possible treatment options. (See "Overview of the management of osteoarthritis", section on 'Education'.)

Self-management programs – Self-management programs are more complex interventions targeted at behavior modification that encourage patients to take an active role in the management of their condition. Two well-designed randomized controlled trials specifically targeting patients with hand OA have reported contradictory results. In one trial, there were no effects of an intensive treatment program including self-management, joint protection, and exercises.[6] The other randomized trial showed that a self-management program specifically targeting joint protection led to small improvements in pain and function after six months (measured as number of Osteoarthritis Research Society International [OARSI] responders), although this was not maintained over 12 months.[7] Joint protection encompasses specific

education and training in ergonomic principles and pacing of activity. Additional evidence for the effectiveness of self-management education programs comes from several systematic reviews and meta-analyses showing that these programs are effective in addressing pain and function, although effect sizes are very small and clinically negligible.[8,9] More evidence is needed to determine whether there is an optimal combination of non-pharmacologic therapies to offer patients as part of a multidisciplinary program. (See "Overview of the management of osteoarthritis", section on 'Self-management' and "Overview of joint protection".)

MANAGEMENT

General approach — A combination of nonpharmacologic and pharmacologic interventions is typically used in clinical practice for the management of hand osteoarthritis (OA), prioritizing therapies that are safer (eg, topical nonsteroidal antiinflammatory drugs [NSAIDs]) before considering drugs that can potentially cause adverse effects (eg, oral NSAIDs). The choice of therapy will also be guided by the presence of other joint involvement and comorbidities. Surgical interventions are generally reserved for patients with disabling symptoms refractory to nonpharmacologic and pharmacologic interventions. (See "Overview of the management of osteoarthritis", section on 'Overview of management' and "Comorbidities that impact management of osteoarthritis".)

It is also important to recognize the presence of different hand OA subsets, which often coincide, and may influence some treatment options. For example, patients with thumb-base OA may be more likely to benefit from splinting or surgical interventions. By contrast, erosive OA is known to have a more inflammatory phenotype, although no distinct treatment strategies are recommended for this subset. A more detailed description of the subsets of hand OA, including nodal, erosive, and thumb-base OA, can be found elsewhere. (See "Clinical manifestations and diagnosis of osteoarthritis", section on 'Nodal osteoarthritis' and "Clinical manifestations and diagnosis of osteoarthritis", section on 'Erosive osteoarthritis'.)

Finally, it should be noted that when comparing the effectiveness of different treatment strategies for patients with hand OA, the effect sizes of various nonpharmacologic and pharmacologic interventions are generally low.

Our overall management strategy is generally consistent with guidelines developed by professional organizations, including the American College of Rheumatology and Arthritis Foundation,[3,4] the European League Against Rheumatism,[10] and the National Institute for Health and Care Excellence.[2]

Initial management

Splints and other assistive devices — We suggest the use of splints for hand OA for pain relief, particularly in patients with symptomatic thumb-base OA. Splints and other assistive devices can be offered before or in combination with pharmacologic interventions, depending on the severity and location of symptoms. In some cases, splints for OA of the distal interphalangeal (DIP) joint may also be helpful, although these are less frequently prescribed. The type of splint

and the best instructions for splint use have not been compared in high-quality studies, and this should therefore be a shared decision with the patient. Assistive devices other than splints are also effective in improving a patient's satisfaction with activity performance. An assistive device is equipment that can increase, maintain, or improve functional capabilities of patients with hand OA. Examples include orthoses or splints but also cutlery with built-up handles, ergonomic pens, and devices to facilitate opening bottles, cans, or jars.

Splints are designed to support, protect, or immobilize a joint, which in hand OA patients is usually the thumb base. Many different splints are available: prefabricated or custom-made; incorporating only the first carpometacarpal (CMC-1) joint or also the wrist or the first metacarpophalangeal (MCP-1) joint; and fabricated of rigid, semirigid, or soft material. Instructions for use are also variable, including splints that are to be worn full time, whenever symptoms occur, during activities, or during the day or at night only. A systematic review summarized the evidence from nine studies investigating the effects of splints for thumb-base OA, although only two of these studies were found to be suitable for inclusion in a meta-analysis, which showed a significant but small effect on pain (effect size [ES] 0.37, 95% CI 0.03-0.71).[11] The type of orthosis to prescribe and the instructions for use can be a shared decision with the patient because there is no evidence available to guide this decision. In both studies, a rigid custom-made splint covering the thumb base and the MCP-1 joint was used, which was to be worn either during the day only[12] or during the night only.[13] Another meta-analysis showed that thumb-base splints were only effective when used for prolonged periods of time (at least three months).[14]

Splints for OA in the DIP joint are also available but are used less frequently and have not been investigated extensively. One prospective cohort study with 25 patients demonstrated that splint treatment significantly reduced hand pain,[15] though an open-controlled trial investigating DIP splints in 26 patients found no positive effects of nighttime DIP joint splinting on pain or function at three months follow-up and a small positive effect on pain after six months.[16]

One randomized controlled trial with 70 patients investigated the effect of other assistive devices, showing that the use of assistive devices in general significantly improved activity performance and satisfaction with performance after a three-month follow-up.[17]

Topical NSAIDs — Topical treatments can be an attractive treatment modality, especially in older adult patients with comorbidities. We suggest topical NSAIDs rather than oral NSAIDs for patients with hand OA. Topical NSAIDs appear to be effective for hand OA and do not seem to be associated with an increased risk of systemic adverse events.

Topical NSAIDs have not been studied as extensively in hand OA patients as they have been in patients with knee OA. A Cochrane review including 39 studies demonstrated that topical NSAIDs were effective in relieving pain in patients with chronic musculoskeletal complaints, mostly due to OA (number needed to treat 10, 95% CI 7 to 16).[18] Four studies specifically included hand OA patients, evaluating topical diclofenac (three trials) and ibuprofen (one trial) and showing similar positive results. One of these trials compared a topical with an oral NSAID in hand OA patients, demonstrating similar pain relief but fewer adverse events in the topical NSAID group.[19] Generally, topical application of NSAIDs was

well tolerated in the short to intermediate term evaluated in the randomized controlled trials included in the Cochrane review, although there was evidence of a slight increase in local adverse events (mostly mild skin reactions). (See "Management of knee osteoarthritis", section on 'Topical NSAIDs'.)

Long-term tolerability of up to 12 months of topical NSAIDs in older adult patients and patients with elevated risk of gastrointestinal, cardiovascular, and renal adverse events has been evaluated in a post hoc analysis of open long-term extension studies.[20] Results of this study, performed in 947 knee OA patients, suggest that diclofenac sodium gel is also safe for long-term use in patients at high risk of NSAID-related adverse events.

Exercise — We suggest hand exercises for patients with hand OA to improve function and muscle strength and reduce pain. Exercise regimens for hand OA usually involve both range of motion and strengthening exercises and are often home-based. Occupational therapy may provide patients with useful information regarding hand exercises.[7] A Cochrane review pooled results from five trials of variable quality, mainly concentrating on patients with thumb-base OA, and found that hand exercises led to modest improvements in hand pain (standard mean difference [SMD] -0.27, 95% CI -0.47 to -0.07), function (SMD -0.28, 95% CI -0.58 to 0.02), and stiffness (SMD -0.36, 95% CI -0.58 to -0.15) in the short term.[21] The exercises were generally well tolerated.

Inadequate response to initial management

Oral NSAIDs — We recommend oral NSAIDs for patients who respond inadequately to other therapies. Oral NSAIDs should be used at the lowest effective dose and for the shortest duration possible due to the well-known potential gastrointestinal, cardiovascular, and renal toxicities. This is especially relevant for patients with OA, who are often older and frequently have one or more comorbidities. A more detailed discussion on the choice of NSAIDs for the treatment of OA is presented separately. (See "Management of moderate to severe knee osteoarthritis", section on 'Choice and use of oral NSAID' and "Nonselective NSAIDs: Overview of adverse effects" and "NSAIDs: Adverse cardiovascular effects".)

In hand OA, only four trials have been conducted evaluating the efficacy of meclofenamate,[22] ibuprofen,[23] and lumiracoxib.[24] Of these preparations, meclofenamate is not often used due to the high rate of gastrointestinal side effects, and lumiracoxib has been withdrawn from most markets due to concerns of adverse events. These trials all demonstrated the superiority of NSAIDs over placebo with regard to pain relief. A meta-analysis of two of these trials resulted in an effect size similar to that in knee OA studies (ES 0.4, 95% CI 0.2 to 0.6).[1] The effectiveness of NSAIDs has been studied more extensively in patients with knee OA and has been shown to be superior in pain relief compared with both placebo and acetaminophen, although the additional pain relief of oral NSAIDs compared with acetaminophen is limited.[25] (See "Management of moderate to severe knee osteoarthritis", section on 'Efficacy of oral NSAIDs'.)

Refractory symptoms

Surgery — When nonpharmacologic and pharmacologic options do not result in adequate relief of symptoms, we refer patients for surgical management. Surgical intervention is generally reserved for patients with severe disease and refractory symptoms, whose quality of life is severely impacted. Several surgical options are available, the choice of which is mainly dependent on the type of joint causing complaints (DIP joint, proximal interphalangeal [PIP] joint, or CMC-1 joint); patient characteristics, including functional demands and personal preference; and preferences of the surgeon. Surgical intervention is most often done in thumb-base OA, although arthroplasty and arthrodesis of the DIP and PIP joints are not uncommon in severe hand OA patients.

Available surgical techniques for CMC-1 OA include trapeziometacarpal arthrodesis, trapeziectomy (with or without ligament reconstruction and tendon interposition [LRTI]), and trapeziometacarpal joint replacement. A Cochrane review from 2015 summarized the available evidence of seven different surgical techniques for thumb OA from 11 studies.[26] Most studies were low quality and none of the trials compared surgery with sham surgery or nonsurgical interventions. No single technique was clearly superior to another in terms of pain and physical function. In general, more complex procedures led to more complications. A systematic review with less stringent inclusion criteria, leading to inclusion of 35 studies, led to similar conclusions.[27] Trapeziectomy with or without LRTI is probably the most prevalently used surgical technique for thumb-base OA.

Even fewer studies have investigated surgical interventions in the finger joints, which are mostly retrospective case series often reported by an advocate of the technique.[28,29] For finger OA, the two main surgical techniques are arthroplasty and arthrodesis. There are no trials that compare surgical treatment of finger OA with a sham procedure or nonsurgical intervention. In general, arthroplasty has the advantage of retaining some joint motion, whereas with arthrodesis, range of motion is completely lost. The disadvantages of arthroplasty, however, are that it is associated with more complications and instability compared with arthrodesis.[30] Arthroplasties are typically done in PIP joints except for the index finger and arthrodesis in DIP joints.[29]

THERAPIES WITH LIMITED EFFICACY OR OF UNCERTAIN BENEFIT

Based on limited data and indirect evidence (eg, from knee osteoarthritis [OA]), there are other therapies that are of uncertain benefit in hand OA and thus not routinely recommended. Furthermore, several therapies exist that we do not routinely recommend due to lack of data demonstrating efficacy.

Acetaminophen — We do not routinely initiate treatment with acetaminophen for hand OA due to increased evidence of its limited efficacy on pain and the safety concerns pertaining to its use. No randomized trials have been published to investigate the efficacy of acetaminophen in hand OA, and its effects, if any, are likely small, based on indirect evidence from knee OA. A

network meta-analysis of pharmacologic interventions for knee OA concluded that the effect size (ES) of acetaminophen on pain at three months compared with oral placebo was small and not clinically relevant (ES 0.18, 95% CI 0.04 to 0.33).[25] In addition to the limited effects on pain, there is also a potential risk of harm associated with acetaminophen use. One review of eight observational cohort studies including more than 650,000 participants found a dose-response relationship between acetaminophen and increasing incidence of mortality and cardiovascular, gastrointestinal, and renal adverse events; however, limited conclusions can be drawn due to serious limitations in the study design.[31] (See "Management of knee osteoarthritis", section on 'Acetaminophen'.)

Chondroitin sulfate and glucosamine — We do not routinely recommend glucosamine or chondroitin for the treatment of hand OA, but, because of the beneficial safety profile, we do not discourage patients who wish to try these substances. Chondroitin sulfate and glucosamine are thought to be chondroprotective. They are among the most widely used over-the-counter nutraceutical products for OA but are scarcely studied in hand OA. Three placebo-controlled studies have been performed investigating chondroitin sulfate, of which one was a high-quality trial with 162 patients reporting improvements in pain and function in the treated arm,[32] and the other two were smaller, low-quality trials concluding positive effects on structural damage in erosive hand OA patients after follow-up of one to three years.[33,34] Studies of glucosamine have not been performed in hand OA patients. The substances are not associated with more adverse events than placebo, although glucosamine should not be given to patients with allergies to shellfish due to cross-reactivity. More data on the efficacy of chondroitin sulphate and glucosamine are available from randomized controlled trials in knee and hip OA patients. In meta-analyses summarizing the available evidence for the use of glucosamine, chondroitin, or combination preparations in knee and hip OA patients, a clinically meaningful effect could not be shown.[35,36]

Topical capsaicin – Topical capsaicin is available as an over-the-counter product. It may be used as an additive analgesic therapy for hand OA patients in whom other therapies do not suffice or are contraindicated. However, local side effects, mainly burning and stinging sensations, are often reported, and there is some uncertainty about possible long-term side effects associated with this medication. Its mechanism of action involves desensitization of skin nerve fibers through counterirritation. A randomized trial performed in 59 adults with hand OA reported better pain relief in patients treated with capsaicin cream compared with placebo, though patients using capsaicin cream experienced more local adverse effects.[37] Much of the clinical application for hand OA has been extrapolated from its use for knee OA. (See "Management of knee osteoarthritis", section on 'Topical capsaicin'.)

Other small clinical trials investigating topical capsaicin in OA patients in general have reported statistically significant but limited effects on pain relief.[38] Local adverse events are regularly reported, especially early in treatment, and patients commonly discontinue treatment because of these adverse events. Serious adverse events have not been reported, although some evidence suggests that capsaicin-mediated denervation might not be entirely reversible and that it might not be limited to the sensory nerves but may also affect autonomic nerve fibers.

Topical salicylates – We do not recommend the use of topical salicylates for treating pain in hand OA patients due to their lack of efficacy. Topical salicylates are available in the United States and Europe as over-the-counter products. The evidence for the use of topical salicylates is scarce. Two low-quality trials including patients with OA at various sites have been performed. No superiority over placebo was reported, whereas adverse events are common and more serious than those of topical nonsteroidal antiinflammatory drugs (NSAIDs).[38]

Nutritional supplements — Nutritional supplements such as avocado soybean unsaponifiables (ASUs) have also been considered for the treatment of hand OA, but there is no strong evidence to recommend the use of these supplements. ASUs, produced from avocado and soybean oil, are thought to block pro-inflammatory cytokines. Trials in hand OA patients are lacking. However, the use of ASUs has been studied in the context of knee and hip OA and is discussed in more detail separately. (See "Management of knee osteoarthritis", section on 'Other nutritional supplements'.)

Thermal modalities — Local application of heat may have positive effects on pain and grip strength in patients with hand OA. Heat application is commonly done with paraffin wax, but other applications include heat wraps, steam, and infrared radiation, and the choice of the type of delivery depends on the patient's personal preferences. Three small, low-quality trials (n = 174) investigating the effects of thermal modalities were summarized in a systematic review, reporting a possible effect on pain and grip strength.[39]

Diacerein — Diacerein is an oral interleukin (IL)-1beta inhibitor. It is available in a limited number of countries in Europe but not in the United States. One trial has been performed in hand OA patients and found no effect of diacerein compared with placebo.[40] Most data come from trials in knee and hip OA patients. A Cochrane review summarized the evidence from 10 trials with 2210 participants, concluding a minimal beneficial effect in terms of pain reduction.[41] More importantly, major safety signals have been identified, mainly diarrhea and liver toxicity, leading the European Medicines Agency (EMA) to issue a statement restricting the use of diacerein-containing medicines to patients younger than 65 with no concurrent diagnosis or history of liver disease and only half the normal dose (ie, 50 mg daily instead of 100 mg).[42]

Intraarticular glucocorticoids – Intraarticular glucocorticoid injections are widely used in patients with OA of the thumb base but can be applied to any of the hand joints. The use of glucocorticoid injections is in general not recommended in our clinical practice due to the limited efficacy, though intraarticular injections are known to be associated with a large placebo effect.[43] In some cases where there is severe local inflammation of an interphalangeal joint, glucocorticoid injections may be indicated. There is some evidence suggesting that intraarticular glucocorticoids could be beneficial for interphalangeal OA, whereas this is not true for thumb-base OA.[44] A systematic review of evidence for the different intraarticular treatments for hand OA found that in patients with thumb-base OA, intraarticular injections with glucocorticoids (three studies) were not more effective than placebo.[44] However, one high-quality placebo-

controlled trial with 60 interphalangeal OA patients showed that intraarticular glucocorticoid injection led to relief of pain during motion and decreased joint swelling during the 12-week follow-up period.[45] Only local adverse events were reported in the trials.

Intraarticular hyaluronans – The use of intraarticular hyaluronic acid (HA; also known as viscosupplementation) is not recommended due to the lack of data demonstrating benefit. This form of treatment has been used for OA of the thumb base. A systematic literature review of the evidence for intraarticular treatments for hand OA included three studies with intraarticular HA injections and found that they were not more effective than placebo.[44] Additional information on the use of hyaluronans for knee OA can be found elsewhere. (See "Management of knee osteoarthritis", section on 'Hyaluronans'.)

Opioids (including tramadol) — Due to the relatively high incidence of adverse effects associated with tramadol and other opioid analgesics, particularly among older adults, we recommend against using opioids whenever possible. Opioids are widely used in painful conditions, typically when patients respond insufficiently to conventional treatment or if other analgesics are contraindicated. These drugs, however, are associated with various adverse effects, including nausea, vomiting, dizziness, and constipation. (See "Overview of the treatment of chronic non-cancer pain", section on 'Opioids'.)

Although no direct evidence for the use of opioids for hand OA patients is available, the results from trials performed in knee and hip OA patients question whether the benefits of these analgesics outweigh the well-known risks, especially considering that hand OA patients are often older adults and more prone to these side effects (effect size [ES] tramadol 0.34, 95% 0.20 to 0.48,[46] and ES nontramadol opioids 0.28, 95% CI 0.20 to 0.35).[47] Additional information regarding the use of opioids for knee and hip OA can be found elsewhere. (See "Management of knee osteoarthritis", section on 'Opioids'.)

Systemic glucocorticoids – Several randomized studies have investigated the efficacy of low-dose systemic glucocorticoids on pain for hand OA with mixed results.[48-50] Data suggest that glucocorticoids can provide short-term pain relief in patients with signs of active joint inflammation who experience a flare of the disease, which is most commonly seen in patients with features of erosive hand OA (See "Clinical manifestations and diagnosis of osteoarthritis", section on 'Erosive osteoarthritis'). However, given the known side effects of systemic glucocorticoids, we discourage their routine use for the treatment of hand OA. Most patients with hand OA tend to have an insidious and progressive disease course rather than episodic flares. Also, identification of patients likely to benefit from this therapy is challenging given the limitations of being able to demonstrate active inflammation with standard imaging. The largest randomized trial to study the role of glucocorticoids in hand OA included 92 patients, all of whom were eligible if they had symptomatic hand OA as well as clinical and sonographic signs of inflammation in their distal and proximal interphalangeal joints.[50] Patients who received 10 mg of prednisolone during six weeks reported greater improvements in pain (measured on a visual analog scale) compared with placebo. After discontinuation of prednisolone, the beneficial

effect disappeared. Thus, a short course of oral glucocorticoids could provide transient relief in selected patients with signs of active joint inflammation who want short-term pain relief. Prolonged prescription of glucocorticoids is discouraged.

Hydroxychloroquine – Hydroxychloroquine, an antimalarial drug, is not uncommonly prescribed (off-label) for hand OA patients with inflammatory signs, analogous to the treatment of other inflammatory rheumatic diseases (see "Antimalarial drugs in the treatment of rheumatic disease"). Though previous small, mostly open-label studies indicated possible benefits, data from two randomized trials could not support these findings.[51-53] Both trials reported no difference in symptom relief after 6 and 12 months' follow-up compared with placebo. One trial also assessed structural damage, but found no beneficial effect of hydroxychloroquine treatment.[52] The use of hydroxychloroquine is therefore not recommended for hand OA.

Methotrexate – Methotrexate is regularly used in the treatment of rheumatoid arthritis (RA) patients (see "Use of methotrexate in the treatment of rheumatoid arthritis"). Although synovitis is often present in osteoarthritic hand joints, little evidence is available that methotrexate is an effective treatment modality for hand OA patients. One small open study was performed in erosive hand OA patients.[51]

Biologic agents – The use of tumor necrosis factor (TNF)-alpha inhibitors, which are effective for the treatment of RA and psoriatic arthritis, has been applied to OA with mixed results,[54-58] and is discussed in detail separately (see "Investigational approaches to the management of osteoarthritis", section on 'Tumor necrosis factor-alpha inhibitors'). A case series of three erosive hand OA patients receiving anakinra, an IL-1 receptor antagonist, reported positive results,[59] but more data investigating the efficacy of IL-1 receptor antagonists in hand OA are needed.

PROGNOSIS

Although radiographic progression in hand osteoarthritis (OA) is thought to be a slow but ongoing process, the course of pain and disability is heterogeneous. For example, one study showed that over a period of six years, symptoms of half of the patients deteriorated, although 25 percent reported fewer symptoms.[60] Moreover, the same study showed a mismatch between radiographic and clinical progression, although this could be due to lack of sensitivity of the measurement instruments used. Erosive OA is considered to have a higher clinical burden and worse prognosis than nonerosive OA.[60-62] Furthermore, studies have shown that thumb-base OA contributes more to pain and disability than finger OA.[63] There are no interventions to date that can alter the course of the disease.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Osteoarthritis".)

SUMMARY AND RECOMMENDATIONS

- All patients with hand osteoarthritis (OA) should be thoroughly assessed with regard to their knowledge about the disease and their expectations of treatment. Educating patients about their hand OA is essential, with the aim of enhancing the patient's understanding of their disease. (See 'General principles' above.)
- A combination of nonpharmacologic and pharmacologic interventions is typically used in clinical practice for the management of hand OA. The choice of therapy will also be guided by the presence of other joint involvement and comorbidities. Surgical interventions are reserved for patients with symptoms refractory to nonpharmacologic and pharmacologic interventions. (See 'General approach' above.)
- In patients with hand OA, particularly involving the thumb base, we suggest the use of a splint for pain relief (*Grade 2C*). Splints and other assistive devices can be offered before or in combination with pharmacologic interventions, depending on the severity and location of symptoms. The type of splint and the best instructions for splint use have not been compared in high-quality studies, and this should, therefore, be a shared decision with the patient. Assistive devices other than splints are also effective in improving a patient's satisfaction with activity performance. (See 'Splints and other assistive devices' above.)
- In patients with OA localized to the hand, we suggest initial treatment with a topical nonsteroidal antiinflammatory drug (NSAID) rather than an oral NSAID (*Grade 2B*). The risk of gastrointestinal, renal, and cardiovascular toxicity is lower with topical NSAIDs as compared with their oral formulations due to the reduced systemic absorption. The tolerability profile is also better with topical NSAIDs, with mild skin rashes being the most commonly reported side effect. (See 'Topical NSAIDs' above.)
- We suggest hand exercises for patients with hand OA to improve function, muscle strength, and reduce pain (*Grade 2C*). Exercise regimens for hand OA usually involve both range of motion and strengthening exercises and are often home-based. (See 'Exercise' above.)
- For patients with hand OA who respond inadequately to initial therapy, we suggest oral NSAIDs, preferably on an as-needed basis (*Grade 2B*). Oral NSAIDs should be used at the lowest effective dose and for the shortest duration possible due to the well-known potential gastrointestinal, cardiovascular, and renal toxicities. This is especially relevant for patients with OA, who are often older adults and frequently have one or more comorbidities. (See 'Oral NSAIDs' above.)

- We refer patients to surgery when significant joint-related symptoms persist despite the use of nonsurgical interventions. Surgical intervention is generally reserved for patients with severe disease and refractory symptoms, whose quality of life is severely impacted. (See 'Surgery' above.)
- There are several approaches that have been used to treat patients with hand OA that are of uncertain benefit and thus not routinely recommended. These include acetaminophen, glucosamine and chondroitin, thermal modalities, topical capsaicin, topical salicylates, nutritional supplements, thermal modalities, diacerein, intraarticular glucocorticoids, intraarticular hyaluronans, opioids (including tramadol), systemic glucocorticoids, hydroxychloroquine, methotrexate, and biologic agents.
- Although radiographic progression in hand OA is thought to be a slow but ongoing process, the course of pain and disability is heterogeneous. Erosive OA is considered to have a higher clinical burden and worse prognosis than nonerosive OA. Furthermore, studies have shown that thumb-base OA contributes more to pain and disability than finger OA. There are no interventions to date that can alter the course of the disease. (See 'Prognosis' above.)

REFERENCES

1. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
2. Osteoarthritis: Care and Management in Adults. National Clinical Guideline Centre Clinical Guideline CG177, National Institute for Health and Care, London, 2014.
3. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020;72:220-33.
4. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)* 2020;72:149-62.
5. Hill S, Dziedzic KS, Nio Ong B. Patients' perceptions of the treatment and management of hand osteoarthritis: a focus group enquiry. *Disabil Rehabil* 2011;33:1866-72.
6. Stukstette MJ, Dekker J, den Broeder AA, et al. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term - results of a randomized controlled trial. *Osteoarthritis Cartilage* 2013;21:901-10.
7. Dziedzic K, Nicholls E, Hill S, et al. Self-management approaches for osteoarthritis in the hand: a 2×2 factorial randomised trial. *Ann Rheum Dis* 2015;74:108-18.
8. Kroon FP, van der Burg LR, Buchbinder R, et al. Self-management education programmes for osteoarthritis. *Cochrane Database Syst Rev* 2014;1:CD008963.
9. Stamm TA, Machold KP, Smolen JS, et al. Joint protection and home hand exercises improve hand function in patients with hand osteoarthritis: a randomized controlled trial. *Arthritis Rheum* 2002;47:44-49.
10. Kloppenburg M, Kroon FP, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019;78:16-24.
11. Kjeken I, Smedslund G, Moe RH, et al. Systematic review of design and effects of splints and exercise programs in hand osteoarthritis. *Arthritis Care Res (Hoboken)* 2011;63:834-48.
12. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. *J Rehabil Med* 2010;42:469-74.
13. Rannou F, Dimet J, Boutron I, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. Ann *Intern Med* 2009;150:661-9.
14. Kroon FPB, Carmona L, Schoones JW, et al. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *RMD Open* 2018; 4:e000734.
15. Ikeda M, Ishii T, Kobayashi Y, et al. Custom-made splint treatment for osteoarthritis of the distal interphalangeal joints. *J Hand Surg Am* 2010;35:589-93.
16. Watt FE, Kennedy D, Carlisle K, et al.. Night-time splinting of the distal interphalangeal joint reduces pain and improves extension at the joint: results from the splint-OA study. *Osteoarthritis Cartilage* 2013;21:S25.
17. Kjeken I, Darre S, Smedslund G, et al. Effect of assistive technology in hand osteoarthritis: a randomised controlled trial. *Ann Rheum Dis* 2011;70:1447-52.
18. Derry S, Conaghan P, Da Silva JA, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2016;4:CD007400.
19. Zacher J, Burger KJ, Färber L, et al. [Topical diclofenac versus oral ibuprofen: a double blind, randomized clinical trial to demonstrate efficacy and tolerability in patients with activated osteoarthritis of the finger joints (Heberden and/or Bouchard arthritis)]. [*German*]. *Aktuel Rheumatol* 2001;26:7-14.
20. Peniston JH, Gold MS, Wieman MS, et al. Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. *Clin Interv Aging* 2012;7:517-23.
21. Østerås N, Kjeken I, Smedslund G, et al. Exercise for hand osteoarthritis. *Cochrane Database Syst Rev* 2017;1:CD010388.
22. Seiler V. Meclofenamate sodium in the treatment of degenerative joint disease of the hand (Heberden nodes). *Arzneimittelforschung* 1983;33:656-9.
23. Dreiser RL, Gersberg M, Thomas F, et al. [Ibuprofen 800 mg in the treatment of arthrosis of the fingers or rhizarthrosis]. [*French*]. *Rev Rhum Ed Fr* 1993;60:836-41.
24. Grifka JK, Zacher J, Brown JP, et al. Efficacy and tolerability of lumiracoxib versus placebo in patients

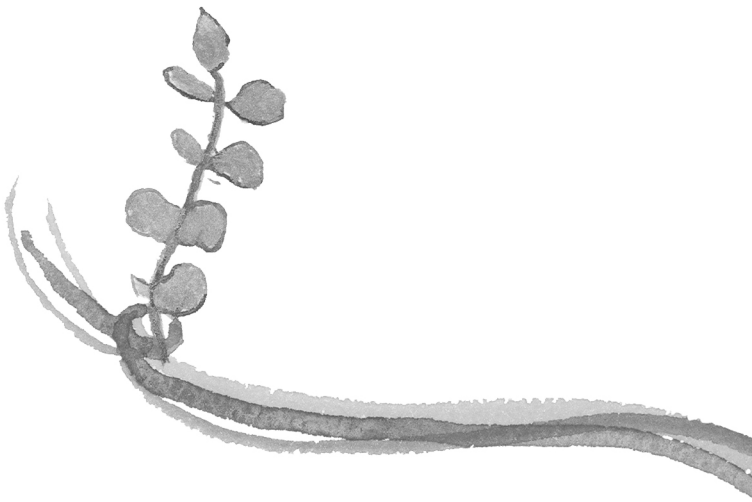
with osteoarthritis of the hand. *Clin Exp Rheumatol* 2004;22:589-96.
25. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162:46-54.
26. Wajon A, Vinycomb T, Carr E, et al. Surgery for thumb (trapeziometacarpal joint) osteoarthritis. *Cochrane Database Syst Rev* 2015;2:CD004631.
27. Vermeulen GM, Slijper H, Feitz R, et al. Surgical management of primary thumb carpometacarpal osteoarthritis: a systematic review. *J Hand Surg Am* 2011;36:157-69.
28. Sweets TM, Stern PJ. Proximal interphalangeal joint prosthetic arthroplasty. *J Hand Surg Am* 2010;35:1190-93.
29. Rongières M. Surgical treatment of degenerative osteoarthritis of the fingers. *Chir Main* 2013;32:193-98.
30. Vitale MA, Fruth KM, Rizzo M, et al. Prosthetic Arthroplasty Versus Arthrodesis for Osteoarthritis and Posttraumatic Arthritis of the Index Finger Proximal Interphalangeal Joint. *J Hand Surg Am* 2015;40:1937-48.
31. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016;75:552-59.
32. Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum* 2011;63:3383-91.
33. Rovetta G, Monteforte P, Molfetta G, et al. A two-year study of chondroitin sulfate in erosive osteoarthritis of the hands: behavior of erosions, osteophytes, pain and hand dysfunction. *Drugs Exp Clin Res* 2004;30:11-16.
34. Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin Rheumatol* 2002;21:231-43.
35. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:c4675.
36. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015;1:CD005614.
37. Schnitzer T, Morton C, Coker S. Topical capsaicin therapy for osteoarthritis pain: Achieving a maintenance regimen. *Semin Arthritis Rheum* 1994;23:34-40.
38. Altman RD, Barthel HR. Topical therapies for osteoarthritis. *Drugs* 2011;71:1259-79.
39. Valdes K, Marik T. A systematic review of conservative interventions for osteoarthritis of the hand. *J Hand Ther* 2010;23:334-50.
40. Shin K, Kim JW, Moon KW, et al. The efficacy of diacerein in hand osteoarthritis: a double-blind, randomized, placebo-controlled study. *Clin Ther* 2013;35:431-39.
41. Fidelix TS, Macedo CR, Maxwell LJ, et al. Diacerein for osteoarthritis. *Cochrane Database Syst Rev* 2014;2:CD005117.
42. www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diacerein/European_Commission_final_decision/WC500173144.pdf [Accessed on January 31, 2017].
43. Bannuru RR, McAlindon TE, Sullivan MC, et al. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. *Ann Intern Med* 2015;163:365-72.
44. Kroon FP, Rubio R, Schoones JW, et al. Intra-Articular Therapies in the Treatment of Hand Osteoarthritis: A Systematic Literature Review. *Drugs Aging* 2016;33:119-33.
45. Spolidoro Paschoal NO, Natour J, Machado FS, et al. Effectiveness of Triamcinolone Hexacetonide Intraarticular Injection in Interphalangeal Joints: A 12-week Randomized Controlled Trial in Patients with Hand Osteoarthritis. *J Rheumatol* 2015;42:1869-77.
46. Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis. *Cochrane Database Syst Rev* 2006;3:CD005522.
47. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2014;9:CD003115.
48. Kvien TK, Fjeld E, Slatkowsky-Christensen B, et al. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942-48.
49. Wenham CY, Hensor EM, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology (Oxford)* 2012;51:2286-94.
50. Kroon FPB, Kortekaas MC, Boonen A, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019; 394:1993-2001.
51. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242-51.
52. Kingsbury SR, Tharmanathan P, Keding A, et al. Hydroxychloroquine Effectiveness in Reducing

Symptoms of Hand Osteoarthritis: A Randomized Trial. *Ann Intern Med* 2018;168:385-95.
53. Lee W, Ruijgrok L, Boxma-de Klerk B, et al. Efficacy of Hydroxychloroquine in Hand Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care Res (Hoboken)* 2018;70:1320-25.
54. Fioravanti A, Fabbroni M, Cerase A, et al. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. *Rheumatol Int* 2009;29:961-65.
55. Magnano MD, Chakravarty EF, Broudy C, et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J Rheumatol* 2007;34:1323-27.
56. Verbruggen G, Wittoek R, Vander Cruyssen B, et al. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891-98.
57. Chevalier X, Ravaud P, Maheu E, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697-705.
58. Kloppenburg M, Ramonda R, Kwok W, et al. Randomized, placebo-controlled trial to evaluate clinical efficacy and structure modifying properties of subcutaneous etanercept (ETN) in patients with erosive inflammatory hand osteoarthritis (OA). *Ann Rheum Dis* 2016;75:90.
59. Bacconnier L, Jorgensen C, Fabre S. Erosive osteoarthritis of the hand: clinical experience with anakinra. *Ann Rheum Dis* 2009;68:1078-79.
60. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.
61. Kwok WY, Kloppenburg M, Rosendaal FR, et al. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. *Ann Rheum Dis* 2011;70:1238-42.
62. Haugen IK, Mathiessen A, Slatkowsky-Christensen B, et al. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? *Osteoarthritis Cartilage* 2016;24:647-54.
63. Bijsterbosch J, Visser W, Kroon HM, et al. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. *Ann Rheum Dis* 2010;69:585-87.



CHAPTER 3

Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis



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ABSTRACT

To update the evidence on efficacy and safety of non-pharmacological, pharmacological and surgical interventions for hand osteoarthritis (OA), a systematic literature review was performed up to June 2017, including (randomised) controlled trials or Cochrane systematic reviews. Main efficacy outcomes were pain, function and hand strength. Risk of bias was assessed. Meta-analysis was performed when advisable. Of 7036 records, 127 references were included, of which 50 studies concerned non-pharmacological, 64 pharmacological and 12 surgical interventions. Many studies had high risk of bias, mainly due to inadequate randomisation or blinding. Beneficial non-pharmacological treatments included hand exercise and prolonged thumb base splinting, while single trials showed positive results for joint protection and using assistive devices. Topical and oral non-steroidal anti-inflammatory drugs (NSAIDs) proved equally effective, while topical NSAIDs led to less adverse events. Single trials demonstrated positive results for chondroitin sulfate and intra-articular glucocorticoid injections in interphalangeal joints. Pharmacological treatments for which no clear beneficial effect was shown include paracetamol, intra-articular thumb base injections of glucocorticoids or hyaluronic acid, low-dose oral glucocorticoids, hydroxychloroquine and anti-tumour necrosis factor. No trials compared surgery to sham or non-operative treatment. No surgical intervention for thumb base OA appeared more effective than another, although in general more complex procedures led to more complications. No interventions slowed radiographic progression. In conclusion, an overview of the evidence on efficacy and safety of treatment options for hand OA was presented and informed the task force for the updated European League Against Rheumatism management recommendations for hand OA.

INTRODUCTION

In 2007, the first European League Against Rheumatism (EULAR) recommendations for the management of hand osteoarthritis (OA) were published, based on expert opinion and an overview of the literature.[1] Many propositions, however, were based mainly on expert opinion, as evidence was lacking.

Despite it being a prevalent disease, for years, options to treat hand OA patients have been limited. In search of better alternatives for symptom relief, and in hopes of finding a disease-modifying anti-osteoarthritic drug, many clinical trials have been performed in the last decade, expanding the possible range of therapeutic options. At the same time, data has become available showing that some treatments which were believed to be beneficial do not appear to be efficacious after all. New evidence has emerged on various therapies, including but not limited to self-management, application of thumb base splints, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, various intra-articular therapies and treatment with conventional and biological disease-modifying anti-rheumatic drugs (cs/bDMARDs), for example, hydroxychloroquine and tumour necrosis factor (TNF) inhibitors.

In light of the newly accrued data, it was therefore time to update the 2007 management recommendations. This paper presents the systematic literature review (SLR) that accompanies the update of the recommendations. The aim of this SLR was to inform the task force on the current evidence for efficacy and safety of all non-pharmacological, pharmacological and surgical treatments for hand OA.

METHODS

Search strategy

A systematic search was conducted in PubMed/MEDLINE, Embase and the Cochrane CENTRAL databases up to 6 June 2017. Additionally, conference abstracts of the EULAR, American College of Rheumatology (ACR) and OsteoArthritis Research Society International (OARSI) annual conferences of the last two years, and reference lists of included studies and other relevant SLRs were screened. The search strategy can be found in the online supplementary file 1. Eligible study types were randomised controlled trials (RCTs) and clinical controlled trials (CCTs). Observational longitudinal studies were considered to assess safety, and to assess efficacy of surgical interventions, but only if a comparator group was available and the number of participants per group was at least 50. Cochrane systematic reviews were also included. The following hierarchy of study design was adopted to assess the evidence for each intervention: Cochrane systematic reviews, RCTs, CCTs and lastly observational studies.

Research questions were formulated according to the PICO format: Participants, Interventions, Comparators, Outcomes.[2] Studies of any non-pharmacological, pharmacological or surgical intervention in adults diagnosed with hand OA were included. Studies including participants with other diagnoses were only eligible for inclusion if the results were presented separately for participants with hand OA. The comparator could be placebo, care-as-usual, any

other non-pharmacological, pharmacological or surgical intervention, or the same intervention in a different dose, formulation, regimen or treatment duration. Studies without a comparator were excluded. Other exclusion criteria were a total number of participants in non-surgical trials <20 and premature termination of the trial.

Efficacy outcomes were considered as proposed by the OMERACT core set for domains in clinical trials for hand OA.[3] Main efficacy outcomes were pain (preferably measured on visual analogue scale (VAS), numerical rating scale (NRS), or a validated questionnaire, eg, Australian/Canadian Hand Osteoarthritis Index (AUSCAN) or Michigan Hand Outcomes Questionnaire (MHQ)), hand function (validated questionnaire, eg, Functional Index for Hand OsteoArthritis (FIHOA), AUSCAN or MHQ), and hand strength (grip or pinch strength). Additional efficacy outcomes that were considered included patient global assessment (VAS or NRS), health-related quality of life (Short-Form 36, EuroQoL), structural damage, hand mobility (Hand Mobility in Scleroderma test, modified Kapandji index, fingertip-to-palm-distance) and the number of participants fulfilling the OMERACT-OARSI responder criteria.[4] The primary safety outcome was withdrawals due to adverse events (AEs). In addition, serious AEs and AEs broken up by bodily system (eg, gastrointestinal, cardiovascular) were assessed. Studies that did not assess any efficacy or safety outcomes were excluded.

Study selection, data extraction and risk of bias assessment

One reviewer (FK) screened titles and abstracts to determine eligibility for inclusion, according to predefined inclusion criteria, followed by full-text review where necessary. In case of doubt, a second reviewer was consulted (MK/LC). Relevant data on study characteristics, interventions, study population and the above-mentioned outcomes was extracted (FK). The risk of bias (RoB) was assessed with regard to random sequence generation, allocation concealment, blinding (participants, care provider, outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias according to the 'Cochrane tool' (FK).[5] Each item was judged as low (green colour), high (red) or unclear RoB (yellow; lack of information or uncertainty over potential bias). An 'overall assessment' for each study was based on the judgements for each RoB item. Selection bias (sequence generation, allocation concealment) and blinding were considered 'key domains', that is, the most important domains in a study's RoB.

Data analysis

Data were only pooled in case of sufficient clinical and statistical homogeneity. For continuous outcomes, data were summarised as mean difference (MD) with corresponding 95% CI, unless different measurement instruments were used to measure the same outcome, in which case standardised mean differences (SMDs) were calculated. A random effects model was used. Studies that could not be included in the meta-analysis are presented descriptively. Stata V.14.1 was used for meta-analysis.

RESULTS

The literature search yielded 5020 records (after de-duplication), of which 127 references were included in this review (see figure 1 and online supplementary table S1). Three studies were additionally excluded because of language (Turkish, Chinese). In total, 50 studies assessed benefits and harms of different non-pharmacological therapies, including one Cochrane review. Pharmacological interventions were investigated in 64 studies, including one observational study. Surgical interventions were assessed in 11 trials, all summarised in one Cochrane review.

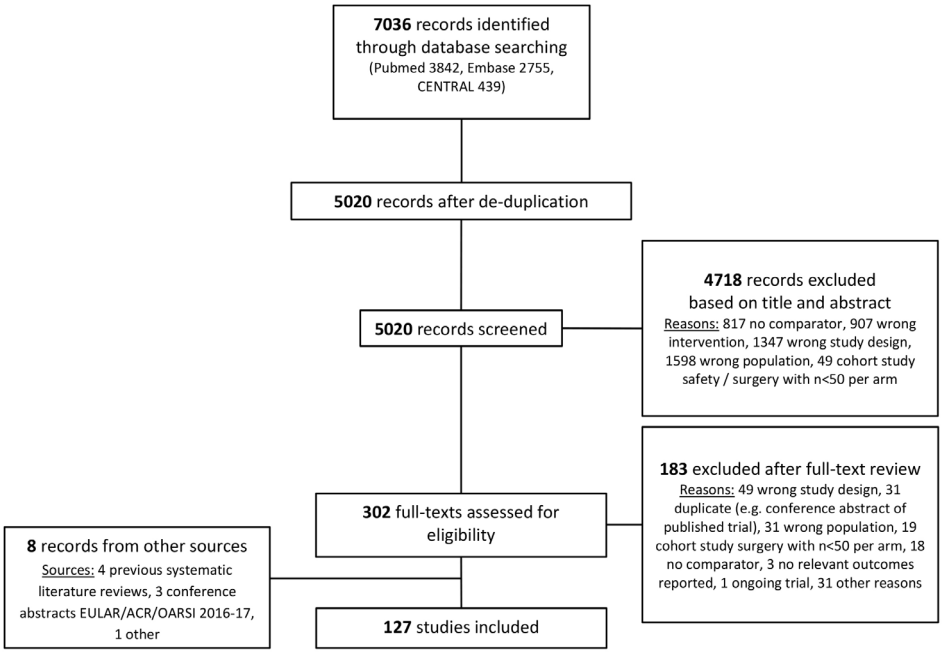


Figure 1. Flowchart of systematic literature review.

Non-pharmacological interventions

Table 1 presents an overview of the characteristics and RoB of the 28 studies of the most relevant non-pharmacological interventions to inform the 2018 update of the EULAR management recommendations for hand OA. The remaining trials studied thermal modalities (n=3), manual therapy (n=3), balneotherapy (n=6), low-level laser therapy (n=4), yoga (n=1), nuclear magnetic resonance (n=1), magnetotherapy (n=1), leeches (n=1) and alkalinisation of diet (n=1), and are described in online supplementary tables (3.1.5, 3.1.7, 3.1.9, 3.1.11).

The studies were heterogeneous, especially with respect to type of intervention, study duration (range: 1 week to 1 year, most up to 8 weeks) and assessed outcomes. Most were RCTs (n=19), and a minority CCTs (n=3) or cross-over trials (n=6). Many studies were small: 15 trials (54%) included 60 participants or less. All studies were judged to be at high or unclear RoB, most often due to lack of blinding. A detailed RoB assessment is presented in online supplementary tables 3.1.1-3.1.12.

Table 2 presents an overview of the main results of the most relevant non-pharmacological trials for which the outcomes pain, function, fulfilment of OARSI-OMERACT criteria[4] or grip strength could be assessed. Safety outcomes are presented in online supplementary table 4.1. If studies were pooled, results are also presented in forest plots (online supplementary figures S1-S8).

In summary, exercise leads to beneficial effects on hand pain, function, joint stiffness and grip strength, although effect sizes are small. Few (non-severe) AEs were reported, showing a signal for increased number of AEs in participants undergoing exercise therapy, in particular increased joint inflammation and hand pain (RR 4.6 (95% CI 0.5 to 39.3); online supplementary table 4.1).[6]

Joint protection led to a higher proportion of participants being classified as responder to treatment according to OARSI-OMERACT criteria after 6 months, though mean AUSCAN pain and function subscales did not differ between groups.[7]

On the short term, thumb base splinting did not lead to pain relief or functional improvement,[8-12] though studies assessing long-term use showed that this was associated with more pain relief and improved function (online supplementary figures S1-S4).[10,12] Studies assessed many different types of splints (eg, short or long, custom-made or prefabricated, neoprene or thermoplast or other material) and instructions for use (eg, during activities of daily living, at night, constantly). Only short versus long thumb base splints (ie, including only CMC joint vs both CMC and MCP joint) could formally be compared and were not associated with different clinical outcomes (online supplementary figures S5-S6).[13-15] For other splint types or instructions, no consistent benefit of one over another could be identified in RCTs/CCTs or cross-over studies.[16-20] A single study assessed night time DIP splinting specifically, but did not show improvements in pain, function or pinch strength after 3 months.[21]

Use of assistive devices led to small improvements in function, as measured with the patient-specific Canadian Occupational Performance Measure (COPM) and the AUSCAN function subscale, but not in pain.[22]

Several studies assessed different combination programmes of multiple non-pharmacological interventions.[7,15,23-28] Three trials compared a programme including education, joint protection and hand exercises to education alone, and though no formal meta-analysis could be performed, no between-group differences in pain, function or grip strength could be confirmed (online supplementary figures S7-8).[7,25,26] The other studies of combination programmes were more heterogeneous, especially in the type of intervention studied. Some reported positive effects of the combination versus non-combination interventions, especially on subjective measures like pain,[23,28] and not on more objective measures like hand strength,[24,28] though others reported no between-group differences.[15,27]

Furthermore, application of heat was assessed in three heterogeneous trials, both in design and type of intervention (high RoB). Two studies reported improvements in, for example, pain and grip strength in the intervention group compared with control,[29,30] and one cross-over trial reported no between-group differences.[31] Three studies (high RoB) focussed on different forms of manual therapy in elderly, severe CMC OA patients (mean age 81.4 years) and showed positive effects on pain sensitivity and hand strength in the intervention group compared with control, both in the treated, symptomatic hand, and in the contralateral non-treated non-symptomatic hand.[32-37] Finally, six studies (five high RoB, one unclear RoB) assessed different forms of balneotherapy to another active intervention,[38-40] sham intervention,[41,42] or usual care.[43] The studies comparing balneotherapy to another active intervention or to usual care all report positive effects of balneotherapy on pain, function and hand strength compared with the chosen control group.[38-40,43] However, balneotherapy (mud application or mineral thermal bath) was not convincingly better than a sham intervention.[41,42]

Pharmacological interventions

Table 3 presents an overview of the characteristics and RoB of the 33 trials of the most relevant pharmacological interventions to inform the 2018 update of the EULAR management recommendations for hand OA. Trials not listed in table 3 studied topical capsaicin (n=1), topical salicylates (n=2), paracetamol (n=4), glucosamine (n=1), diacerhein (n=1), different herbal formulations (n=3), anti-interleukin-1 (n=1), clodronate (n=1), several types of periarticular injections (n=3), intra-articular hyaluronic acid (n=9), other intra-articular therapies (n=2), folate/cobalamin supplementation (n=1), apremilast (n=1), galactosaminoglycuronglycan sulfate (n=1), and pregabalin and duloxetine (n=1). A description can be found in online supplementary tables (3.2.2, 3.2.4, 3.2.6, 3.2.10, 3.2.12, 3.2.15, 3.2.17, 3.2.22).

The longest trial lasted up to 3 years, though most trials had a duration of 3 weeks. Most studies focussed on clinical outcomes, while structure modification was the primary outcome of two trials.[44,45] The majority were RCTs (n=30), and few were set-up as CCTs (n=1) or cross-over trials (n=2). Seven trials specifically included participants with signs of "inflammatory OA", all investigating anti-inflammatory agents (ie, NSAIDs, glucocorticoids and anti-TNF).[45-51] Compared with non-pharmacological interventions, less studies were small (n≤60; 15 trials, 45%). Twelve studies (36%) were at low RoB. Reason to judge studies to be at high or unclear RoB was most often due to problems with randomisation or blinding, and for six studies only a conference abstract was available thus RoB remained unclear. The detailed RoB assessment is presented in online supplementary tables (3.2.1-3.2.23).

Table 4 presents an overview of the main results of the most relevant pharmacological trials for which the outcomes pain, function, fulfilment of OARSI-OMERACT criteria[4] or grip strength could be assessed. Safety outcomes are presented in online supplementary table 4.2. Forest plots of pooled results are presented in online supplementary figures S9-S20.

Topical pharmacological interventions

Topical diclofenac gel was shown to be superior to placebo in a large RCT (low RoB), leading to small improvements in pain and function, and not more AEs, after 8 weeks.[52] Topical NSAIDs led to similar pain relief as oral NSAIDs,[50,51] yet lower risk of any AE (RR 0.40 (95% CI 0.09

to 1.74)),[50,51] gastro-intestinal AEs (RR 0.64 (0.35 to 1.20)),[51] severe AEs (RR 0.54 (0.17 to 1.71)),[51] and withdrawals due to AEs (RR 0.15 (0.03 to 0.63)) (online supplementary table 5.2, figures S9-11).[51] Pooled safety data from two RCTs comparing topical diclofenac gel to placebo in patients with hand OA showed similar and low rates of AEs in subgroups at low versus high risk of NSAID-related AEs (ie, age ≥65 years, and with comorbid hypertension, type 2 diabetes or cerebrovascular or cardiovascular disease).[53] A trial (low RoB) comparing topical ibuprofen cream to arnica cream found no between-group differences.[54] Two studies (one high RoB, one unclear RoB) comparing topical NSAIDs with a non-pharmacological treatment reported superiority of the comparator.[39,55] Topical capsaicin was assessed in one RCT (unclear RoB), reporting better pain relief than placebo at the cost of increased risk of local AEs (burning and stinging sensation, RR 3.1 (95% CI 1.1 to 8.5)), which likely also compromised the trial's success of blinding.[56] A single application of topical salicylates was reported in two trials (high RoB) to lead to improvements in pain and stiffness, but also numerically more local AEs.[57,58]

Oral analgesics

Paracetamol was included as a treatment arm in three conference abstracts (unclear RoB) and one cross-over trial (high RoB), in various dosages and for different duration.[48,59-61] Three trials intended paracetamol to be the control group. One trial (unclear RoB) included a placebo arm, and reports no between-group difference in pain or morning stiffness.[59] Paracetamol was not superior to any of the active comparators.[48,60,61]

Oral NSAIDs lead to moderate improvements in pain and function compared with no intervention,[49] placebo[62-64] and other active interventions (glucosamine/chondroitin sulfate,[65] paracetamol[48]).

Nutraceuticals

The effectiveness of chondroitin sulfate was studied in two papers. One trial (low RoB) focused on clinical outcomes after six months, reporting beneficial effects on pain and function compared with placebo.[66] The other study (high RoB) assessed structural outcomes in two long-term trials (published in one paper), assessing chondroitin sulfate and chondroitin polysulphate.[44] Only for chondroitin polysulphate, a preparation not commercially available, less erosive damage after 3 years was reported, and not for chondroitin sulfate. The trials did not report higher risk of AEs in the intervention groups.

Glucosamine is reported to have beneficial effects on pain and function after 6 weeks in an RCT (unclear RoB) published as conference abstract (no raw data provided).[61]

Diacerhein was not better than placebo for pain relief or any of the other secondary outcomes in a study (unclear RoB) of Korean patients with hand OA, while more (mild) AEs were reported in the intervention group, especially discoloration of urine (88% vs 20%) and abdominal pain (31% vs 14%), but remarkably not diarrhoea (21% vs 20%).[67]

Intra-articular treatments

Several intra-articular therapies were assessed, of which glucocorticoids and hyaluronic acid are the most commonly used. Intra-articular injection of glucocorticoids in the thumb base was not more beneficial than placebo with respect to pain and function (online supplementary figures S12-13),[68-70] while in one study (low RoB) participants reported less pain during movement and soft swelling after intra-articular glucocorticoid injection in IP joints.[71] However, the latter study did not find beneficial effects on pain in rest or function.

Intra-articular injection of hyaluronic acid in the thumb base did not lead to improvements in pain or function compared with placebo (online supplementary figure S14).[68,69,72] Six trials (four high RoB, two unclear RoB) compared intra-articular thumb base injection of glucocorticoids to hyaluronic acid, but no consistent beneficial effect of one treatment over the other could be shown.[68,69,73-76] Single studies (two high RoB, two unclear RoB) assessed alternative dosages (ie, one, two or three hyaluronic acid injections,[77] low vs high molecular weight hyaluronic acid[78]) and therapies (ie, intra-articular infliximab,[79] dextrose[80]), and are not described in depth.

Glucocorticoids and conventional or biological DMARDs

Short-term treatment with low-dose oral glucocorticoids were evaluated in two RCTs (low RoB). Six-week treatment with prednisolone/dipyridamole led to more improvement in pain (MD 12.3 (95% CI 3.0 to 21.5) on 100 mm VAS), at the cost of more withdrawals due to AEs (38% vs 15%), mostly due to headache.[81] In a trial of 4-week treatment with prednisolone 5 mg, however, no between-group differences were observed (eg, 100 mm VAS pain 19.9 mm in prednisolone vs 16.8 mm in placebo group).[82] Results could not be combined due to clinical heterogeneity and remain inconclusive.

Three RCTs (unclear RoB), only published as conference abstracts, show that hydroxychloroquine does not have beneficial effects on pain (online supplementary figure S15), function, grip strength or radiographic progression (only assessed by Kingsbury *et al*).[59,83,84] One trial also included a paracetamol arm and found no between-group differences compared with hydroxychloroquine on pain (MD 2.5 (95% CI -9.9 to 14.9) on 100 mm VAS, in favour of paracetamol).[59]

Four studies (two unclear RoB, two low RoB) assessed the efficacy of different TNF inhibitors (adalimumab[45,46,85] and etanercept[47,86,87]), but no beneficial effect over placebo could be shown on pain, function or grip strength (online supplementary figures S16-20). Two studies (one unclear RoB, one low RoB) report less erosive radiological progression after 1 year in treated joints with soft tissue swelling at baseline (no data to pool).[45,47] One RCT (low RoB) and one cross-over trial (unclear RoB) report no between-group differences in MRI synovitis, while only the RCT found a decrease in bone marrow lesions and the cross-over trial did not.[46,87]

Table 1. Characteristics of studies of main non-pharmacological interventions (n=28 studies)

RoB	Study	Design	Intervention
Exercise			
	Østeras 2017[6]	SLR (6 RCT, 1 CO)	Hand exercise vs no exercise (N=6); different CMC exercise programmes (N=1)
Joint protection			
	Dziedzic 2015[7]	Factorial RCT	Group-based joint protection programme (incl. splints) (JP+, HEx-) Group-based exercise programme (HEx+, JP-) Group-based combination programme: education, joint protection (incl. splints), exercise (JP+, HEx+) Education alone (JP-, HEx-)
Splints			
	Adams 2014[8] (A)	RCT	Splint + occupational therapy Placebo splint + occupational therapy Occupational therapy only
	Arazpour 2016[9]	RCT	Splint (custom-made, thermoplast, CMC) No intervention
	Bani 2013[16]	CO (WA+)	Splint (custom-made, thermoplast) Splint (prefabricated, neoprene, CMC/MCP) No intervention
	Becker 2013[13]	RCT	Splint (custom-made, thermoplast, CMC/MCP) Splint (prefabricated, neoprene, CMC)
	Cantero-Tellez 2016[14]	CCT	Splint (custom-made, thermoplast, CMC/MCP) Splint (custom-made, thermoplast, CMC)
	Gomes-Carreira 2010[10]	RCT	Splint (custom-made, CMC/MCP) No intervention
	Hermann 2013[11]	RCT	Splint + hand exercises (prefabricated, fabrifoam, CMC/MCP) Hand exercises
	Rannou 2009[12]	RCT	Splint (custom-made, neoprene, CMC/MCP) Usual care
	Sillem 2011[17]	CO (WA+)	Splint (custom-made, neoprene, CMC/MCP) Splint (prefabricated, neoprene, IP to wrist)
	Wajon 2005[15]	RCT	Splint (custom-made, thermoplast, CMC) + abduction exercise regimen Splint (custom-made, thermoplast, CMC/MCP) + pinch exercise regimen
	Watt 2014[21]	CCT	Splint (custom-made, thermoplast, DIP) No intervention

	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	6 w to 12 mo	534	Hand (6) or CMC (1), ACR or clinical diagnosis	Median 90	Mean 60-81	-
	4 sessions in 4 w	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
		65		63	64.5 (9.0)	
		65		71	66.0 (9.3)	
	4 w	65		62	67.2 (9.5)	
	4 w (NR)	9	CMC, NR	78	61.2 (9.4)	AUSCAN pain
		9				
		9				
	4 w (use during ADLs, not at night)	16	CMC, clinical diagnosis and E-L stage I-II	87	50.2 (5.7)	NR
		9		88	52.3 (6.4)	
	4 w (use during ADLs, not at night)	24	CMC, clinical diagnosis and E-L stage I-II	67	53.4	NR
				75	54.9	
	4 w	11		73	58.6	
	8-10 w (use as needed during ADLs and at night)	58	CMC, clinical diagnosis	80	62.8 (7.7)	DASH
		61		75	63.3 (8.5)	
	12 w (use during ADLs (3-4 h/d) and at night)	44	CMC, clinical and Rx diagnosis	93	59.7 (9.6)	NR
		40		90	60.5 (9.8)	
	12 w (NR)	20	CMC, clinical diagnosis and E-L stage II-III	100	62.8 (8.5)	VAS pain
		20		90	65.1 (10.1)	
	8 w (use as needed)	30	CMC, ACR, thumb pain	97	70.7 (7.3)	NRS pain
		29		100	70.2 (6.2)	
	1 y (use at night)	57	CMC, clinical and Rx diagnosis	93	63.0 (7.9)	VAS pain
		55		85	63.5 (7.6)	
	4 w (use when symptomatic, during heavy tasks, and at night if preferred)	56	CMC, clinical diagnosis	91	64.1 (8.6)	AUSCAN function
	2 w splint only, 4 w splint + exercise (use full-time)	19	CMC, clinical diagnosis and E-L stage I-III	74	59.7 (9.0)	NR
		21		81	61.2 (12.5)	
	12 w (use at night)	26	DIP, ACR, Rx damage DIP	88	63 (51-78)	NRS pain
		26				

Table 1. Continued

RoB	Study	Design	Intervention
	Weiss 2000[19]	CO (WA-)	Splint (custom-made, thermoplast, CMC) Splint (custom-made, thermoplast, CMC to wrist)
	Weiss 2004[20]	CO (WA-)	Splint (custom-made, thermoplast, CMC) Splint (prefabricated, neoprene, CMC/MCP)
	Van der Vegt 2017[18]	CO (WA+)	Splint (custom-made, thermoplast, CMC/MCP) Splint (prefabricated, semi-rigid, CMC)
Assistive devices			
	Kjeken 2011[22]	RCT	Provision of assistive devices + information Information alone
Combination programmes			
	Boustedt 2009[23]	RCT	Group-based combination programme: education, joint protection, exercise, splints Group-based joint protection programme
	Dziedzic 2015[7]	Factorial RCT	Group-based joint protection programme (incl. splints) (JP+, HEx-) Group-based exercise programme (HEx+, JP-) Group-based combination programme: education, joint protection (incl. splints), exercise (JP+, HEx+) Education alone (JP-, HEx-)
	Perez-Marmol 2017[24]	RCT	Fine motor skills occupational therapy Conventional occupational therapy
	Stamm 2002[25]	CCT	Individual combination programme: education, joint protection, exercise Education alone
	Stukstette 2013[26]	RCT	Group-based combination programme: education, joint protection (incl. splints), exercise Education alone
	Stukstette 2014[27] (A)	RCT	Group-based booster session after combination programme[26] No booster session after combination programme[26]
	Villafane 2013[28]	RCT	Individual combination programme: manual therapy, exercise Sham intervention (nontherapeutic ultrasound of the thumb region)
	Wajon 2005[15]	RCT	Splint (custom-made, thermoplast, CMC) + abduction exercise regimen Splint (custom-made, thermoplast, CMC/MCP) + pinch exercise regimen

Values are mean (SD) or median (min-max). Colours denote RoB (green: low, yellow: unclear, red: high). (A) indicates conference abstract. ACR, American College of Rheumatology; ADLs, activities of daily living; AUSCAN, Australian/Canadian Hand Osteoarthritis Index, CMC, first carpometacarpal joint; CO, cross-over trial; COPM, Canadian Occupational Performance Measure; d, day(s); DASH, Disabilities of the Arm, Shoulder and Hand; DIP, distal

Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
1 w (use when symptomatic)	26	CMC, clinical and Rx diagnosis	81	57 (36-88)	NR
1 w (use when symptomatic)	25	CMC, clinical diagnosis and E-L stage I-II	84	NR	NR
2 w (NR)	63	CMC, clinical and Rx diagnosis	70	60.1 (8.2)	VAS pain
12 w (NR)	35	ACR	97	61.1 (6.0)	COPM
	35		97	59.9 (7.5)	
10 sessions in 5 w	22	CMC, clinical and Rx diagnosis	100	61 (40-76)	NR
	20			61 (50-76)	
4 sessions in 4 w	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
	65		63	64.5 (9.0)	
	65		71	66.0 (9.3)	
4 w	65		62	67.2 (9.5)	
24 sessions in 8 w	25	Clinical diagnosis	84	82.8 (8.3)	DASH
	23		74	79.2 (10)	
Single session, 3 mo	20	ACR	85	60.5 (8.3)	Grip strength
3 mo	20		90	60.4 (6.4)	
4 sessions in 12 w	76	ACR	82	60 (7)	AUSCAN function, OARSI-OMERACT responder
12 w	75		84	58 (9)	
Single session, 1 y	147	ACR	84	59 (8)	AUSCAN function, OARSI-OMERACT responder
1 y					
12 sessions in 4 w	30	CMC, clinical diagnosis and Rx damage	90	82 (2)	VAS pain
	30		80	83 (1)	
2 w splint only, 4 w splint + excercise; use full-time	19	CMC, clinical diagnosis and E-L stage I-III	74	59.7 (9.0)	NR
	21		81	61.2 (12.5)	

interphalangeal joint; E-L, Eaton-Litter; FIHOA, Functional Index for Hand OsteoArthritis; h, hour(s); IP, interphalangeal joint; IQR, interquartile range; min, minute(s); N, number; NR, not reported; NRS, numerical rating scale; MCP, metacarpophalangeal; mo, month(s); OA, osteoarthritis; RCT, randomised controlled trial; RoB, risk of bias; Rx, radiography; SLR, systematic literature review; VAS, visual analogue scale; w, week(s); WA, wash-out period; y, year(s).

Table 2. Efficacy of main non-pharmacological interventions for hand osteoarthritis from RCTs/CCTs

Intervention	Control	Outcome	Number of participants (studies)	Duration
Exercise				
Hand exercise	No exercise	Pain	381 (5)	12 w
		Function	369 (4)	12 w
		OARSI-OMERACT responder	305 (3)	12 w
		Grip strength	362 (5)	12 w
Joint protection				
Joint protection	No joint protection	Pain	257 (1)	26 w
		Function	257 (1)	26 w
		OARSI-OMERACT responder	257 (1)	26 w
		Grip strength	257 (1)	26 w
Splints				
Thumb splint	Usual care or no intervention	Pain	221 (4)	4-8 w
		Pain	137 (2)	13-52 w
		Function	144 (3)	4 w
		Function	112 (1)	52 w
		Grip strength	95 (2)	6-8 w
		Grip strength	40 (1)	13 w
Long thumb splint (MCP + CMC joint)	Short thumb splint (only CMC joint)	Pain	185 (3)	2-12 w
		Function	146 (2)	9-12 w
DIP splint	No intervention	Pain	26 (1)	12 w
		Function	26 (1)	12 w
Assistive devices				
Assistive device	Information provision	Pain	70 (1)	12 w
		Function	70 (1)	12 w
Combination programmes				
Combination programme: education, joint protection, exercise	Education alone	Pain	321 (3)	12 w
		Function	321 (3)	12 w

	Quality of evidence	Effect estimate (95% CI)	References; Comments
	GRADE: Low	SMD -0.27 (-0.47;-0.07)*	[6]; Cochrane review
	GRADE: Low	SMD -0.28 (-0.58;0.02)*	idem
	Not reported	RR 2.8 (1.4;5.6)*	idem
	Not reported	SMD 0.34 (-0.01;0.69)*	idem
	RoB: High	MD -0.79 (-1.7;0.12) on AUSCAN pain scale (range 0-20)*	[7]; Adjusted for age, gender, social class, center, disease duration
	RoB: High	MD -0.6 (-1.9;1.1) on AUSCAN function scale (range 0-36)*	idem
	RoB: High	OR 2.1 (1.1;4.0)*	idem
	RoB: High	MD -0.47 (-1.9;0.94) kg†	idem
	RoB: High	MD -2.9 (-12.2;6.5) on 100 mm VAS*	[9-12]
	RoB: High	MD -17.4 (-25.6;-9.2) on 100 mm VAS*	[10,12]
	RoB: High	SMD 0.24 (-0.11;0.60)†	[8,9,12]; Effect estimate based on 2 trials (n=126)[9,12]
	RoB: High	MD -6.3 (-10.9;-1.7) on Cochin hand function scale (range 0-90)*	[12]
	RoB: High	SMD 0.39 (-0.35;1.1)*	[10,11]
	RoB: High	MD 0.8 (-3.1;4.7) kg*	[10]
	RoB: High	MD -0.85 (-5.1;3.4) on 100 mm VAS*	[13-15]; Wajon: results after splint period used for pooling
	RoB: High	MD 1.7 (-0.94;4.3)†	[13,14]
	RoB: High	Median difference -0.5 (range -7;3.5, p=0.53) on 10 cm VAS*	[21]; Outcome: average pain
	RoB: High	No between-group difference	[21]; No raw data presented
	RoB: High	MD 0.4 (-9.8;10.6) on 100 mm VAS†	[22]; Adjusted for baseline
	RoB: High	MD -0.3 (-0.6;0.01) on AUSCAN function scale (range 1-5)*	[22]; Adjusted for baseline, COPM scores (primary outcome) also significant improvements*
	RoB: High	MD 0.40 (-0.50;1.3) on AUSCAN pain scale (range 0-20)**	[7,25,26]; Effect estimate based on 1 trial (n=151)[26], adjusted for baseline
	RoB: High	MD 0.49 (-1.0;2.0) on AUSCAN function scale (range 0-36)*	[7,25,26]; Effect estimate based on 1 trial (n=151)[26], adjusted for baseline

Table 2. Continued

Intervention	Control	Outcome	Number of participants (studies)	Duration
		OARSI-OMERACT responder	281 (2)	12 w
		Grip strength	321 (3)	12 w
Quality of evidence:	GRADE: very low / low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low	

*In favour of the intervention group, †In favour of the control group. AUSCAN, Australian/Canadian hand osteoarthritis index; CMC, first carpometacarpal; COPM, Canadian Occupational Performance Measure; DIP, distal interphalangeal joint; idem, same as above; MCP, metacarpophalangeal joint; MD, mean difference; OA, osteoarthritis; RoB, risk of bias; RR, risk ratio; SMD, standardised mean difference; VAS, visual analogue scale; w, week(s).

Table 3. Characteristics of studies of main pharmacological interventions (n=33 studies)

RoB	Study	Design	Intervention
Topical NSAIDs			
	Altman 2009[52]	RCT	Topical diclofenac gel 1% Topical placebo cream
	Graber 1997[39]	RCT	Topical ibuprofen cream Berthollet treatment (local steam bath and finger shower)
	Michalsen 2008[92]	RCT	Diclofenac gel 10mg/g Medicinal leeches
	Romero 2013[55]	RCT	Topical diclofenac gel 2% Topical herbal cream
	Talke 1985[50]	RCT	Topical etofenamate 100 mg/g Oral indomethacin 150 mg/d
	Widrig 2007[54]	RCT	Topical ibuprofen cream 5% Topical arnica cream 50%
	Zacher 2001[51]	RCT	Topical diclofenac gel 1% Oral ibuprofen 1200 mg/d
Oral NSAIDs			
	Dreiser 1993[62]	RCT	Ibuprofen 800 mg/d Placebo
	Grifka 2004[63]	RCT	Lumiracoxib 200 mg/d Lumiracoxib 400 mg/d Placebo
	Muratore 2004[65] (A)	RCT	Ketoprofen lysine salt 160 mg/d + glucosamine + chondroitin sulfate Glucosamine + chondroitin sulfate

	Quality of evidence	Effect estimate (95% CI)		References; Comments
	RoB: High	OR 0.82 (0.42;1.6)†		[7,26]; Effect estimate based on 1 trial (n=151)[26]
	RoB: High	SMD -0.21 (-0.49;0.08)†		[7,25,26]; Effect estimate based on 2 trials (n=186)[25,26]
		Effect estimate:	No effect	Between-group difference

Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
4 per day, 8 w	198 187	ACR, Rx KL 1-3	77 77	63.6 (10.3) 64.7 (9.6)	VAS pain, AUSCAN, VAS patient global
3 per day, 2 w Daily, 3 w	57 59	ACR or clinical diagnosis isolated CMC OA	91 86	65.8 (8.6) 63.2 (10.0)	FIHOA
2 per day, 4 w Once in 4 w	16 16	CMC, clinical diagnosis and Rx damage	100	64.3 (9.1) 64.1 (6.4)	VAS pain
3 per day, 4 w	65 65	ACR	86 95	62 (10.2)	NR
3 per day, 3 w 3 w	30 30	IP, clinical diagnosis, "activated"	83 90	64.3 (13.5) 63.3 (11.0)	NR
3 per day, 3 w	99 105	ACR	61 67	64 (11.4) 64 (12.0)	VAS pain, FIHOA
4 per day, 3 w 3 w	165 156	IP, clinical diagnosis, "activated"	86 90	60.7 (9.4) 63.2 (9.4)	VAS pain improve ≥40%
2 w	30 30	Rx damage, pain exacerbation	80 90	58.5 (1.7) 60.3 (2.0)	NR
4 w	205 193 196	ACR	82 83 83	62.0 (12.1) 61.0 (12.4) 62.7 (11.7)	VAS pain
20 d	30 28	Hand, NR	100	NR	NR

Table 3. Continued

RoB	Study	Design	Intervention
	Rovetta 2001-B[49]	CCT	Dexketoprofen-trometamol 50 mg/d No intervention
	Rovetta 2001-A[48]	CO (WA-)	Dexketoprofen-trometamol 50 mg/d Paracetamol 1000 mg/d
	Seiler 1983[64]	RCT	Meclofenamate socium 300 mg/d Placebo
	Talke 1985[50]	RCT	Oral indomethacin 150 mg/d Topical etofenamate 100 mg/g
	Zacher 2001[51]	RCT	Oral ibuprofen 1200 mg/d Topical diclofenac gel 1%
Chondroitin sulfate			
	Gabay 2011[66]	RCT	Chondroitin sulfate 800 mg/d Placebo
	Verbruggen 2002[44]	RCT	Chondroitin polysulphate 50 mg/d i.m Placebo i.m.
		RCT	Chondroitin sulfate 1200 mg/d Placebo
Intra-articular glucocorticoids			
	Bahadir 2009[73]	RCT	Glucocorticoid i.a. 20 mg/0.5 ml Hyaluronic acid i.a. 5 mg/ 0.5 ml
	Fuchs 2006[74]	RCT	Glucocorticoid i.a. 10 mg/1 ml Hyaluronic acid i.a. 10 mg/1 ml
	Heyworth 2008[68]	RCT	Glucocorticoids i.a. 1 ml Hyaluronic acid i.a. 8 mg/1 ml Placebo i.a. (1 ml, saline)
	Jahangiri 2014[93]	RCT	Gluocorticoid i.a. 40 mg/0.5 ml + 0.5 ml lidocaine Dextrose i.a. 100 mg/0.5 ml + 0.5 ml lidocaine
	Mandl 2012[69](A)	RCT	Glucocorticoid i.a. 40 mg/1 ml Hyaluronic acid i.a. 8 mg/1 ml Placebo i.a. (1 ml, bupivacaine)
	Meenagh 2004[70]	RCT	Glucocorticoid i.a. 5 mg/0.25 ml Placebo i.a. (0.25 ml, saline)
	Monfort 2014[75]	RCT	Glucocorticoid i.a. 3 mg/ 0.5 ml Hyaluronic acid i.a. 5 mg/0.5 ml

Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
3 w	35	ACR, "active OA"	86	57.7 (3.4)	Morning stiffness (WOMAC)
	19		63		
13 d	36	ACR, "active OA"	NR	NR	Morning stiffness and pain (WOMAC)
4 w	22	Clinical diagnosis, ≥1 inflamed DIP and Rx damage	95	62.5 (34-77)	NR
	19		84	65.0 (49-80)	
3 w	30	IP, clinical diagnosis, "activated"	83	64.3 (13.5)	NR
3 per day, 3 w	30		90	63.3 (11.0)	
3 w	156	IP, clinical diagnosis, "activated"	90	63.2 (9.4)	VAS pain improve ≥40%
4 per day, 3 w	165		86	60.7 (9.4)	
6 mo	80	ACR	73	63.9 (8.5)	VAS pain, FIHOA
	82		76	63.0 (7.2)	
3 y	66	IP, clinical diagnosis and Rx damage	91	55.2 (6.7)	Rx progression
	64		97	56.1 (9.2)	
3 y	44	IP, clinical diagnosis and Rx damage	91	57.6 (7.1)	Rx progression
	48		88	55.9 (8.9)	
Once	20	CMC, Rx E-L stage II-III	100	62.9 (9.1)	NR
1 per w, 3 w	20			60.8 (7.3)	
1 per w, 3 w	28	CMC, clinical diagnosis and Rx KL >0	80	Median 61.0	NR
	28			Median 59.5	
Once + 1 i.a. placebo, 2 w	22	CMC, Rx E-L stage I-IV	90	60 (9.4)	NR
1 per w, 2 w	28		80	65 (10.6)	
1 per w, 2 w	18		89	64 (8.5)	
Once + 2 i.a. placebo, 3 w	30	CMC, clinical diagnosis and Rx E-L stage >I	70	63.3 (10.1)	VAS pain
1 per w, 3 w	30		77	63.9 (9.4)	
Once + 1 i.a. placebo, 2 w	65	CMC, clinical diagnosis and Rx KL >0	68	66.5 (45-89)	NR
1 per w, 2 w	62				
1 per w, 2 w	61				
Once	20	CMC, NR	95	60.6 (41-71)	VAS pain improve ≥20%
	20		85	59.3 (46-69)	
1 per w, 3w	40	CMC, clinical diagnosis and Rx KL 1-3	88	62.8 (8.7)	FIHOA
	48				

Table 3. Continued

RoB	Study	Design	Intervention
	Spolidoro 2015[71]	RCT	Glucocorticoid i.a. 4 mg/0.2 ml (DIP) or 6 mg/0.3 ml (PIP) + 0.1 ml lidocaine Placebo i.a. (0.1 ml, lidocaine)
	Stahl 2005[76]	RCT	Glucocorticoid i.a. 40 mg/1 ml Hyaluronic acid i.a. 15 mg/1 ml
Oral glucocorticoids			
	Kvien 2008[81]	RCT	Prednisone 3 mg/d + dipyridamole 200 mg/d Placebo
	Wenham 2012[82]	RCT	Prednisone 5 mg/d Placebo
Hydroxychloroquine			
	Basoski 2015[83](A)	RCT	Hydroxychloroquine 400 mg/d Placebo
	Kingsbury 2016[84](A)	RCT	Hydroxychloroquine 200-400 mg/d Placebo
	McKendry 2001[59] (A)	RCT	Hydroxychloroquine 400 mg/d Paracetamol 3900 mg/d Placebo
TNF inhibitors			
	Aitken 2017[46](A)	CO (WA+)	Adalimumab 40 mg sc. Placebo sc.
	Chevalier 2015[85]	RCT	Adalimumab 40 mg sc. Placebo sc.
	Kloppenburg 2016[47,86,87] (A)	RCT	Etanercept 25-50 mg sc. Placebo sc.
	Verbruggen 2012[45]	RCT	Adalimumab 40 mg sc. Placebo sc.

Values are mean (SD) or median (min-max). Colours denote RoB (green: low, yellow: unclear, red: high). (A) indicates conference abstract. ACR, American College of Rheumatology; AUSCAN, Australian/Canadian Hand Osteoarthritis Index, CCT, clinical controlled trial; CMC, first carpometacarpal joint; CO, cross-over trial; d, day(s); E-L, Eaton-Litter; FIHOA, Functional Index for Hand OsteoArthritis; i.a., intra-articular injection; IP, interphalangeal joint; IQR,

	Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	Once	30 30	IP, clinical diagnosis and Rx osteophyte	100 93	60.7 (9.1) 60.7 (7.3)	VAS pain, VAS joint swelling
	Once	25 27	CMC, Rx E-L stage II	84 92.5	62 (50-91) 62 (37-80)	NR
	6 w	42 41	ACR, Rx KL >1	93 93	61.1 (5.0) 59.6 (5.3)	AUSCAN pain
	4 w	35 35	ACR, Rx KL >0	74 89	61.9 (6.6) 61.1 (9.0)	VAS pain
	24 w	98 98	ACR	86	57	VAS pain
	1 y	124 124	ACR	NR	NR	NRS pain
	24 w	29 29 30	Hand, NR	NR	NR	NR
	2 sc. per 2 w, 12 w	43	ACR, erosive (Rx erosion), MRI synovitis	77	61 (8.4)	AUSCAN pain
	Once 2 sc., 2 w	42 43	ACR, Rx damage IPs	87 83	62.8 (6.9) 62.2 (7.0)	VAS pain improve ≥50%
	1 sc. per w, 1 y	45 45	IP, ACR, erosive (Rx erosion IP)	82 80	59.4 (6.5) 60.1 (8.7)	VAS pain
	1 sc. per 2 w, 1 y	30 30	IP, ACR, erosive (Rx erosion IP)	87 83	61.9 (6.1) 60.7 (6.9)	Rx progression

interquartile range; KL, Kellgren-Lawrence; NR, not reported; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; RCT, randomised controlled trial; RoB, risk of bias; Rx, radiography; sc., subcutaneous injection; TNF, tumour necrosis factor; VAS, visual analogue scale; w, week(s); WA, wash-out period; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; y, year(s).

Table 4. Efficacy of main pharmacological interventions for hand osteoarthritis from RCTs/CCTs

Intervention	Control	Outcome	Number of participants (studies)	Duration	Specific OA location or type
Topical NSAIDs					
Topical NSAID	Topical placebo	Pain	385 (1)	8 w	-
		Function	385 (1)	8 w	-
		OARSI-OMERACT response	385 (1)	8 w	-
Topical NSAID	Oral NSAID	Pain	381 (2)	3 w	"activated" IP OA
		Grip strength	381 (2)	3 w	"activated" IP OA
Oral NSAIDs					
Oral NSAID	Placebo	Pain	695 (3)	2-4 w	-
		Function	695 (3)	2-4 w	-
Chondroitin sulfate					
Chondroitin sulfate	Placebo	Pain	162 (1)	26 w	-
		Function	162 (1)	26 w	-
		Grip strength	162 (1)	26 w	-
Intra-articular therapies					
Intra-articular glucocorticoids	Intra-articular placebo	Pain	206 (3)	26 w	CMC
		Function	166 (2)	26 w	CMC
Intra-articular glucocorticoids	Intra-articular placebo	Pain	60 (1)	12 w	IP
		Function	60 (1)	12 w	IP
		Grip strength	60 (1)	12 w	IP
Intra-articular hyaluronic acid	Intra-articular placebo	Pain	235 (3)	26 w	CMC
		Function	235 (3)	26 w	CMC
Hydroxychloroquine					
Hydroxychloroquine	Placebo	Pain	503 (3)	24-52 w	-
		Function	444 (2)	24-52 w	-
		Grip strength	248 (1)	52 w	-

	Quality of evidence	Effect estimate (95% CI)	References; Comments
	RoB: Low	MD -5.9 (-11.7;-0.06) on 100mm VAS*	[52]
	RoB: Low	MD -7.3 (-12.9;-1.7) on AUSCAN function scale (range 0-36)*	[52]
	RoB: Low	RR 1.2 (0.99;1.4)*	[52]
	RoB: Low	SMD -0.05 (-0.27;0.17)*	[50,51]; Effect estimate based on 1 trial (n=321)[51]; same studies as previous SLR[1]
	RoB: Low	MD -0.01 (-0.03;0.01) bar*	[50,51]; Effect estimate based on 1 trial (n=321)[51]
	RoB: Low	SMD 0.40 (0.20;0.60)*	[62-64]; Effect estimate based on 2 trials with ibuprofen 800mg and lumiracoxib 200-400mg (n=654)[62,63]; same studies as previous SLR[1]
	RoB: Low	SMD 0.17 (-0.03;0.36)*	idem
	RoB: Low	MD -8.7 (p=0.016) on 100mm VAS*	[66]
	RoB: Low	MD -2.1 (p=0.008) on FIHOA (range 0-30)*	[66]
	RoB: Low	MD 1.9 (-0.02;3.8) kg*	[66]
	RoB: Low (1), unclear (1)	MD -3.6 (-13.9;6.8) on 100mm VAS*	[68-70]; Effect estimate based on 2 trials (n=166)[69,70]
	RoB: Unclear	MD -1.5 (-6.3;3.3) on DASH (range 0-100)*	[68,69]; Effect estimate based on 1 trial (n=126)[69]
	RoB: Low	MD -18.0 (-33.5;-2.6) on 100mm VAS*	[71]; Outcome: pain on movement; for pain in rest no between-group differences observed
	RoB: Low	MD -4.4 (-9.4;0.56) on AUSCAN function scale (range 0-36)*	[71]
	RoB: Low	MD 0.98 (-2.6;4.5) kg*	[71]
	RoB: Unclear	MD 3.3 (-5.2;11.8) on 100mm VAS†	[68,69,72]; Effect estimate based on 1 trial (n=123)[69]
	RoB: Unclear	MD -2.1 (-6.3;2.1) on DASH (range 0-100)*	idem
	RoB: Unclear	MD 2.9 (-3.4;9.2) on 100mm VAS†	[59,83,84]; Effect estimate based on 2 trials (n=307)[59,84]
	RoB: Unclear	MD -0.79 (-2.4;0.78) on AUSCAN function scale (range 0-36)†	[83,84]; Effect estimate based on 1 trial (n=248)[84]
	RoB: Unclear	MD 0.95 (-0.82;2.72) kg†	[84]

Table 4. Continued

Intervention	Control	Outcome	Number of participants (studies)	Duration	Specific OA location or type
TNF inhibitors					
TNF inhibitor	Placebo	Pain	235 (3)	24-52 w	Erosive OA (2/3 trials)
		Function	235 (3)	24-52 w	Erosive OA (2/3 trials)
		Grip strength	150 (2)	52 w	Erosive OA
Quality of evidence:	GRADE: very low / low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low		

*In favour of the intervention group, †In favour of the control group. AUSCAN, Australian/Canadian hand osteoarthritis index; CMC, first carpometacarpal joint; DASH, Disabilities of the Arm, Shoulder and Hand; DIP, distal interphalangeal joint; idem, same as above; IP, interphalangeal joint; MD, mean difference; mm, millimetre; NSAID, non-steroidal anti-

Surgical interventions

A Cochrane review summarised all available trials of thumb base surgery.[88] No trials compared surgery to sham surgery or non-operative treatment. The trials all compared different surgical interventions for thumb base OA. Most trials compared trapeziectomy with and without ligament reconstruction tendon interposition (LRTI), but there was no difference in pain (three trials with 162 participants, MD -2.8 (95% CI -9.8 to 4.2) on 100 mm VAS) or function (three trials with 211 participants, SMD 0.01 (95% CI -0.30 to 0.32)), while the risk for more complications was increased in the trapeziectomy with LRTI groups (RR 1.9 (95% CI 0.96 to 3.7)). Single, low-quality studies compared other surgical interventions to each other, but did not show that one intervention was clearly superior over another in terms of efficacy or complication rate. Most importantly, compared with trapeziectomy, both arthrodesis (one trial, 37 participants) and joint replacement surgery (one trial, 26 participants) did not lead to different clinical outcomes. No studies of IP joint surgery could be included in our review.

DISCUSSION

This SLR summarises the current evidence for efficacy and safety of all non-pharmacological, pharmacological and surgical treatments for hand OA. Non-pharmacological treatments that were shown to result in symptom relief included hand exercise and prolonged splinting of the thumb base, while single trials showed positive results for joint protection and use of assistive devices. However, the RoB in most trials was high, mainly due to lack of blinding and effect sizes were modest. Pharmacological treatments that most evidently proved to be efficacious in relieving symptoms were NSAIDs, both topical and oral preparations, as assessed in high-quality trials. Single trials, also judged to be at low RoB, reported beneficial results for

	Quality of evidence	Effect estimate (95% CI)		References; Comments
	RoB: Low	MD -4.9 (-12.5;2.8) on 100mm VAS*		[45,85,86]; Effect estimate based on 2 trials (n=175)[85,86]
	RoB: Low (1), unclear (1)	SMD -0.02 (-0.35;0.32)*		[45,85,86]; Effect estimate based on 2 trials (n=145)[45,85]
	RoB: Low (1), unclear (1)	MD 0.70 (-0.59;2.0) kg*		[45,86]; Effect estimate based on 1 trial (n=60)[45]
	Effect estimate:	No effect	Between-group difference	

inflammatory drug; OA, osteoarthritis; OR, odds ratio; RoB, risk of bias; RR, risk ratio; SLR, systematic literature review; SMD, standardised mean difference; TNF, tumour necrosis factor; VAS, visual analogue scale; w, week(s).

chondroitin sulfate and intra-articular injections of glucocorticoids in interphalangeal OA. Also for pharmacological interventions, effect sizes were modest, as considered using the cut-offs proposed by Cohen *et al* (ie, 0.2 representing a small, >0.5 a moderate and >0.8 a large effect).[89] The effect of oral NSAIDs on pain, with an SMD of 0.4, was the largest effect. Taking an effect size of 0.37 as a minimal clinically important difference (MCID; based on the median MCID in four recent OA trials[90]), corresponding to 9 mm on a 100 mm VAS, only the effects of prolonged thumb base splinting, oral NSAIDs and intra-articular glucocorticoid injections in interphalangeal joints crossed the margin of clinical meaningful difference. Promising pharmacological treatments for which no clear beneficial effect was demonstrated include paracetamol, intra-articular injections of glucocorticoids or hyaluronic acid in the thumb base joint, low-dose oral glucocorticoids, hydroxychloroquine and TNF inhibitors. Disease-modifying properties, especially radiographic progression, were studied in only a few trials. No convincing effects were found for the formulations investigated, namely chondroitin sulfate (one trial) and TNF inhibitors (two trials). A signal for less erosive damage after 1 year of treatment with anti-TNF was reported in subgroup analyses of joints with clinical signs of inflammation at baseline in two separate trials, yet studies powered for this research question have not been performed to confirm this finding.

Safety was also evaluated in this SLR, though it should be noted that this outcome is best studied in large long-term observational studies with high-quality follow-up since RCTs are usually underpowered to assess this outcome and include a more selected population. Although we aimed to include observational studies for this purpose, we did not find any with our search strategy. Based on this SLR, it is therefore not possible to draw strong conclusions on the safety aspect of many of the assessed therapies. Importantly, the included trials of topical and oral NSAIDs showed that, while no difference in efficacy could be proven, topical NSAIDs were indeed associated with less AEs than oral NSAIDs. Furthermore, no increased risk of AEs was shown for topical NSAIDs compared with placebo. These observations support topical

NSAIDs as a useful option for first-line pharmacological treatment. Regarding surgical options, no specific intervention for thumb base OA appeared more effective than another, although in general more complex procedures led to more complications.

The trials included in this review were rather heterogeneous in many aspects, for example in the type of intervention, study duration, and assessed outcomes. This precluded meta-analysis in most instances. Some more recently published trials assessed more of the outcome measures summarised in the OMERACT core set for domains in clinical trials for hand OA.[3] A core set for the instruments best used to measure these core domains is still underway. It may be expected that such a core set of instruments will help to harmonise outcome assessment in future clinical trials, which will ultimately improve the assessment of new treatment options.

Despite the large increase in the amount of trials published in the field of hand OA since the previous EULAR management recommendations in 2007 (39 out of 50 and 43 out of 64 included trials of non-pharmacological and pharmacological therapies, respectively, were published in 2007 or later), some important questions remain. For example, placebo-controlled trials of thumb base splints, paracetamol, tramadol and surgery (both for thumb base and interphalangeal OA) are lacking. Moreover, while some trials specifically include a subset of participants with OA of the thumb base, or with "inflammatory" or "activated" (finger) OA, more trials targeting specific subsets of patients expected to respond to the investigated treatment are needed. Furthermore, many studies were assessed to be at high RoB, often due to lack of blinding or inadequate method of randomisation. So although the number of trials may have increased, their quality is not consistent. For some interventions, especially non-pharmacological therapies, it is difficult to perform a double-blind trial, and therefore the evidence currently available is probably the best we can get. Recently, the Consolidated Standards of Reporting Trials has issued a statement addressing methodological issues specific to trials of non-pharmacological treatments to provide more guidance in this respect.[91] However, other interventions, especially pharmacological therapies, are more easily studied in a double-blind fashion, and therefore, well-performed trials are needed and may change the conclusions of this review, for example for paracetamol.

This SLR has a few strengths, most importantly the methodological rigour with which it was performed, and the presentation of a comprehensive summary of the vast amount of data on the management of hand OA that has accrued so far. However, some limitations have to be acknowledged. Study selection and data extraction was performed by one review author, whereas this should ideally be performed by two independent persons. Many studies were only published as a conference abstract at the time of manuscript preparation, precluding an assessment of the RoB (now categorised as 'unclear').

In conclusion, this paper presents the current evidence on efficacy and safety of all non-pharmacological, pharmacological, and surgical treatments for hand OA, and was used to inform the task force for the 2018 update of the EULAR recommendations for the management of hand OA.

REFERENCES

1. Zhang W, Doherty M, Leeb B, et al. EULAR evidence based recommendations for the management of hand osteoarthrtitis: Report of a Task Force of the EULAR standing committee for international clinical studies including therapeutics *Ann Rheum Dis* 2007;66:377-88.
2. Sackett D, WS R, Rosenberg W. *Evidence-based medicine: how to practice and teach EBM*. London: Churchill Livingstone, 1997.
3. Kloppenburg M, Bøyesen P, Vissser W, et al. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies. 2015;42:2190-7.
4. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12:389-99.
5. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
6. Østerås N, Kjeken I, Smedslund G, et al. Exercise for hand osteoarthritis. *Cochrane Database Syst Rev* 2017;1:CD010388.
7. Dziedzic K, Nicholls E, Hill S, et al. Self-management approaches for osteoarthritis in the hand: A 2x2 factorial randomised trial. *Ann Rheum Dis* 2015;74:108-18.
8. Adams J, Boucas SB, Hislop K, et al. The effectiveness and efficacy of splints for thumb base osteoarthritis: A pilot randomized controlled trial. *Rheumatology* 2014;53:i41-i42.
9. Arazpour M, Soflaei M, Ahmadi Bani M, et al. The effect of thumb splinting on thenar muscles atrophy, pain, and function in subjects with thumb carpometacarpal joint osteoarthritis. *Prosthet Orthot Int* 2017;41:379-86.
10. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. *J Rehabil Med* 2010;42:469-74.
11. Hermann M, Nilsen T, Eriksen CS, et al. Effects of a soft prefabricated thumb orthosis in carpometacarpal osteoarthritis. *Scand J Occup Ther* 2014;21:31-39.
12. Rannou F, Dimet J, Boutron I, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. *Ann Int Med* 2009;150:661-9.
13. Becker SJ, Bot AG, Curley SE, et al. A prospective randomized comparison of neoprene vs thermoplast hand-based thumb spica splinting for trapeziometacarpal arthrosis. *Osteoarthritis Cartilage* 2013;21:668-75.
14. Cantero-Téllez R, Villafane JH, Valdes K, et al. Effect of immobilization of metacarpophalangeal joint in thumb carpometacarpal osteoarthritis on pain and function. A quasi-experimental trial. *J Hand Ther* 2016;31:68-73.
15. Wajon A, Ada L. No difference between two splint and exercise regimens for people with osteoarthritis of the thumb: a randomised controlled trial. *Aust J Physiother* 2005;51:245-9.
16. Bani MA, Arazpour M, Kashani RV, et al. Comparison of custom-made and prefabricated neoprene splinting in patients with the first carpometacarpal joint osteoarthritis. *Disabil Rehabil Assist Technol* 2013;8:232-7.
17. Sillem H, Backman CL, Miller WC, et al. Comparison of two carpometacarpal stabilizing splints for individuals with thumb osteoarthritis. *J Hand Ther* 2011;24:216-26.
18. Van der Vegt AE, Grond R, Gruschke JS, et al. The effect of two different orthoses on pain, hand function, patient satisfaction and preference in patients with thumb carpometacarpal osteoarthritis: a multicentre, crossover, randomised controlled trial. *Bone Joint J* 2017;99B:237-44.
19. Weiss S, LaStayo P, Mills A, et al. Prospective analysis of splinting the first carpometacarpal joint: An objective, subjective, and radiographic assessment. *J Hand Ther* 2000;13:218-27.
20. Weiss S, Lastayo P, Mills A, et al. Splinting the degenerative basal joint: Custom-made or prefabricated neoprene? *J Hand Ther* 2004;17:401-6.
21. Watt FE, Kennedy DL, Carlisle KE, et al. Night-time immobilization of the distal interphalangeal joint reduces pain and extension deformity in hand osteoarthritis. *Rheumatology* 2014;53:1142-9.
22. Kjeken I, Darre S, Smedslund G, et al. Effect of assistive technology in hand osteoarthritis: A randomised controlled trial. *Ann Rheum Dis* 2011;70:1447-52.
23. Boustedt C, Nordenskiöld U, Lundgren Nilsson A. Effects of a hand-joint protection programme with an addition of splinting and exercise. *Clin Rheumatol* 2009;28:793-9.
24. Pérez-Mármol JM, Garcia-Rios MC, Ortega-Valdivieso MA, et al. Effectiveness of a fine motor skills rehabilitation program on upper limb disability, manual dexterity, pinch strength, range of fingers motion, performance in activities of daily living,

functional independency, and general self-efficacy in hand osteoarthritis: A randomized clinical trial. *J Hand Ther* 2017;30:262-73.
25. Stamm TA, Machold KP, Smolen JS, et al. Joint protection and home hand exercises improve hand function in patients with hand osteoarthritis: A randomized controlled trial. *Arthritis Care Res* 2002;47:44-49.
26. Stukstette MJ, Dekker J, den Broeder AA, et al. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term; results of arandomized controlled trial. *Osteoarthritis Cartilage* 2013;21:901-10.
27. Stukstette MJ, Van Den Ende CHM, Hoogeboom TJ, et al. In patients with hand osteoarthritis there is no evidence that a booster session after multidisciplinary treatment is effective;results of a randomised controlled trial. *J Hand Ther* 2014;27:e2-e3.
28. Villafañe JH, Cleland JA, Fernández-de-Las-Peñas C. The Effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: A randomized controlled trial. *J Orthop Sports Phys Ther* 2013;43:204-13.
29. Dilek B, Gözüm M, Şahin E, et al. Efficacy of paraffin bath therapy in hand osteoarthritis: A single-blinded randomized controlled trial. *Arch Phys Med Rehabil* 2013;94:642-9.
30. Favaro L, Frisoni M, Baffoni L, et al. Successful treatment of hand erosive osteoarthritis by infrared radiation. *Eur J Phys Rehab Med* 1994;30:45-8.
31. Stange-Rezende L, Stamm TA, Schiffert T, et al. Clinical study on the effect of infrared radiation of a tiled stove on patients with hand osteoarthritis. *Scand J Rheumatol* 2006;35:476-80.
32. Villafañe JH, Silva GB, Diaz-Parreño SA, et al. Hypoalgesic and motor effects of Kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial. *J Manipulative Physiol Ther* 2011;34:547-56.
33. Villafañe JH, Fernandez-de-Las-Peñas C, Silva GB, et al. Contralateral sensory and motor effects of unilateral kaltenborn mobilization in patients with thumb carpometacarpal osteoarthritis: a secondary analysis. *J Phys Ther Sci* 2014;26:807-12.
34. Villafañe JH, Silva GB, Bishop MD, et al. Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial. *Arch Phys Med Rehabil* 2012;93:396-403.
35. Villafañe JH, Bishop MD, Fernandez-de-Las-Peñas C, et al. Radial nerve mobilisation had bilateral sensory effects in people with thumb carpometacarpal osteoarthritis: a randomised trial. *J Physiother* 2013;59:25-30.
36. Villafañe JH, Silva GB, Fernandez-Carnero J. Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis. *J Manipulative Physiol Ther* 2012;35:110-20.
37. Villafañe JH, Cleland JA, Fernandez-de-Las-Peñas C. Bilateral sensory effects of unilateral passive accessory mobilization in patients with thumb carpometacarpal osteoarthritis. *J Manipulative Physiol Ther* 2013;36:232-7.
38. Kasapoğlu Aksoy M, Altan L, Eröksüz R, et al. The efficacy of peloid therapy in management of hand osteoarthritis. *Ann Rheum Dis* 2017;76:974.
39. Graber-Duvernay B, Forestier R, Francon A. Efficacy of the Berthollet technique at Aix les Bains spa on functional impairment in hand ostheoarthritis. A controlled therapeutic study. (French). *Rhumatologie* 1997;49:151-6.
40. Horváth K, Kulisch Á, Németh A, et al. Evaluation of the effect of balneotherapy in patients with osteoarthritis of the hands: a randomized controlled single-blind follow-up study. *Clin Rehabil* 2012;26:431-41.
41. Gyarmati N, Kulisch Á, Németh A, et al. Evaluation of the effect of hévíz mud in patients with hand osteoarthritis: A randomized, controlled, single-blind follow-up study. *Isr Med Assoc J* 2017;19:177-82.
42. Kovács C, Pecze M, Tihanyi Á, et al. The effect of sulphurous water in patients with osteoarthritis of hand. Double-blind, randomized, controlled follow-up study. *Clin Rheumatol* 2012;31:1437-42.
43. Fioravanti A, Tenti S, Giannitti C, et al. Short- and long-term effects of mud-bath treatment on hand osteoarthritis: a randomized clinical trial. *Int J Biometeorol* 2014;58:79-86.
44. Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin Rheumatol* 2002;21:231-43.
45. Verbruggen G, Wittoek R, Vander Cruyssen B, et al. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891-8.
46. Aitken D, Pan F, Laslett L, et al. A randomised double-blind placebo-controlled crossover trial of humira (adalimumab) for erosive hand osteoarthritis: the HUMOR trial. *Osteoarthritis Cartilage* 2017;25:S9.
47. Kloppenburg M, Ramonda R, Kwok WY, et al. Randomized, placebo-controlled trial to evaluate clinical efficacy and structure modifying properties of subcutaneous etanercept (ETN) in patients with erosive inflammatory hand osteoarthritis (OA). *Ann*

Rheum Dis 2016;75:90-91.
48. Rovetta G, Monteforte P. (Dexketoprofen-trometamol in patients with osteoarthritis of the hands). (*Italian*). *Minerva Ortop Traumatol* 2001;52:27-30.
49. Rovetta G, Monteforte P, Brignone A, et al. Early-morning administration of dexketoprofen-trometamol in morning stiffness induced by nodal osteoarthritis of the hands. *Int J Tissue React* 2001;23:63-66.
50. Talke M. Treatment of Heberden and Bouchard types of finger osteoarthritis. Comparison between local etofenamate and oral indomethacin. *Die Therapiewoche* 1985;35:3948-54.
51. Zacher J, Burger KJ, Farber L, et al. (Topical diclofenac versus oral ibuprofen: A double blind, randomized clinical trial to demonstrate efficacy and tolerability in patients with activated osteoarthritis of the finger joints (Heberden and/or Bouchard arthritis)). (*German*). *Aktuel Rheumatol* 2001;26:7-14.
52. Altman RD, Dreiser RL, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: A randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009;36:1991-99.
53. Baraf HS, Gold MS, Petruschke RA, et al. Tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. *Am J Geriatr Pharmacother* 2012;10:47-60.
54. Widrig R, Suter A, Saller R, et al. Choosing between NSAID and arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study. *Rheumatology Int* 2007;27:585-91.
55. Romero-Cerecero O, Meckes-Fischer M, Zamilpa A, et al. Clinical trial for evaluating the effectiveness and tolerability of topical Sphaeralcea angustifolia treatment in hand osteoarthritis. *J Ethnopharmacol* 2013;147:467-73.
56. Schnitzer T, Morton C, Coker S. Topical capsaicin therapy for osteoarthritis pain: achieving a maintenance regimen. *Semin Arthritis Rheum* 1994;23:34-40.
57. Rothacker D, Difigilo C, Lee I. A clinical trial of topical 10% trolamine salicylate in osteoarthritis. *Curr Ther Res Clin Exp* 1994;55:584-97.
58. Rothacker DQ, Lee I, Littlejohn TW. Effectiveness of a single topical application of 10% trolamine salicylate cream in the symptomatic treatment of osteoarthritis. *J Clin Rheumatol* 1998;4:6-12.
59. McKendry R, Thorne C, Weisman M, et al. Hydroxychloroquine (HCQ) versus acetaminophen (ACM) versus placebo (PL) in the treatment of nodal osteoarthritis (NOA) of the hands. *J Rheumatol* 2001;28:1421.
60. Patru S, Marcu I, Matei D. Efficacy and safety of rumalaya forte to patients with hand osteoarthritis (HOA). *Ann Rheum Dis* 2016;74:1194.
61. Patru S, Marcu IR, Bighea AC. Efficacy of glucosamine sulfate (GS) in hand osteoarthritis. *Osteoporos Int* 2012;23:S169.
62. Dreiser RL, Gersberg M, Thomas F, et al. (Ibuprofen 800 mg in the treatment of arthrosis of the fingers or rhizarthrosis). (*French*). *Rev Rhum Ed Fr* 1993;60:836-41.
63. Grifka JK, Zacher J, Brown JP, et al. Efficacy and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand. *Clin Exp Rheumatol* 2004;22:589-96.
64. Seiler V. Meclofenamate sodium in the treatment of degenerative joint disease of the hand (Heberden nodes). *Arzneimittelforschung* 1983;33:656-9.
65. Muratore M, Quarta L, Grimaldi A, et al. Efficacy of ketoprofen lysine salt in reducing inflammation and pain in primary osteoarthritis of the hand: Preliminary results of a retrospective and prospective clinical trial. *Arthritis Rheumatol* 2014;66:S974.
66. Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: A randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum* 2011;63:3383-91.
67. Shin K, Kim JW, Moon KW, et al. The Efficacy of Diacerein in Hand Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Study. *Clin Ther* 2013;35:431-9.
68. Heyworth BE, Lee JH, Kim PD, et al. Hylan Versus Corticosteroid Versus Placebo for Treatment of Basal Joint Arthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. *J Hand Surg Am* 2008;33:40-48.
69. Mandl LA, Wolfe S, Daluiski A, et al. A randomized controlled trial of hylan G-F 20 for the treatment of carpometacarpal osteoarthritis. *Arthritis Rheum* 2012;64:S475-6.
70. Meenagh GK, Patton J, Kynes C, et al. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004;63:1260-3.
71. Spolidoro Paschoal NO, Natour J, Machado FS, et al. Effectiveness of Triamcinolone Hexacetonide Intraarticular Injection in Interphalangeal Joints: A 12-week Randomized Controlled Trial in Patients with Hand Osteoarthritis. *J Rheumatol* 2015;42:1869-77.
72. Figen Ayhan F, Ustün N. The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up. *Clin Rheumatol* 2009;28:535-41.
73. Bahadir C, Onal B, Dayan VY, et al. Comparison of therapeutic effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint

osteoarthritis. *Clin Rheumatol* 2009;28:529-33.
74. Fuchs S, Mönikes R, Wohlmeiner A, et al. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. *Osteoarthritis Cartilage* 2006;14:82-88.
75. Monfort J, Rotés-Sala D, Segalés N, et al. Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: results of a 6-month single-masked randomized study. *Joint Bone Spine* 2015;82:116-21.
76. Stahl S, Karsh-Zafrir I, Ratzon N, et al. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. *J Clin Rheumatol* 2005;11:299-302.
77. Roux C, Fontas E, Breuil V, et al. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. *Joint Bone Spine* 2007;74:368-72.
78. Massarotti M, Crotti C, Ughi N, et al. Comparison of two different intra-articular hyaluronic acid compounds for carpo-metacarpal joint osteoartrhitis. *Ann Rheum Dis* 2013;71:695.
79. Fioravanti A, Fabbroni M, Cerase A, et al. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: A pilot study. *Rheumatol Int* 2009;29:961-5.
80. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: Evidence of clinical efficacy. *J Altern Complement Med* 2000;6:311-20.
81. Kvien TK, Fjeld E, Slatkowsky-Christensen B, et al. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942-8.
82. Wenham CYJ, Hensor EM, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* 2012;51:2286-94.
83. Basoski N, Lee W, Ruijgrok L, et al. Efficacy of hydroxychloroquine in primary hand osteoarthritis: A randomized, double-blind, placebo controlled trial. *Ann Rheum Dis* 2015;74:188.
84. Kingsbury SR, Tharmanathan P, Keding A, et al. Hydroxychloroquine is not effective in reducing symptoms of hand osteoarthritis: Results from a placebo-controlled randomised trial. *Arthritis Rheumatol* 2016;68:4189-91.
85. Chevalier X, Ravaud P, Maheu E, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697-705.
86. Kroon F, Wittoek R, Kwok W-Y, et al. Effect of etanercept on several soluble biomarkers in a randomized controlled trial of patients with erosive hand osteoarthritis. *Arthritis Rheum* 2016;68:3093-4.
87. Kroon FP, Wittoek R, Verbruggen G, et al. Effect of etanercept on synovitis and bone marrow lesions in erosive hand osteoarthritis. *Ann Rheum Dis* 2016;75:91-92.
88. Wajon A, Vinycomb T, Carr E, et al. Surgery for thumb (trapeziometacarpal joint) osteoarthritis. *Cochrane Database Syst Rev* 2015;2:CD004631.
89. Cohen J. *Statistical power analysis for the behavioral sciences, 2nd ed*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
90. Rutjes AW, Jüni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Int Med* 2012;157:180-91.
91. Boutron I, Altman DG, Moher D, et al. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Int Med* 2017;167:40-7.
92. Michalsen A, Lüdtke R, Cesur O, et al. Effectiveness of leech therapy in women with symptomatic arthrosis of the first carpometacarpal joint: a randomized controlled trial. *Pain* 2008;137:452-9.
93. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. *J Orthop Sci* 2014;19:737-43.

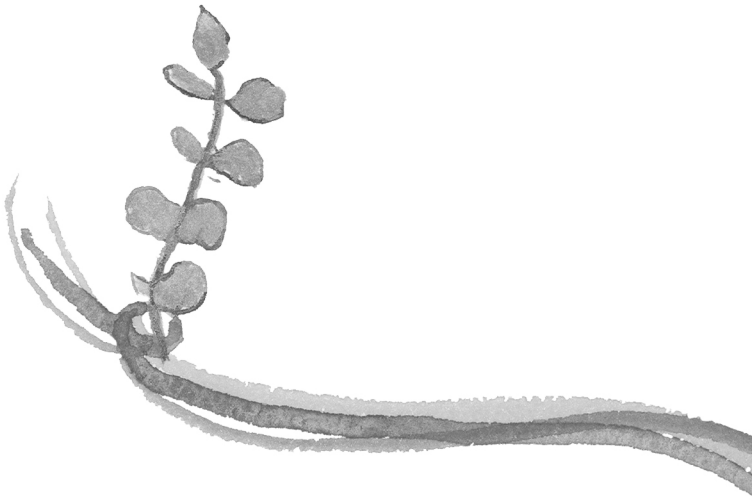


CHAPTER 4

2018 update of the EULAR recommendations for the management of hand osteoarthritis

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ABSTRACT

Since publication of the European League Against Rheumatism (EULAR) recommendations for management of hand osteoarthritis (OA) in 2007 new evidence has emerged. The aim was to update these recommendations. EULAR standardised operating procedures were followed. A systematic literature review was performed, collecting the evidence regarding all non-pharmacological, pharmacological and surgical treatment options for hand OA published to date. Based on the evidence and expert opinion from an international task force of 19 physicians, healthcare professionals and patients from 10 European countries overarching principles and recommendations were formulated. Level of evidence, grade of recommendation and level of agreement were allocated to each statement. Five overarching principles and 10 recommendations were agreed on. The overarching principles cover treatment goals, information provision, individualisation of treatment, shared decision-making and the need to consider multidisciplinary and multimodal (non-pharmacological, pharmacological, surgical) treatment approaches. Recommendations 1-3 cover different non-pharmacological treatment options (education, assistive devices, exercises and orthoses). Recommendations 4-8 describe the role of different pharmacological treatments, including topical treatments (preferred over systemic treatments, topical non-steroidal anti-inflammatory drugs (NSAIDs) being first-line choice), oral analgesics (particularly NSAIDs to be considered for symptom relief for a limited duration), chondroitin sulfate (for symptom relief), intra-articular glucocorticoids (generally not recommended, consider for painful interphalangeal OA) and conventional/biological disease-modifying antirheumatic drugs (discouraged). Considerations for surgery are described in recommendation 9. The last recommendation relates to follow-up. The presented EULAR recommendations provide up-to-date guidance on the management of hand OA, based on expert opinion and research evidence.

INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disease, with prevalence rising steeply with increasing age.[1-3] The disease is associated with hand pain, stiffness, functional limitation, decreased grip strength and reduced quality of life.[4-6] Clinical hallmarks of the disease include bony enlargement and deformities of the hand joints, at times accompanied by soft tissue swelling.[7] Hand OA has a variable disease course.[8] The first European League Against Rheumatism (EULAR) recommendations for the management of hand OA were published in 2007.[9] The American College of Rheumatology (ACR) published management recommendations for hand, hip and knee OA in 2012, including evidence available to the end of 2010, and other societies, including an expert group of occupational therapists and the Italian Society for Rheumatology, formulated treatment recommendations in 2011 and 2013, respectively.[10-12]

For a long time, hand OA was a "forgotten disease", resulting in a paucity of clinical trials to guide recommendations, and therefore many of the propositions of previous recommendations were based mainly on expert opinion.[13] However, in recent years, hand OA has attracted more attention, and new data have become available on several pharmacological and non-pharmacological treatments, including but not limited to: self-management, application of thumb base orthoses, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, various intra-articular therapies and treatment with conventional synthetic and biological disease-modifying antirheumatic drugs (cs/bDMARDs), for example, hydroxychloroquine and tumour necrosis factor (TNF) inhibitors.

These more recent data have given new insights into treatment options. It was therefore timely to update the 2007 management recommendations. In this paper, we present the 2018 update of the EULAR recommendations for the management of hand OA.

METHODS

The development of the update was performed according to the 2014 EULAR Standard Operating Procedure (SOP).[14] As prescribed by the SOP, the process set out in Appraisal of Guidelines for Research & Evaluation II (AGREE II) was followed.[15] The convenor (MK), methodologist (LC) and fellow (FK) defined research questions for the systematic literature review (SLR) and prepared a 1-day task force meeting. The task force further comprised 10 rheumatologists, 1 plastic surgeon (MR), 3 healthcare professionals in the field of physiotherapy and occupational therapy (KD, IK, TS) and 2 patient research partners (EG, WS). Two task force members were Emerging EUlar NETwork members (IKH, FK). The task force represented 10 countries across Europe.

Under guidance of the methodologist, the fellow performed an SLR on the efficacy and safety of all non-pharmacological, pharmacological and surgical therapies available for hand OA. Although published separately, the SLR[16] and the current updated management recommendations are complementary and should be considered together.

To explore current clinical practice in hand OA treatment and which topics healthcare professionals and patients felt should be covered in the update of the recommendations, members of the task force completed an online survey prior to the 1-day meeting.

Using the previous recommendations as a basis, together with the data obtained from the survey and the SLR, the convenor, methodologist and fellow prepared a proposal for wording for the update of the recommendations.

The results of the survey and the SLR were sent to the task force members in advance of a 1-day meeting where they were again presented. Through group discussion, overarching principles were formulated and the recommendations were updated. For every proposed overarching principle and recommendation, the results from the survey, evidence from the SLR and a proposed formulation were presented. Following discussion and rewording of the statement, voting was undertaken. A 75% majority was required to approve the statement. In case of disagreement, discussion was resumed and changes to the statement were made. The second voting round required a 67% majority, and if the formulation remained unagreed, an additional round of discussion followed. The third voting round required only 50% support for approval of the statement. The wording of the statements was considered final after the 1-day meeting.

After the meeting, the level of evidence (LoE) and grade of recommendation (GoR) were added to each recommendation, derived from the evidence from the SLR and according to the Oxford Centre for Evidence-Based Medicine standards.[17] Finally, the overarching principles and recommendations (including LoE and GoR, and rationale for each statement based on the survey data, evidence from the SLR and discussion during the 1-day meeting) were sent to all task force members, who were asked to add their level of agreement (LoA) to each of the statements. The vote for the LoA was carried out anonymously on a numerical rating scale of 0-10 (0: do not agree at all, 10: fully agree). The mean and SD were calculated.

The final manuscript was reviewed, revised and approved by all task force members, followed by a final review by the EULAR Executive Committee.

RESULTS

Overarching principles

Overarching principles were not stated in the 2007 recommendations and were a new inclusion in the 2018 update. Overarching principles are generic statements, serving as the basis for management of patients with hand OA. Some of the 2007 recommendations were included in the 2018 update in the form of an overarching principle. The LoA of each overarching principle is presented in table 1.

Table 1. 2018 Update of the EULAR recommendations for the management of hand OA

	Overarching principles	LoE*	GoR†	LoA (0-10)
A.	The primary goal of managing hand OA is to control symptoms, such as pain and stiffness, and to optimise hand function, in order to maximise activity, participation and quality of life			9.7 (0.7)
B.	All patients should be offered information on the nature and course of the disease, as well as education on self-management principles and treatment options			9.8 (0.8)
C.	Management of hand OA should be individualised taking into account its localisation and severity, as well as comorbidities			9.9 (0.2)
D.	Management of hand OA should be based on a shared decision between the patient and the health professional			9.6 (1.1)
E.	Optimal management of hand OA usually requires a multidisciplinary approach. In addition to non-pharmacological modalities, pharmacological options and surgery should be considered			9.3 (1.2)
	Recommendations			
1.	Education and training in ergonomic principles, pacing of activity, and use of assistive devices, should be offered to every patient	1b	A	9.3 (1.1)
2.	Exercises to improve function and muscle strength, as well as to reduce pain, should be considered for every patient	1a	A	9.1 (1.6)
3.	Orthoses should be considered for symptom relief in patients with thumb base OA. Long term use is advocated	1b	A	9.3 (1.0)
4.	Topical treatments are preferred over systemic treatments because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice	1b	A	8.6 (1.8)
5.	Oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms	1a	A	9.4 (0.9)
6.	Chondroitin sulfate may be used in patients with hand OA for pain relief and improvement in functioning	1b	A	7.3 (2.7)
7.	Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA*, but may be considered in patients with painful interphalangeal joints**	*1a-**1b	A	7.9 (2.4)
8.	Patients with hand OA should not be treated with conventional or biological disease modifying antirheumatic drugs	1a	A	8.8 (1.8)
9.	Surgery should be considered for patients with structural abnormalities when other treatment modalities have not been sufficiently effective in relieving pain. Trapeziectomy should be considered in patients with thumb base OA and arthrodesis or arthroplasty in patients with interphalangeal OA	5	D	9.4 (1.4)
10.	Long-term follow-up of patients with hand OA should be adapted to the patient's individual needs	5	D	9.5 (1.7)

*1a: Systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg, <80% follow-up); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".[17] †A: Based on consistent level 1 evidence; B: Based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: Based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: Based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.[17] EULAR, European League Against Rheumatism; GoR, grade of recommendation; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomised clinical trial.

The primary goal of managing hand OA is to control symptoms, such as pain and stiffness, and to optimise hand function, in order to maximise activity, participation and quality of life

Management should aim to achieve the best possible activity performance, participation and quality of life. Studies have shown that patients with hand OA have a decreased health-related quality of life.[18] Symptoms such as pain, stiffness and decreased hand function are hallmarks of the disease, and contribute to altered quality of life.[6,19] This overarching principle was based on the International Classification of Functioning, Disability and Health framework.[20] The wording 'optimise' and 'maximise' were chosen to reflect that management of hand OA should be more ambitious than merely aiming for a patient-acceptable symptom state.

All patients should be offered information on the nature and course of the disease, as well as education on self-management principles and treatment options

Education is considered a core treatment in the management of patients with hand OA, and should be offered to all patients. This overarching principle is an additional, more generic statement on education, besides the first recommendation concerning specific education and training. In patients with chronic complaints returning for follow-up, information and education provision should be an ongoing process involving reinforcement and expansion. Explicit evidence supporting the efficacy and content of provision of information and education in hand OA is lacking. Trained health professionals other than the physician can play an important role in the provision of information and education.

Management of hand OA should be individualised taking into account its localisation and severity, as well as comorbidities

This overarching principle was modified from the 2007 recommendation about individualisation of treatment. In the premeeting survey, >75% of health professionals indicated that patient characteristics that are considered important include: age, type of complaint (eg, pain or disability), mechanical factors, patient's wishes and expectations, presence of inflammation, severity of structural damage and presence of erosions. In the survey, most health professionals also supported different treatment approaches according to disease location (especially thumb base OA) or OA subset (especially erosive or "inflammatory" OA). The 2007 recommendation included consideration of many of these individual factors. Yet although many of these factors are known to be determinants of worse outcome (eg, presence of inflammation is known to be associated with disease progression[21-23]), evidence of effect modification is lacking for most of these factors.[24] Moreover, it is unknown whether treatment of modifiable factors will in turn change disease outcomes (eg, there is no evidence that treatment of inflammation reduces disease progression). OA localisation (most importantly finger vs thumb base OA), OA severity and presence of comorbidities were thought to be the only aspects that may currently influence treatment decisions. This is also reflected in the recommendations. 'Severity' can encompass several features, including a high number of hand joints with OA, one or two severely affected joints or acute joint inflammation due to OA. The patient's wishes and expectations were not mentioned separately in this overarching principle, since this concept is incorporated in the overarching principle concerning shared decision-making.

Management of hand OA should be based on a shared decision between the patient and the health professional

Shared decision-making, an approach to healthcare in which health professionals and patients mutually share information to reach consensus about the preferred management strategy, should be the basis of management in hand OA.[25] This overarching principle implies that not only the best available evidence, but also the patients' wishes and expectations are important to be considered when making decisions on managing the disease. Achieving shared decision-making depends on building and maintaining a good relationship between patient and health professional, and sharing the best evidence, in order to be able to make an informed decision. It pertains to all stages of management, including, for example, setting a treatment goal, choosing the best strategy to achieve it or considering other strategies when the treatment goal is not reached.

Optimal management of hand OA usually requires a multidisciplinary approach. In addition to non-pharmacological modalities, pharmacological options and surgery should be considered

Hand OA is both a heterogeneous disease, leading to a variety of signs and symptoms, and a chronic disease. Over the course of the disease, patients with hand OA therefore often require multidisciplinary care. Health professionals involved in care for patients with hand OA, may include, for example, the general practitioner, rheumatologist, occupational or physical therapist, orthopaedic or plastic surgeon and the rehabilitation specialist. Which care is delivered by each health professional differs by country, depending for example on local preferences or customs and social security systems. In some clinics, structured multidisciplinary care programmes or integrated care pathways are provided. However, it is unclear whether such programmes providing a structured combination of different non-pharmacological therapies are efficacious. For example, no consistent beneficial effect of combination programmes including education, joint protection and exercises over education alone has been determined.[26-28]

The second part of this overarching principle, that different treatment modalities should be considered, was modified from the first 2007 recommendation, and initially discussed as a separate overarching principle (LoA: 100%). Later, the concept 'multidisciplinary care' was added, since it was recognised that different modalities may be provided by different health professionals. By modifying the 2007 recommendation, this overarching principle now also reflects that the first step in hand OA management should focus on non-pharmacological therapies, which may be complemented by pharmacological and/or surgical options, although not necessarily for all patients with hand OA, depending on the level of symptoms.

Recommendations

In total, 10 recommendations were formulated (table 1). Table 1 also presents the LoE, GoR and LoA for each recommendation. Many of the 2007 recommendations were modified because new evidence has emerged since the previous SLR, and were formulated as recommendations rather than 'statements' reflecting the state of the evidence and/or expert opinion. Two recommendations are new (#8, #10), one recommendation was split into two (old #3 into new

#1 and #2), two recommendations were combined into one (old #7 and #8 into new #5), and one recommendation was deleted (old #4). The recommendation that was deleted concerned the use of heat and ultrasound, which was based on expert opinion and extrapolation from hip or knee OA studies.

Education and training in ergonomic principles, pacing of activity, and use of assistive devices, should be offered to every patient

Education and training in ergonomic principles and pacing of activity, formerly included in the recommendations under the term 'joint protection', is an important aspect of management, and has been shown to be efficacious in one study.[26] The term 'joint protection', although still often used, was viewed by the task force as an outdated concept, implying that one should protect the joints and refrain from using them. It was thus replaced by a more explicit statement of what the education and training should consist of. The use of assistive devices is an important and commonly used strategy to improve patient's self-management, and shown to be efficacious.[29,30] No evidence is available that intensive programmes delivering this care are more effective or cost-effective than more simple strategies.[31] This care can be delivered by any health professional specialised in these interventions (eg, an occupational or physical therapist or a trained nurse).

Exercises to improve function and muscle strength, as well as to reduce pain, should be considered for every patient

Although exercise was endorsed in the 2007 recommendations, no supporting evidence was available at that time. Since then, multiple trials (n=7) have been performed, and their results were summarised in a Cochrane review.[32] It was shown that hand exercises have small beneficial effects on self-reported pain and function, joint stiffness and grip strength, while resulting in few and non-severe adverse effects. However, the interventions studied were heterogeneous, varying from home-based exercises after a single instruction session to multiple supervised sessions per week for several weeks, and also the frequency of exercising, number of repetitions per exercise, and type of exercises (eg, strengthening or stretching) were variable. Furthermore, the review authors debated whether the effects that were found constituted a clinically relevant improvement, and the beneficial effects were not sustained when patients stopped exercising. Exercises should aim at improving joint mobility, muscle strength and thumb base stability. Exercise regimens aimed at the first carpometacarpal (CMC-1) joint differ from those for interphalangeal joints.

Orthoses should be considered for symptom relief in patients with thumb base OA. Long term use is advocated

Since the 2007 recommendations many orthosis trials have been performed, of which five compared orthoses to usual care or a non-pharmacological intervention.[33-37] These trials provide evidence for beneficial effects of a thumb base orthosis, especially on pain and to a lesser extent on function, but not on grip strength, when used for a prolonged period (at least 3 months). No improvements were evident when used for shorter periods. Long-term use is

thus advocated. The 2007 recommendations advised the use of orthoses to "prevent/correct lateral angulation and flexion deformity" in patients with thumb base OA, yet no evidence to date supports an effect of orthoses on angulation or deformity, and therefore the statement was reworded.

No straightforward advice can be given for the type of orthosis (short or long, custom-made or prefabricated, neoprene, thermoplast or other material) or instructions for use (eg, during activities of daily living, at night, constantly), as studies are heterogeneous and no consistent benefit of one type of orthosis over the other could be identified. Trials showing a long-term beneficial effect of orthosis use investigated a custom-made thermoplast long orthosis to be worn during activities of daily living,[35] and a custom-made neoprene long orthosis to be worn at night.[37]

It is important to pay attention to prescribing a well-fitted orthosis, preferably custom-made by a specialised health professional. This will likely improve patients' compliance and increase long-term use.

Most trials were performed in patients with thumb base OA, and only one trial investigated night-time distal interphalangeal joint (DIP) orthoses, which did not prove to be efficacious, and is therefore not specifically recommended.[38]

Topical treatments are preferred over systemic treatments because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice

Topical NSAIDs are recommended as a first-line pharmacological treatment, due to their favourable safety profile compared with oral analgesics and beneficial effects on pain and function.[39-41] Topical diclofenac gel showed small improvements in pain and function after 8 weeks compared with placebo in one high-quality study.[41] Moreover, topical NSAIDs can show similar pain relief as oral NSAIDs.[39,40] Pooled safety data from randomised clinical trials comparing topical diclofenac gel to placebo in patients with hand and knee OA also showed similar low rates of adverse effects in subgroups of low-risk versus high-risk patients (ie, age ≥65 years, and with comorbid hypertension, type 2 diabetes or cerebrovascular or cardiovascular disease).[42] When a large number of joints are affected, systemic pharmacological treatment may be preferred. At present, no data is available on long-term effects of topical NSAIDs.[43]

Capsaicin is another topical treatment, which is however known to be associated with frequent local adverse effects (burning and stinging sensation), and therefore success of blinding of the (positive) placebo-controlled trial investigating its efficacy is questionable.[44]

Topical application of heat was regarded by the task force as a self-management strategy that patients can apply at home, with weak and conflicting evidence for a possible beneficial effect.[45-47] It was therefore not included as a separate recommendation in this update. Cold packs, in case of inflammation during an OA flare, may also give symptomatic relief, though studies in hand OA have not been performed, and a single knee OA study comparing hot and cold application to usual care found no between-group differences.[48]

Oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms

This recommendation is a combination of the 2007 recommendations concerning paracetamol and oral NSAIDs.

Oral NSAIDs effectively improved pain and function after 2-4 weeks in three high-quality studies.[49-51] However, adverse effects are well-known, especially in the elderly. No new evidence was identified compared with the 2007 recommendations. The advice to prescribe NSAIDs at the lowest effective dose, for a limited duration (preferably on-demand), with attention for the risk-benefit-ratio, especially in patients at high risk of gastrointestinal, cardiovascular or renal adverse effects, remains unchanged.

Paracetamol is prescribed by many health professionals, and also in the premeeting survey the vast majority of health professionals indicated that they prescribed paracetamol to their patients with hand OA. Patients' experience with paracetamol is known to be variable. It has generally been regarded as a safe treatment option, although lately its risk-benefit profile has been a topic of debate, even leading to controversy about including it in the National Institute for Health and Care Excellence (NICE) guidelines on OA.[52] Three small trials, two only published as conference abstracts, have studied paracetamol (1000-3900 mg daily) in hand OA.[53-55] In these trials, paracetamol was not superior over placebo or an active comparator. Two large meta-analyses of trials in patients with knee and hip OA found small effects on pain, with doubtful clinical significance.[56,57] Evidence from these trials showed that paracetamol was associated with an increased risk of liver test abnormalities, although the clinical relevance of this finding is unknown, but not with increased risk of any other safety parameter.[57] A narrative review of long-term observational studies in the general adult population found a dose-response increased risk of mortality (n=2 trials), cardiovascular (n=4), gastrointestinal (n=1) and renal adverse effects (n=4). This should, however, be interpreted with caution, as these observational studies were associated with a large risk of bias (most importantly confounding by indication) and imprecision of measurement of paracetamol exposure (eg, reliance on self-reported medication use or prescription databases).[58] In conclusion, the efficacy of paracetamol in hand OA is still uncertain and likely to be small, and this drug is also not free from adverse effects, although for now there is no reason to refrain from prescribing paracetamol, preferably for a limited duration, in selected patients (eg, when oral NSAIDs are contraindicated). Tramadol (with or without paracetamol), was also regarded by the task force as an alternative oral analgesic, although currently no evidence in patients with hand OA is available to support its use.

Chondroitin sulfate may be used in patients with hand OA for pain relief and improvement in functioning

Chondroitin sulfate and glucosamine are among the most widely used over-the-counter nutraceutical products for OA. Chondroitin sulfate was shown to be effective for relief of hand OA symptoms in one well-performed trial, although in patients with knee and hip OA a clinically meaningful effect of glucosamine and chondroitin preparations has not been proven.[59-61] A single report of two (independent) placebo-controlled trials reported structure-modifying effects of chondroitin polysulfate (a preparation that is not commercially available), but not of chondroitin

sulfate.[62] However, this evidence was judged unconvincing to promote chondroitin sulfate for structure modification. No placebo-controlled trials of glucosamine have been performed in patients with hand OA. Owing to the limited evidence available to support this recommendation, and even less convincing data from trials in knee and hip OA which led to discouragement of chondroitin sulfate and glucosamine use by NICE, this recommendation was formulated more as a suggestion than a recommendation to use.[63]

In addition to the nutraceuticals discussed here, other so-called Symptomatic Slow Acting Drugs for Osteoarthritis ('SYSADOA') were included in the 2007 recommendation, namely avocado soybean unsaponifiables, diacerhein and intra-articular hyaluronan. Currently, however, there is no evidence for clinical efficacy of these preparations.[16] The task force further agreed that at this moment in OA no drugs are available with disease-modifying properties, and therefore these substances should also not be advocated as such.

Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA, but may be considered in patients with painful interphalangeal joints

This recommendation was completely revised, since the previous recommendation was largely based on expert opinion and new evidence could not confirm a beneficial effect of intra-articular glucocorticoids over placebo in patients with thumb base OA.[64-66] In contrast, in one trial of patients with painful interphalangeal OA, intra-articular glucocorticoid injections were more effective than placebo for pain during joint movement and joint swelling.[67] The formulation 'should not generally be used' was chosen, since the task force recognised that in specific cases where, for example, clear joint inflammation is present, injection with glucocorticoids may still be a therapeutic option. Evidence pertaining specific subgroups that could benefit from intra-articular glucocorticoids, for example, patients with active joint inflammation due to a flare of the disease, is lacking. It is also unknown whether image-guided injections are more beneficial or safer than blind injections, although a Cochrane review of shoulder injections could not establish clinical advantages of guided injection.[68] Injections in small finger joints are preferably performed by a rheumatologist.

Patients with hand OA should not be treated with conventional or biological disease modifying antirheumatic drugs

This recommendation was newly added, after several studies have emerged demonstrating the lack of efficacy of csDMARD/bDMARD. In clinical practice, severe cases of inflammatory, often erosive, hand OA are occasionally prescribed csDMARDs or even bDMARDs. However, the 2007 recommendations did not include advice on the use of these drugs, and no evidence was available at that time. Trials investigating the efficacy of hydroxychloroquine,[53,69,70] different TNF-inhibitors,[71-74] and anti-interleukin-1,[75] could not demonstrate efficacy of these antirheumatic drugs in patients with hand OA. Trials investigating methotrexate, sulfasalazine or colchicine have not been performed. Two trials investigated low-dose oral glucocorticoids (3-5 mg daily), one in combination with dipyridamole, yet reached conflicting conclusions.[76,77] Evidence for short-term use of oral glucocorticoids is therefore still equivocal; at this moment, there is no reason to prescribe glucocorticoids for prolonged periods of time in patients with hand OA.

Surgery should be considered for patients with structural abnormalities when other treatment modalities have not been sufficiently effective in relieving pain. Trapeziectomy should be considered in patients with thumb base OA and arthrodesis or arthroplasty in patients with interphalangeal OA
This recommendation was slightly modified compared with the 2007 recommendation on surgery. Trials with a placebo-controlled or sham-controlled group have not been performed, and so this recommendation remains mostly based on expert opinion.

In the first part of the updated recommendation, treatment failure has now been defined more specifically as 'not sufficiently effective in relieving pain', since surgical interventions are mostly effective to relieve pain, and are less effective in improving function (expert opinion). Surgery should only be considered in persistently symptomatic patients with structural abnormalities despite conventional treatments, including both non-pharmacological and pharmacological therapies. Second, the recommendation does not solely focus on the thumb base joint as before, since surgery can be a viable treatment option in cases with severe painful interphalangeal OA as well.

Surgical interventions vary for the different hand joints. In the CMC-1 joint, trapeziectomy is generally the surgical technique of choice. An updated Cochrane review of the evidence of surgery for thumb base OA found no consistent benefit of one surgical technique over the other, although in general more complicated interventions than simple trapeziectomy led to more adverse effects and were not more effective.[78] Complications reported in the studies included pain, instability, nerve dysfunction, superficial wound infections, tendon pulling sensation and chronic regional pain syndrome. Arthroplasty (typically silicone implants) is the preferred surgical technique for the proximal interphalangeal (PIP) joints, with the exception of PIP-2, for which arthrodesis may be considered. Arthrodesis is the recommended approach for the distal interphalangeal joints. No controlled trials of surgery for interphalangeal OA have been published so far.

It is important that patients receive rehabilitation postoperatively. Osteotomy was deleted from the recommendation, as it is an obsolete technique for treating hand OA.

Long-term follow-up of patients with hand OA should be adapted to the patient's individual needs
A recommendation on follow-up was not included in the previous recommendations. Due to the lack of evidence for the cost-effectiveness of long-term follow-up, an evidence-based statement could not be made. Hand OA is a heterogeneous disease, and the spectrum of patients seen with hand OA is diverse, which resulted in a general recommendation. 'Individual needs' that may be taken into consideration when assessing the need for follow-up include severity of symptoms, presence of erosive disease, use of a pharmacological therapy that needs re-evaluation, and patient's wishes and expectations.

It was discussed whether long-term follow-up is always indicated for patients with erosive OA. In spite of evidence that these patients have more clinical and structural progression,[79,80] the task force perceived that currently follow-up does not add a benefit. In the absence of a disease-modifying treatment, the goal of follow-up differs from the situation in many other rheumatic diseases. Follow-up will likely increase adherence to non-pharmacological therapies like exercise or orthoses, and provides an opportunity for re-evaluation of treatment (eg, revision of orthoses, or adjustment of pharmacological treatment). For most patients, standard radiographic follow-up is not useful at

this moment. Follow-up does not necessarily have to be performed by the rheumatologist. At what moment other health professionals should refer a patient back to the rheumatologist, should be considered at an individual patient level.

Research agenda

A research agenda was developed (table 2).

Table 2. Research agenda for hand OA

Theme	Research questions
Pathophysiology	▪ Does treatment of inflammation lead to a decrease in structural progression?
Treatment strategy	▪ Which contextual factors influence treatment effects? ▪ Assessing efficacy of stratified treatment based on contextual factors.
Trial methodology	▪ Clear definition of study population to accommodate later subgroup analyses or stratification based on patient characteristics.
Outcomes	▪ Evaluation of outcome measures in hand OA, and use of existing outcome core sets for future hand OA trials. ▪ Cost-effectiveness studies. ▪ Defining treatment targets for disease-modifying drugs.
Education	▪ Evaluation of efficacy of education without concomitant exercise. ▪ Definition of the desired content of education.
Exercise	▪ Assessment of most effective type of hand exercises, most optimal method of delivery, and most optimal frequency. ▪ Assessment of methods to increase adherence to exercise.
Orthoses	▪ Assessment of orthosis design (material, which joints are supported), and instructions or frequency for use of orthoses. ▪ Evaluation of daytime orthoses, night-time orthoses and a combination of daytime and night-time orthoses. ▪ Placebo-controlled trial of orthoses for thumb base OA. ▪ Evaluation of effect of use of orthoses on CMC-1 subluxation.
Topical treatments	▪ Another placebo-controlled trial of topical NSAID.
Oral analgesics	▪ Placebo-controlled trial of paracetamol. ▪ Placebo-controlled trial of tramadol.
Nutraceuticals	▪ Placebo-controlled trial of glucosamine. ▪ Another placebo-controlled trial of chondroitin sulfate, also to assess possible effect on structural damage.
Intra-articular therapies	▪ Placebo-controlled trial of intra-articular glucocorticoids specifically in CMC-1 joints with OA inflammation ▪ Image-guided injection versus blind injection
DMARDs	▪ Placebo-controlled trial of methotrexate. ▪ Placebo-controlled trial of low-dose oral glucocorticoids.
Surgery	▪ Randomised controlled trial of most commonly used surgical interventions. ▪ Assessment of best timing of referral to surgery. ▪ Evaluation of whether early non-pharmacological interventions may prevent or delay surgery.
Follow-up	▪ Investigation of trajectories in hand OA to define subgroups.
Implementation	▪ Determination of optimal implementation of the guidelines in people with hand OA.

CMC-1, first carpometacarpal; DMARDs, disease-modifying antirheumatic drugs; OA, osteoarthritis.

DISCUSSION

This is the first update of the EULAR recommendations for the management of hand OA, containing five overarching principles and 10 recommendations. After a decade, it was timely to update the recommendations, as many new studies had emerged during this period. In light of this new evidence, many of the 2007 recommendations were modified and new recommendations were added. Furthermore, recommendations were formulated as recommendations rather than 'statements' reflecting the state of the evidence and/or expert opinion.

In this update, two patient research partners with hand OA were included as active members of the task force, while the 2007 task force did not include patient research partners. This is an important improvement, since patients are one of the important target-users of these recommendations, and in evidence-based clinical decision making, the patient perspective is valued as equally important to research evidence and clinical expertise.[81]

New in the 2018 update is also the use of overarching principles. This is in line with other EULAR sets of management recommendations. Some of the 2007 recommendations were in retrospect already more an overarching principle, and were (modified and) included in the 2018 update as such, for example, statements regarding individualised treatment, and combination of non-pharmacological and pharmacological treatment modalities.

Moreover, the 2018 update of the SLR summarising the evidence for the recommendations, is published as a separate manuscript.[16] As pointed out in their discussion, Zhang *et al* did perform a systematic search of the literature to underpin the recommendations, but rather than reviewing all possible treatments, a limited number of key propositions were highlighted. The publication of the complete SLR, including a detailed description of its methodology and results, provides the interested reader with a full update of the currently available evidence concerning the management of hand OA and provides more insight in the size of the effects of different interventions compared with placebo or control treatment. It is important to note that the recommendations as presented in table 1 cannot be read and interpreted without the accompanying text, and this manuscript and the separately published SLR form an integral part, and should be considered together.

Guidelines for the management of OA from other large (international) societies, including the 2012 ACR recommendations and the NICE guidelines, mainly focus on large joint OA (ie, knee and hip).[10,63] However, these recommendations cannot readily be extrapolated to the situation of OA in the hand because of the unique functionality of the hands compared with large joints, and emerging evidence for different risk factors and possibly even pathophysiological mechanisms of OA at different joint sites.

These recommendations are targeted at all health professionals who care for patients with hand OA. Since hand OA is a prevalent disease encountered by a variety of healthcare providers in primary and secondary care, this not only includes rheumatologists, but also for example general practitioners, orthopaedic and plastic surgeons, occupational and physical therapists and rehabilitation physicians. Furthermore, these recommendations aim to inform patients about their disease to support shared decision-making, as well as students. Other targeted stakeholders include pharmaceutical industry, policy makers and health insurance companies.

Efforts to implement these recommendations will be made by dissemination across national societies, online and by presentations in (inter)national congresses and educational sessions for healthcare providers. A slide deck to facilitate dissemination will be provided on the EULAR website. Evidence of optimal systematic implementation is lacking and this was highlighted in the research agenda.

Although a relatively long period passed between the first set of recommendations and the current update, it is expected that the next update of the recommendations may be needed sooner, as the field of hand OA is growing. Advances in research of OA pathophysiology as well as outcome measurement, increase the likelihood of finding new therapeutic options. The next update should be undertaken when sufficient new data are available, either on the current treatment options, or on new therapies.

REFERENCES

1. Branco JC, Rodrigues AM, Gouveia N, et al. Prevalence of rheumatic and muskuloskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt- a national health survey. *RMD Open* 2016;2:e000166.
2. Carmona L, Ballina J, Gabriel R, et al. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 2001;60:1040-5.
3. Dahagin S, Bierma-Zeinstra SM, Ginai AZ, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
4. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2012;8:22-31.
5. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
6. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
7. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: a report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
8. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.
9. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthrtitis: Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
10. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacological and pharmacological therapies in osteoarthritis of the hand, hip and knee. *Arthritis Care Res* 2012;64:465-74.
11. Kjeken I. Occupational therapy-based and evidence-supported recommendations for assessment and exercises in hand osteoarthritis. *Scand J Occup Ther* 2011;18:265-81.
12. Manara M, Bortoluzzi A, Favero M, et al. Italian Society for Rheumatology recommendations for the management of hand osteoarthritis. *Reumatismo* 2013;65:167-85.
13. Kloppenburg M, Stamm T, Watt I, et al. Research in hand osteoarthritis: time for reappraisal and demand for new strategies. An opinion paper. *Ann Rheum Dis* 2007;66:1157-61.
14. van der Heijde D, Aletaha D, Carmona L, et al. Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8-13.
15. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839-E842.
16. Kroon FPB, Carmona L, Schoones JW, et al. *Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis*, 2018. [submitted for publication].
17. OCEBM Levels of Evidence Working Group. *The Oxford Levels of Evidence 2*: Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.
18. Slatkowsky-Christensen B, Mowinckel P, Loge JH, et al. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. *Arthritis Rheum* 2007;57:1404-9.
19. Kwok WY, Vliet Vlieland TP, Rosendaal FR, et al. Limitations in daily activities are the major determinant of reduced health-related quality of life in patients with hand osteoarthritis. *Ann Rheum Dis* 2011;70:334-6.
20. World Health Organisation. *International Classification of Functioning, Disability and Health (ICF)*. Geneva: WHO, 2001.
21. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-7.
22. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. *Ann Rheum Dis* 2016;75:117-23.
23. Kortekaas MC, Kwok WY, Reijnierse M, et al. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. *Ann Rheum Dis* 2015;74:1720-4.
24. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary

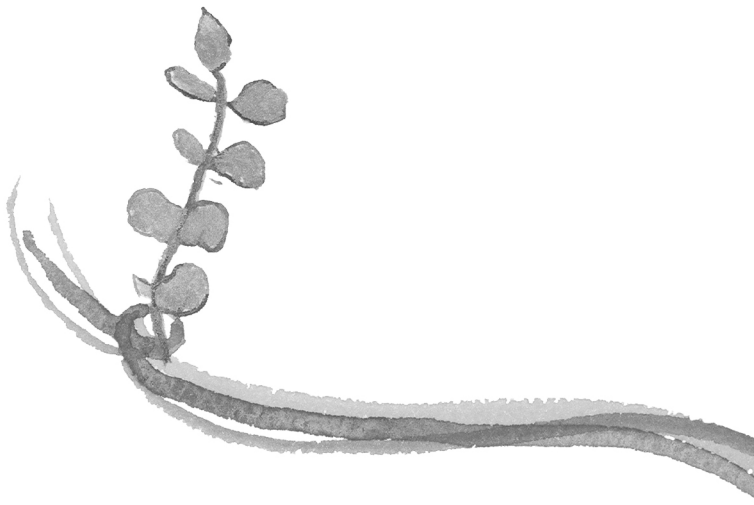
Set of Instruments for Use in Clinical Trials and Observational Studies. *J Rheumatol* 2015;42:2190-7.
25. Légaré F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. *Health Aff* 2013;32:276-84.
26. Dziedzic K, Nicholls E, Hill S, et al. Self-management approaches for osteoarthritis in the hand: A 2x2 factorial randomised trial. *Ann Rheum Dis* 2015;74:108-18.
27. Stamm TA, Machold KP, Smolen JS, et al. Joint protection and home hand exercises improve hand function in patients with hand osteoarthritis: A randomized controlled trial. *Arthritis Care Res* 2002;47:44-9.
28. Stukstette MJ, Dekker J, den Broeder AA, et al. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term; results of arandomized controlled trial. *Osteoarthritis Cartilage* 2013;21:901-10.
29. Hill S, Dziedzic KS, Ong BN. The functional and psychological impact of hand osteoarthritis. *Chronic Illn* 2010;6:101-10.
30. Kjeken I, Darre S, Smedslund G, et al. Effect of assistive technology in hand osteoarthritis: A randomised controlled trial. *Ann Rheum Dis* 2011;70:1447-52.
31. Oppong R, Jowett S, Nicholls E, et al. Joint protection and hand exercises for hand osteoarthritis: an economic evaluation comparing methods for the analysis of factorial trials. *Rheumatology (Oxford)* 2015;54:876-83.
32. Østerås N, Kjeken I, Smedslund G, et al. Exercise for hand osteoarthritis. *Cochrane Database Syst Rev* 2017;1:CD010388.
33. Adams J, Bouças SB, Hislop K, et al. The effectiveness and efficacy of splints for thumb base osteoarthritis: A pilot randomized controlled trial. *Rheumatology* 2014;53:i41-i42.
34. Arazpour M, Soflaei M, Ahmadi Bani M, et al. The effect of thumb splinting on thenar muscles atrophy, pain, and function in subjects with thumb carpometacarpal joint osteoarthritis. *Prosthet Orthot Int* 2017;41.
35. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. *J Rehabil Med* 2010;42:469-74.
36. Hermann M, Nilsen T, Eriksen CS, et al. Effects of a soft prefabricated thumb orthosis in carpometacarpal osteoarthritis. *Scand J Occup Ther* 2014;21:31-9.
37. Rannou F, Dimet J, Boutron I, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. *Ann Intern Med* 2009;150:661-9.
38. Watt FE, Kennedy DL, Carlisle KE, et al. Night-time immobilization of the distal interphalangeal joint reduces pain and extension deformity in hand osteoarthritis. *Rheumatology* 2014;53:1142-9.
39. Talke M. Treatment of Heberden and Bouchard types of finger osteoarthritis. Comparison between local etofenamate and oral indomethacin. *Therapiewoche* 1985;35:3948-54.
40. Zacher J, Burger KJ, Farber L, et al. [Topical diclofenac versus oral ibuprofen: A double blind, randomized clinical trial to demonstrate efficacy and tolerability in patients with activated osteoarthritis of the finger joints (Heberden and/or Bouchard arthritis)]. [*German*]. *Aktuelle Rheumatologie* 2001;26:7-14.
41. Altman RD, Dreiser RL, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: A randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009;36:1991-99.
42. Baraf HS, Gold MS, Petruschke RA, et al. Tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. *Am J Geriatr Pharmacother* 2012;10:47-60.
43. Zeng C, Wei J, Persson MSM, et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. *Br J Sports Med* 2018;52:642-50.
44. Schnitzer T, Morton C, Coker S. Topical capsaicin therapy for osteoarthritis pain: achieving a maintenance regimen. *Semin Arthritis Rheum* 1994;23:34-40.
45. Dilek B, Gözüm M, Şahin E, et al. Efficacy of paraffin bath therapy in hand osteoarthritis: A single-blinded randomized controlled trial. *Arch Phys Med Rehabil* 2013;94:642-49.
46. Favaro L, Frisoni M, Baffoni L, et al. Successful treatment of hand erosive osteoarthritis by infrared radiation. *Europa Medico-Physica* 1994;30:45-8.
47. Stange-Rezende L, Stamm TA, Schiffert T, et al. Clinical study on the effect of infrared radiation of a tiled stove on patients with hand osteoarthritis. *Scand J Rheumatol* 2006;35:476-80.
48. Aciksoz S, Akyuz A, Tunay S. The effect of self-administered superficial local hot and cold application methods on pain, functional status and quality of life in primary knee osteoarthritis patients. *J Clin Nurs* 2017;26:5179-90.
49. Dreiser RL, Gersberg M, Thomas F, et al. [Ibuprofen 800 mg in the treatment of arthrosis of the fingers or rhizarthrosis]. [*French*]. *Rev Rhum Ed Fr* 1993;60:836-41.
50. Grifka JK, Zacher J, Brown JP, et al. Efficacy and

tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand. *Clin Exp Rheumatol* 2004;22:589-96.
51. Seiler V. Meclofenamate sodium in the treatment of degenerative joint disease of the hand (Heberden nodes). *Arzneimittelforschung* 1983;33:656-9.
52. Wise J. NICE keeps paracetamol in UK guidelines on osteoarthritis. *BMJ* 2014;348:g1545.
53. McKendry R, Thome C, Weisman M, et al. Hydroxychloroquine (HCQ) versus acetaminophen (ACM) versus placebo (PL) in the treatment of nodal osteoarthritis (NOA) of the hands. *J Rheumatol* 2001;28:1421.
54. Patru S, Marcu IR, Bighea AC, et al. Efficacy of glucosamine sulfate (GS) in hand osteoarthritis. *Osteoporosis Int* 2012;23:S169.
55. Rovetta G, Monteforte P. [Dexketoprofen-trometamol in patients with osteoarthritis of the hands]. [*Italian*]. *Minerva Ortop Traumatol* 2001;52:27-30
56. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162:46-54.
57. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* 2015;350:h1225.
58. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016;75:552-9.
59. Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: A randomized, double-blind, placebo-controlled clinical trial at a single center. Arthritis Rheum 2011; 63.
60. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015;1:CD005614.
61. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:c4675.
62. Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clin Rheumatol* 2002;21:231-43.
63. *National Clinical Guideline Centre. Osteoarthritis: Care and Management in Adults.* London: National Institute for Health and Care Excellence (UK), 2014.
64. Heyworth BE, Lee JH, Kim PD, et al. Hylan Versus Corticosteroid Versus Placebo for Treatment of Basal Joint Arthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. *J Hand Surg* 2008;33:40-8.
65. Mandl LA, Wolfe S, Daluiski A, et al. A randomized controlled trial of hylan G-F 20 for the treatment of carpometacarpal osteoarthritis. *Arthritis Rheum* 2012;64:S475-6.
66. Meenagh GK, Patton J, Kynes C, et al. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004;63:1260-3.
67. Spolidoro Paschoal NO, Natour J, Machado FS, et al. Effectiveness of Triamcinolone Hexacetonide Intraarticular Injection in Interphalangeal Joints: A 12-week Randomized Controlled Trial in Patients with Hand Osteoarthritis. *J Rheumatol* 2015;42:1869-77.
68. Bloom JE, Rischin A, Johnston RV, et al. Image-guided versus blind glucocorticoid injection for shoulder pain. *Cochrane Database Syst Rev* 2012:CD009147.
69. Lee W, Ruijgrok L, Boxma-de Klerk B, et al. Efficacy of hydroxychloroquine in hand osteoarthritis: a randomized, double blind, placebo-controlled trial. *Arthritis Care Res* 2017;74:188.1–188.
70. Kingsbury SR, Tharmanathan P, Keding A, et al. Hydroxychloroquine is not effective in reducing symptoms of hand osteoarthritis: Results from a placebo-controlled randomised trial. *Arthritis Rheumatol* 2016;68:4189-91.
71. Aitken D, Laslett LL, Pan F, et al. A randomised double-blind placebo-controlled crossover trial of humira (adalimumab) for erosive hand osteoarthritis: the HUMOR trial. *Osteoarthritis Cartilage* 2018;26:S9.
72. Chevalier X, Ravaud P, Maheu E, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697-705.
73. Kloppenburg M, Ramonda R, Kwok W-Y, et al. Randomized, placebo-controlled trial to evaluate clinical efficacy and structure modifying properties of subcutaneous etanercept (ETN) in patients with erosive inflammatory hand osteoarthritis (OA). *Ann Rheum Dis* 2016;75:90-1.
74. Verbruggen G, Wittoek R, Vander Cruyssen B, et al. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891-98.
75. Kloppenburg M, Peterfy C, Haugen I, et al. A phase 2a, placebo-controlled, randomized study of ABT-981, an anti-interleukin-1alpha and -1beta dual variable domain immunoglobulin, to treat erosive hand osteoarthritis (EHOA). *Ann Rheum Dis*

2017;76:122.
76. Kvien TK, Fjeld E, Slatkowsky-Christensen B, et al. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942-48.
77. Wenham CY, Hensor EM, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* 2012;51:2286-94.
78. Wajon A, Vinycomb T, Carr E, et al. Surgery for thumb (trapeziometacarpal joint) osteoarthritis. *Cochrane Database Syst Rev* 2015;2:CD004631.
79. Haugen IK, Mathiessen A, Slatkowsky-Christensen B, et al. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? *Osteoarthritis Cartilage* 2016;24:647-54.
80. Kwok WY, Kloppenburg M, Rosendaal FR, et al. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. *Ann Rheum Dis* 2011;70:1238-42.
81. Haynes RB, Sackett DL, Gray JM, et al. Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions. *Evid Based Med* 1996;1:196-8.

PART II

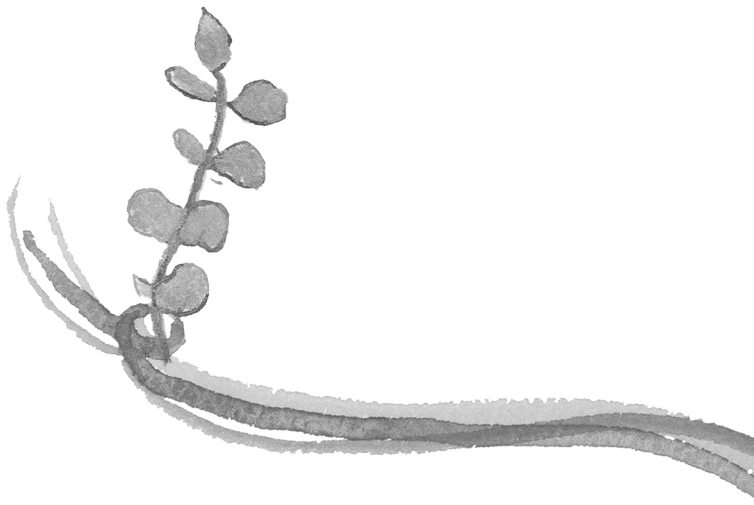
Inflammation as treatment target





CHAPTER 5

Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial



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SUMMARY

Background. Hand osteoarthritis is a prevalent joint condition that has a high burden of disease and an unmet medical need for effective therapeutic options. Since local inflammation is recognized as contributing to osteoarthritic complaints, the Hand Osteoarthritis Prednisolone Efficacy (HOPE) study aimed to investigate the efficacy and safety of short-term prednisolone in patients with painful hand osteoarthritis and synovial inflammation.

Methods. The HOPE study is a double-blind, randomised, placebo-controlled trial. We recruited eligible adults from rheumatology outpatient clinics at two sites in the Netherlands. Patients were considered eligible if they had symptomatic hand osteoarthritis and signs of inflammation in their distal and proximal interphalangeal (DIP/PIP) joints. For inclusion, patients were required to have four or more DIP/PIP joints with osteoarthritic nodes; at least one DIP/PIP joint with soft swelling or erythema; at least one DIP/PIP joint with a positive power Doppler signal or synovial thickening of at least grade 2 on ultrasound; and finger pain of at least 30 mm on a 100-mm visual analogue scale (VAS) that flared up during a 48-h non-steroidal anti-inflammatory drug (NSAID) washout (defined as worsening of finger pain by at least 20 mm on the VAS). Eligible patients were randomly assigned (1:1) to receive 10 mg prednisolone or placebo orally once daily for 6 weeks, followed by a 2-week tapering scheme, and a 6-week follow-up without study medication. The patients and study team were masked to treatment assignment. The primary endpoint was finger pain, assessed on a VAS, at 6 weeks in participants who had been randomly assigned to groups and attended the baseline visit. This study is registered with the Netherlands Trial Registry, number NTR5263.

Findings. We screened patients for enrolment between Dec 3, 2015, and May 31, 2018. Patients completed baseline visits and started treatment between Dec 14, 2015, and July 2, 2018, and the last study visit of the last patient was Oct 4, 2018. Of 149 patients assessed for eligibility, 57 (38%) patients were excluded (predominantly because they did not meet one or several inclusion criteria, most often because of an absence of synovial inflammation or of flare-ups after NSAID washout) and 92 (62%) patients were eligible for inclusion. We randomly assigned 46 (50%) patients to receive prednisolone and 46 (50%) patients to receive placebo, all of whom were included in the modified intention-to-treat analysis of the primary endpoint. 42 (91%) patients in the prednisolone group and 42 (91%) in the placebo group completed the 14-week study. The mean change between baseline and week 6 on VAS-reported finger pain was -21.5 (SD 21.7) in the prednisolone group and -5.2 (24.3) in the placebo group, with a mean between-group difference (of prednisolone *vs* placebo) of -16.5 (95% CI -26.1 to -6.9; p=0.0007). The number of non-serious adverse events was similar between the groups. Five serious adverse events were reported during our study: one serious adverse event in the prednisolone group (a myocardial infarction) and four serious adverse events in the placebo group (an infected traumatic leg haematoma that required surgery, bowel surgery, atrial fibrillation that required a pacemaker implantation,

and symptomatic uterine myomas that required a hysterectomy). Four (4%) patients discontinued the study because of an adverse event: one (2%) patient receiving prednisolone (for a myocardial infarction) and three (7%) patients receiving placebo (for surgery of the bowel and for an infected leg haematoma and for Lyme disease arthritis of the knee).

Interpretation. Treatment with 10 mg prednisolone for 6 weeks is efficacious and safe for the treatment of patients with painful hand osteoarthritis and signs of inflammation. The results of our study provide clinicians with a new short-term treatment option for patients with hand osteoarthritis who report a flare-up of their disease.

Funding. Dutch Arthritis Society.

INTRODUCTION

Around 20% of adults have osteoarthritis.[1,2] A particularly burdensome manifestation is hand osteoarthritis, which is found in 8-10% of the adult general population. The prevalence of hand osteoarthritis is 26% in women older than 70 years, and the estimated lifetime risk of the disease in the general population is 40%.[2-4] A substantial burden of disease is associated with hand osteoarthritis, since the condition presents with hand pain, disability, and reduced quality of life, for which patients frequently consult health-care providers.[3,5,6] Symptoms in the hands usually fluctuate over time, including episodes of joint swelling and erythema.[7]

There are several therapeutic options for patients with painful hand osteoarthritis, which vary from non-pharmacological approaches, such as education and exercise, to analgesics, but their effects are modest. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for symptom relief, yet their effect is moderate at best and safety aspects restrict their use, especially in older people (those older than 65 years).[8-10] Therefore, there is an unmet need for effective therapies for hand osteoarthritis.

The current treatment approach relates to the traditional idea that osteoarthritis is a degenerative disease characterised by cartilage loss and bone deformations. Accumulating evidence from the past decade suggests that osteoarthritis is a disease involving all joint compartments, in which not only mechanical triggers but also local inflammation cause pain and radiographical damage progression.[1,11-16] Therefore, inflammation is a potential treatment target in osteoarthritis.

Glucocorticoids are potent multitargeted anti-inflammatory drugs, and we therefore hypothesised that signs and symptoms in patients with hand osteoarthritis would improve by suppressing local inflammation with glucocorticoids.

We aimed to investigate the clinical efficacy and safety of short-term treatment with the glucocorticoid prednisolone in patients with painful hand osteoarthritis who had evidence of synovial inflammation.

METHODS

Study design and patients

The Hand Osteoarthritis Prednisolone Efficacy (HOPE) study is a double-blind, randomised, placebo-controlled trial. We recruited eligible adults from rheumatology outpatient clinics at two sites in the Netherlands (appendix p 1). Patients were considered eligible if they had symptomatic hand osteoarthritis that fulfilled the American College of Rheumatology criteria[11] and if they had signs of inflammation in their distal and proximal interphalangeal (DIP/PIP) joints. For inclusion, patients were required to have four or more DIP/PIP joints with osteoarthritic nodes; at least one DIP/PIP joint with soft swelling or erythema; at least one DIP/PIP joint with a positive power Doppler signal (PDS) or synovial thickening of at least grade 2 on ultrasound; and finger pain of at least 30 mm on a 100-mm visual analogue scale (VAS) that flared up during

a 48-h NSAID washout (defined as worsening of finger pain by at least 20 mm on the VAS). In patients with NSAID contraindications, flare-ups were assessed by use of paracetamol. We excluded patients who predominantly had pain in their thumb base rather than digital pain. FPBK screened all patients.

Because of slow accrual during the trial, we decided to also include patients who did not have a flare-up during a 48-h NSAID washout but who fulfilled all other inclusion criteria and more stringent pain (VAS ≥40 mm) and ultrasound criteria (positive PDS). This decision was supported by a systematic literature review[12] of 57 trials, which showed that osteoarthritis trials using a study design without flare-up inclusion criteria did not have altered effect sizes relative to those with this criterion.

We excluded patients who had used immune-modulating drugs 90 days or fewer before baseline (eg, anti-malarials or systemic or local glucocorticoids), who were positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies, or who had chronic inflammatory rheumatic diseases, psoriasis, uncontrolled serious comorbidities, cancers, or infectious diseases, among several other exclusion criteria (appendix p 1).

Our study was approved by the medical ethics committees at Leiden University Medical Center and Zuyderland Medical Center, and it was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The study protocol is shown in the appendix (pp 11-46).

Randomisation and masking

We randomly assigned patients (1:1) to receive prednisolone or placebo by use of a block randomisation scheme with a fixed block size of six. The Leiden University Medical Center pharmacy generated the randomisation list and were not subsequently involved in the trial. Study medication (5 mg/mL oral prednisolone solution or placebo solution) was provided in sequentially numbered bottles. Prednisolone and placebo solutions were identical in appearance, smell, and taste. Patients, outcome assessors (not authors), and data analysts (FPBK and SB) remained masked for treatment allocation until the study database was locked.

Procedures

Patients self-administered 2 mL of 5 mg/mL prednisolone solution (ie, a 10 mg dose) or placebo once daily for 6 weeks. Thereafter, medication was tapered: patients self-administered 5 mg prednisolone or placebo for 1 week, followed by 2.5 mg prednisolone or placebo for 1 week. From weeks 9-14, study medication was stopped. Patients recorded their adherence to treatment in a diary.

Up to 3000 mg paracetamol per day was allowed as rescue medication. A stable dosage of chondroitin sulphate, glucosamine, bisphosphonate, tetracycline, or oestrogens were allowed, but NSAIDs and intramuscular or intra-articular glucocorticoid or hyaluronic acid injections were not. Patients were discouraged from starting new non-pharmacological interventions. Patients who were at risk of developing gastric or duodenal ulcers were prescribed a proton-pump inhibitor during the 8-week treatment period.

Trained nurses made clinical assessments at baseline and weeks 2, 6, and 14. At every study visit, the nurses recorded tenderness upon palpation (a score of 0-3 on the Doyle Index in the hand) and soft joint swelling (absent or present) for DIP/PIP joints 2-5, interphalangeal joint 1 (ie, of the thumb), metacarpophalangeal joints 1-5, and the first carpometacarpal joint. Nurses also assessed grip strength (in kg), physician global assessment of the patient by VAS, and rescue medication use. Telephone calls to confirm questionnaire completion and to check for any rescue medication use were made at weeks 4 and 8.

At baseline and weeks 2, 4, 6, 8, and 14, patients completed questionnaires, including a VAS of finger pain, the Australian-Canadian Hand Osteoarthritis Index, the Michigan Hand Outcomes questionnaire, the Functional Index for Hand Osteoarthritis, a VAS of thumb-base pain, a patient global assessment with VAS, a VAS of fatigue, and the Short Form-36 physical component scale. At week 6, patients were also asked which treatment they believed they had received.

Hand radiographs were taken at baseline, unless radiographs had been taken in the previous 6 months. Radiographic damage was assessed with the Kellgren-Lawrence system (a score of 0-4 in 30 joints).[13] Erosive osteoarthritis was defined as having at least one joint in Verbruggen-Veys erosive or remodelling phase.[14] Synovial thickening and PDS (scored as 0-3 in 30 joints)[15] were assessed on ultrasound at baseline and weeks 6 and 14. Contrast-enhanced MRI of DIP/PIP joints 2-5 was done at baseline and week 6 to assess synovitis (scored 0-3.5) and bone marrow lesions (0-3).[16] Details of questionnaires and imaging assessments are shown in the appendix (pp 2-6).

Outcomes

The primary endpoint was finger joint pain after 6 weeks on a 100-mm VAS, assessed in a modified intention-to-treat population (all participants randomly assigned to groups and who attended a baseline visit). Secondary clinical endpoints were finger pain at weeks 8 and 14; fulfilment of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria (appendix pp 2-3)[17] at weeks 6 and 14; scores on the Australian-Canadian Hand Osteoarthritis Index pain (scored as 0-20) and function subscales (0-36), the Functional Index for Hand Osteoarthritis (0-30), an assessment of thumb-base pain (on VAS), a patient global assessment (on VAS), fatigue (on VAS), and a norm-based Short Form-36 physical and mental component scale at weeks 6, 8, and 14; and scores on the Michigan Hand Outcomes questionnaire pain and function subscales (scored as 0-100), a physician global assessment (on VAS), the Doyle Index of tender joints in the hand (scored as 0-90), a swollen joint count (0-30), and grip strength at weeks 6 and 14. Secondary imaging endpoints were synovial thickening and PDS by ultrasound (at weeks 6 and 14) and synovitis and bone marrow lesions by MRI (at week 6). Safety endpoints were the number of adverse events, serious adverse events, withdrawals because of adverse events, and changes in blood glucose concentrations between baseline and week 2. Secondary endpoints were assessed in the modified intention-to-treat population (all participants randomly assigned to groups and who attended a baseline visit).

We did a prespecified exploratory analysis of the primary endpoint (finger joint pain after 6 weeks on a 100-mm VAS) in the per-protocol population (all patients meeting the study entry criteria, with no major protocol violations, who completed the study). We also did a prespecified sensitivity analysis of the primary endpoint, in which we excluded patients who did not report a flare-up after analgesic washout.

Finally, we did a post-hoc subgroup analysis of the primary endpoint in patients with erosive osteoarthritis and a post-hoc analysis of the imaging endpoints at the patient level using sum scores (ie, by adding the scores of each individual joint, we generated a sum score per patient).

Statistical analysis

To detect a 15-mm between-group difference in finger joint pain by VAS after 6 weeks (primary outcome), with an SD of 22 for change from baseline and an α-level of 0.05, we required 35 participants per group to attain a power of 80% or 45 participants per group to attain a power of 90%. Accounting for an expected 10% loss to follow-up, we sought to include 90 patients.

We analysed all endpoints with generalised estimating equations, and we used robust standard errors and the working correlation structure specified as exchangeable. Data from all available timepoints were used. The independent variables included in our model were treatment group, visit number (categorical), interaction between treatment group and visit number, the baseline value of dependent variable (continuous), and study centre (categorical). We also ran a model that additionally adjusted for age and sex for the primary endpoint. We analysed imaging endpoints at a joint level to account for clustering of joints within patients.

The primary analysis was done with generalised estimating equations for the primary endpoint in the described modified intention-to-treat approach. Secondary endpoints were also analysed with this modified intention-to-treat approach.

We analysed data with Stata version 14. The statistical analysis plan, which was written before breaking the randomisation code, is shown in the appendix (pp 47-51). This study is registered with the Netherlands Trial Registry, number NTR5263.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We screened patients for enrolment between Dec 3, 2015, and May 31, 2018. Patients completed baseline visits and started treatment between Dec 14, 2015, and July 2, 2018, and the last study visit of the last patient was Oct 4, 2018. Of 149 patients assessed for their eligibility, 57 (38%) patients were excluded (predominantly because they did not meet one or several inclusion criteria, most often because of an absence of synovial inflammation or of flare-ups after NSAID washout) and 92 (62%) patients were eligible for inclusion (figure 1).

We randomly assigned 46 (50%) patients to receive prednisolone and 46 (50%) patients to receive placebo, all of whom were included in the modified intention-to-treat analysis of the primary endpoint. 42 (91%) patients in the prednisolone group and 42 (91%) in the placebo group completed the 14-week study. The remainder of the participants discontinued participation before this time, including two patients in the prednisolone group (one for poor efficacy and one for a myocardial infarction) and four patients in the placebo group (three with adverse events and one who withdrew consent) who withdrew from the study before the 6-week assessment. Baseline characteristics were well balanced between the groups (table 1).

Table 1. Baseline characteristics of study participants.

	Prednisolone (n=46)	**Placebo (n=46)**
Age, years	62.2 (8.8)	65.6 (8.5)
Sex		
Female	38 (83%)	35 (76%)
Male	8 (17%)	11 (24%)
Body mass index, kg/m^2	26.9 (4.4)	27.2 (4.9)
Disease duration, years	6.9 (7.7)	6.2 (9.0)
Erosive osteoarthritis*	34 (74%)	33 (72%)
Kellgren-Lawrence sum score, 0-120	35.3 (15.4)	39.5 (16.1)
VAS score of pain in fingers, 0-100	54.4 (21.8)	53.6 (19.3)

Data are mean (SD) or n (%). VAS=visual analogue scale. *Defined as a joint in Verbruggen-Veys erosive or remodeling phase.

All patients reported adherence to the study medication of more than 80% in their diary. At week 6, 65 (76%) patients (36 patients in the prednisolone group and 29 patients in the placebo group) agreed to guess their treatment group assignment, of whom 27 patients in each group guessed correctly and nine patients in the prednisolone group and two patients in the placebo group guessed incorrectly. At week 6, nine (20%) of 44 patients in the prednisolone group versus 16 (38%) of 42 patients in the placebo group reported frequent paracetamol use (twice per week or more) as rescue medication for hand complaints over the past 2 weeks (odds ratio for difference 0.43, 95% CI 0.16-1.13; p=0.085).

The mean change between baseline and week 6 on VAS-reported finger pain was -21.5 (SD 21.7) in the prednisolone group and -5.2 (24.3) in the placebo group (figure 2), with a mean between-group difference (of prednisolone vs placebo) of -16.5 (95% CI -26.1 to -6.9; p=0.0007). Adjustment for age and sex yielded similar results, showing a mean difference of -16.4 (-26.0 to -6.9; p=0.0008).

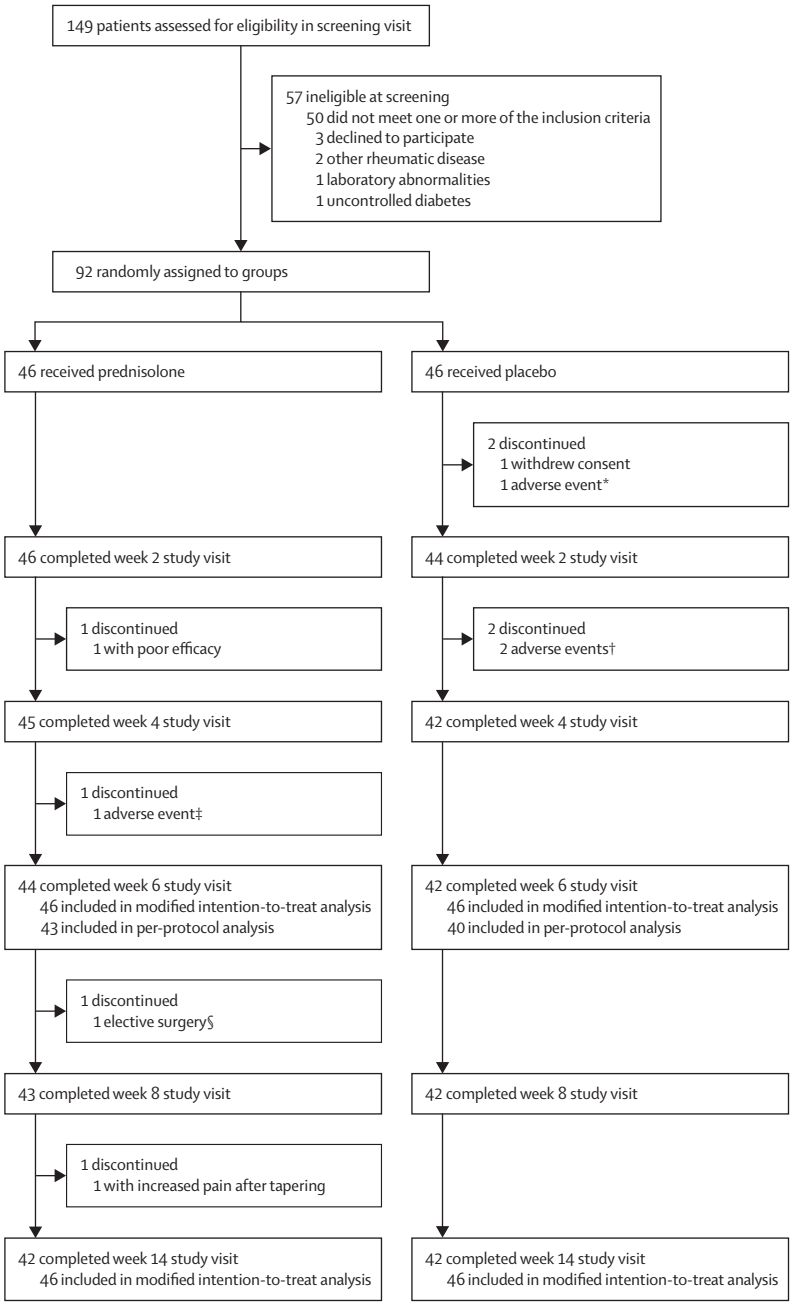


Figure 1. Trial profile.

*Bowel surgery (a serious adverse event). †Infected traumatic leg haematoma that required surgery (a serious adverse event) and Lyme disease arthritis of the knee (an adverse event). ‡Myocardial infarction (a serious adverse event). §An elective repair of a traumatic shoulder tendon rupture (for a trauma that occurred before the study started).

After study drug tapering, the between-group mean difference in VAS-recorded finger pain reduced to -8.5 (95% CI -18.5 to 1.5) at week 8 and 6.6 (-3.7 to 16.9) at week 14 (figure 2). At 6 weeks, 33 (72%) patients in the prednisolone group versus 15 (33%) patients in the placebo group fulfilled OMERACT-OARSI responder criteria. In most secondary endpoints concerning pain and function, prednisolone was superior to placebo at 6 weeks (table 2). Scores in the Short Form-36 physical component summary scale decreased more in patients treated with prednisolone than placebo, whereas no relevant difference in number of soft swollen joints was observed. No differences between the groups were seen for grip strength, fatigue on the VAS, or the Short Form-36 mental component summary scale (appendix p 7). In analogy with our findings on the primary endpoint, between-group differences for secondary endpoints were not sustained after study drug tapering (appendix p 8).

At week 6, the mean synovial thickening score per joint by ultrasound was lower in the prednisolone group than in the placebo group (mean difference -0.08, 95% CI -0.13 to -0.04; p=0.0004; table 2; figure 2). We did not observe a between-group difference in PDS score by ultrasound or synovitis score per joint by MRI (appendix p 9), whereas bone marrow lesions (assessed by MRI) appeared less severe in the prednisolone group (-0.04, -0.06 to -0.01; p=0.007). At week 14, the parameters assessed by ultrasound returned to baseline levels, and between-group differences disappeared (table 2; figure 2).

The number of non-serious adverse events was similar between the groups (43 events in 19 [41%] patients in the prednisolone group *vs* 43 adverse events in 19 [41%] patients in the placebo group; table 3). Five serious adverse events were reported during our study: one serious adverse event in the prednisolone group (a myocardial infarction) and four serious adverse events in the placebo group (an infected traumatic leg haematoma that required surgery, bowel surgery, atrial fibrillation that required a pacemaker implantation, and symptomatic uterine myomas that required a hysterectomy). Four (4%) patients discontinued the study because of an adverse event: one (2%) patient receiving prednisolone (for a myocardial infarction) and three (7%) patients receiving placebo (for surgery of the bowel and for an infected leg haematoma and for Lyme disease arthritis of the knee). The mean change between baseline and week 2 in blood glucose concentrations was 0.2 mmol/L (SD 1.2) in the prednisolone group and 0.4 mmol/L (1.5) in the placebo group. Hyperglycaemia occurred in one (2%) patient in the prednisolone group and three (7%) patients in the placebo group.

Analysis of the primary endpoint in the per-protocol population (43 patients in the prednisolone group and 40 patients in the placebo group) showed similar results as the primary analysis (mean between-group difference -15.1, 95% CI -24.9 to -5.2; p=0.0027), as did the sensitivity analysis, in which we excluded patients (13 patients in the prednisolone group and six patients in the placebo group) who did not have a flare-up after analgesic washout (-17.8, -28.5 to -7.1; p=0.0011), and a subgroup analysis in patients with erosive osteoarthritis only (-16.6, -28.1 to -5.2; p=0.0043). Post-hoc analysis of the imaging endpoints at the patient level using sum scores gave similar results to the joint-level analyses (table 2).

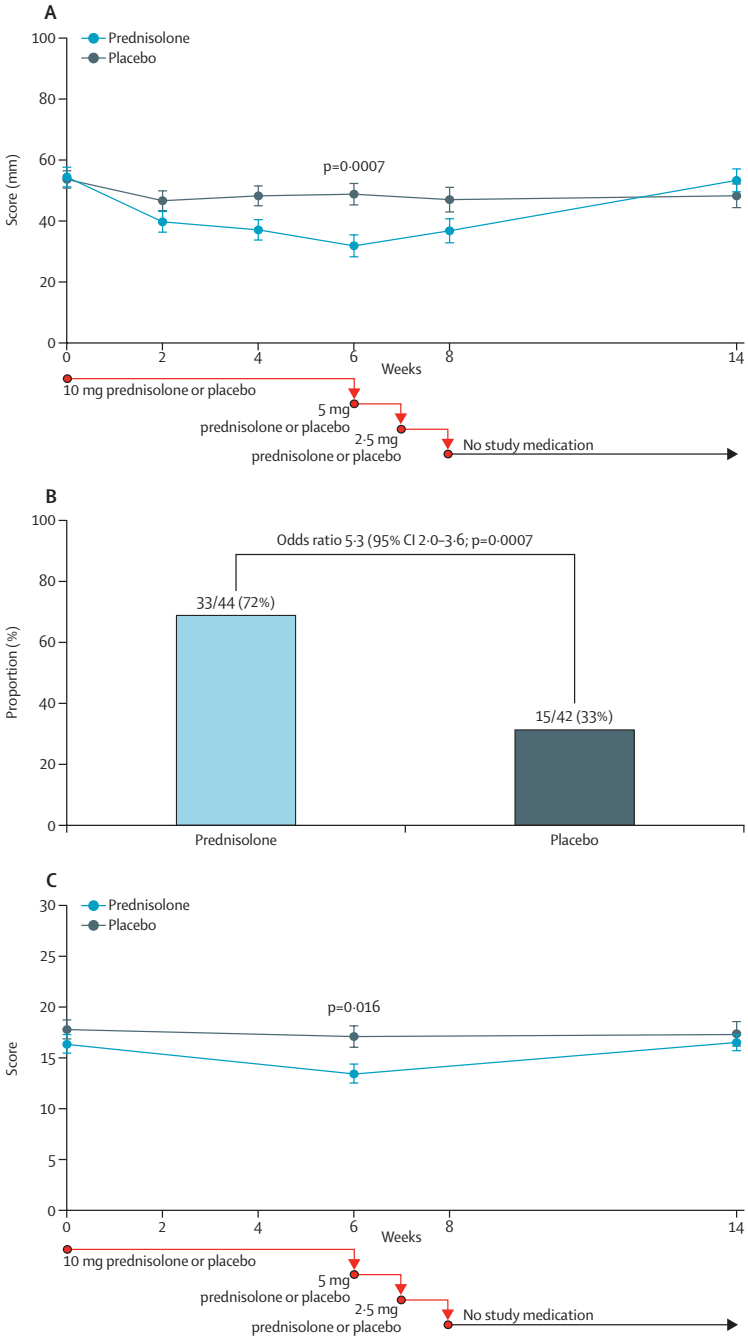


Figure 2. Visual analogue scale-reported pain in the fingers (A), the proportion of patients fulfilling Outcome Measures in Rheumatology-Osteoarthritis Research Society International responder criteria (B), and sum score of synovial thickening on ultrasound (C). Data are mean with standard error over the study period (A, C) or proportion at week 6 (B).

Table 2. Secondary clinical efficacy and imaging outcomes at week 6 (in the modified intention-to-treat population).

	Mean (SD) at baseline	
	Prednisolone (n=46)	Placebo (n=46)
Pain		
AUSCAN pain score	11.3 (3.3)	10.2 (3.1)
VAS score of pain at thumb base	34.3 (29.0)	35.4 (28.5)
Tender joint score	7.5 (6.0)	7.7 (7.3)
Function		
AUSCAN function score	18.6 (7.8)	19.0 (7.1)
FIHOA score	12.4 (5.4)	11.0 (4.7)
Short Form-36 physical component scale score*	44.6 (7.9)	46.2 (6.8)
Patient global assessment score on VAS	55.5 (21.7)	55.7 (22.0)
Soft swollen joint count	3.7 (2.7)	4.2 (2.7)
Grip strength, kg	20.4 (11.3)	20.4 (11.8)
Summed scores of imaging		
Synovial thickening (by ultrasound)	16.4 (6.3)	17.8 (6.3)
Power Doppler signal (by ultrasound)	5.3 (4.1)	7.0 (4.3)
Synovitis (by MRI)	15.6 (7.5)	14.8 (6.0)
Bone marrow lesions (by MRI)	11.0 (6.9)	11.0 (6.7)

Tender joint score was measured with the Doyle Index in the hand. AUSCAN=Australian-Canadian Hand Osteoarthritis Index. FIHOA=Functional Index for Hand Osteoarthritis. VAS=visual analogue scale. *Adjusted for baseline values and study centre. †Norm-based scores of Short Form-36 scale with a standardised mean of 50 and SD of 10 using age-specific and sex-specific Dutch population-based norms.

Mean change (SD) from baseline and week 6		Adjusted mean between-group difference (95% CI)*	p value
Prednisolone (n=46)	Placebo (n=46)		
-4.7 (3.5)	-1.1 (3.1)	-3.5 (-4.9 to -2.1)	<0.0001
-12.3 (28.0)	0.2 (17.3)	-12.0 (-21.7 to -2.3)	0.016
-3.8 (4.9)	-1.1 (8.2)	-2.7 (-5.6 to 0.1)	0.062
-6.5 (7.4)	-2.7 (4.7)	-3.7 (-6.2 to -1.1)	0.0051
-2.6 (5.1)	-0.5 (4.0)	-2.1 (-4.0 to -0.2)	0.031
3.1 (6.7)	-0.3 (6.3)	3.5 (0.8 to 6.2)	0.011
-23.6 (23.5)	-8.0 (25.3)	-15.4 (-25.6 to -5.2)	0.0031
-1.3 (2.7)	-0.9 (3.0)	-0.4 (-1.6 to 0.8)	0.53
3.5 (4.1)	2.2 (5.5)	1.2 (-0.8 to 3.2)	0.24
-2.8 (4.7)	-0.3 (5.0)	-2.5 (-4.5 to -0.5)	0.016
-1.7 (4.3)	-1.3 (4.2)	-0.4 (-2.2 to 1.4)	0.68
-0.7 (2.8)	-0.5 (2.2)	-0.2 (-1.4 to 0.9)	0.66
-0.2 (1.7)	0.5 (1.2)	-0.7 (-1.3 to -0.02)	0.043

Table 3. Reported adverse events (in the modified intention-to-treat population).

	Prednisolone (n=46)	Placebo (n=46)
Non-serious adverse events		
Total	43	43
Infections	21	25
Upper airways (including colds or coughing)	11	15
Lower airways	1	1
Urinary tract	3	1
Skin or mucosal	1	3
Gastrointestinal (including gastroenteritis)	3	4
Other	2	1
Hypertension	0	1
Hyperglycaemia*	1	3
Headache, dizziness, or lightheadedness	7	5
Hyperactivity or sleeping problems	3	0
Musculoskeletal or aspecific aches	3	3
Other†	8	6
Serious adverse events		
Total	1	4
Infected traumatic leg haematoma requiring surgery	0	1
Bowel surgery (no further information available)	0	1
Atrial fibrillation requiring pacemaker implantation	0	1
Symptomatic uterine myomas requiring hysterectomy	0	1
Myocardial infarction	1	0

One participant in the prednisolone group (who had a myocardial infarction) and three participants in the placebo group (one each with bowel surgery, Lyme disease arthritis of the knee, infected traumatic leg haematoma requiring surgery) withdrew after adverse events. *Blood glucose concentrations of at least 8.5 mmol/L (non-fasting) or at least 7.0 mmol/L (fasting) in three patients with known diabetes, and blood glucose concentrations of at least 7.8 mmol/L (non-fasting) or at least 6.5 mmol/L (fasting) in one patient with known prediabetes (metabolic syndrome). †Included stomach ache (n=3), nausea (n=1), abdominal pain after trauma (n=1), haemoptysis (no underlying pathology found in diagnostic investigations; n=1), fatigue (n=1), and urine retention (n=1) in the prednisolone group; and stomach ache (n=1), nausea (n=1), skin rash (n=1), nose bleed (n=1), peeling of skin of the hands (n=1), and postmenstrual vaginal bleeding due to uterine myomas (which required hysterectomy later during the trial, a serious adverse event; n=1) in the placebo group.

DISCUSSION

In this double-blind, randomised, placebo-controlled trial of prednisolone in patients with painful hand osteoarthritis and signs of synovial inflammation, we found that 6 weeks of treatment with 10 mg prednisolone led to a substantial reduction in finger pain. Prednisolone was consistently better than placebo in secondary outcome measures of pain and function, with a large difference in the proportion of OMERACT-OARSI responders between groups (72% *vs* 33%). MRI and ultrasound measures also showed signs of decreasing inflammation.

Previous trials of glucocorticoids in hand osteoarthritis were inconclusive. A trial[18] on the efficacy of once-daily 5 mg prednisolone for 4 weeks found that prednisolone was not superior to placebo in reducing pain. Several reasons could explain this negative result: the dosage might have been too low to reach clinical efficacy, patients had only mild disease (based on the observed radiographic damage), a substantial response to placebo lowered the ability to detect between-group differences, and half of the patients concomitantly used NSAIDs. A trial[19] of a combined prednisolone-dipyridamole preparation found that this preparation improved pain compared with placebo; however, these improvements were at the cost of more study withdrawals because of adverse events, particularly headaches, a known side-effect of dipyridamole. A trial[20] of glucocorticoid injections in DIP/PIP joints showed promising effects in the injected joint, although improvements were confined to the index joint. Moreover, by contrast with our trial, none of these studies ascertained the presence of joint inflammation through imaging at study inclusion.

By contrast with the negative results of placebo-controlled trials[9] of intra-articular glucocorticoids in patients with thumb-base osteoarthritis, we observed an improvement in thumb-base pain in the intervention group, albeit less than in the fingers. Since we deliberately excluded patients with primarily thumb-base complaints, based on evidence that thumb-base osteoarthritis is a distinct hand osteoarthritis subset that requires a distinct approach,[21] patients in our trial probably had milder radiographical damage in the thumb base, which could explain the divergent results.

Inhibitors of tumour necrosis factor and interleukin-1, two biological therapies that have been approved for the treatment of rheumatoid arthritis (the prototypical inflammatory arthritis) have not been successful in hand osteoarthritis, despite the documented role of inflammatory cytokines.[9,22] This contrasting finding suggests that, unlike in rheumatoid arthritis, targeting a single cytokine might not be sufficient in osteoarthritis.

The findings of the HOPE trial could mark a turning point in the treatment of hand osteoarthritis. The large beneficial effect size on pain and function exceeded those of all available therapeutic options in handosteoarthritis,[9] and the results showed that local inflammation in hand osteoarthritis can be modulated. The latter is an important step towards targeted treatment in hand osteoarthritis, with the eventual goal of finding a treatment that can modify its disease course.

Several clinical and imaging markers of inflammation (synovial thickening by ultrasound and bone marrow lesions by MRI) improved in the prednisolone group, yet between-group differences in other parameters did not (soft tissue swelling, PDS by ultrasound, and synovitis by

MRI). The prevalence of these outcomes might be too low, these parameters or scoring methods might not be sensitive to change or might assess several aspects of inflammation, or the 6-week treatment period might have been too short to generate large changes in these outcomes.

Although it is possible that the observed improvements in signs and symptoms in the intervention group are the result of decreased inflammation, we cannot rule out other mechanisms by which prednisolone might have led to these improvements, such as a centrally mediated effect. However, although these effects are documented for high dosages of prednisolone, there is no evidence that such effects already occur at a dosage of 10 mg per day.[23] An argument against a role of inflammation in the observed improvements could come from previous negative trials of strong anti-inflammatory drugs such as tumour necrosis factor inhibitors in hand osteoarthritis.

The clinical course of hand osteoarthritis often fluctuates, with passing flare-ups of the disease accompanied by more pain and joint inflammation. Our study findings provide evidence that such flare-ups, when patients are most in need of treatment, can be effectively and safely treated with a short course of 10 mg prednisolone. Prednisolone is an inexpensive, widely available drug, providing ample opportunity to directly apply these findings in daily clinical practice. However, although the HOPE trial established the efficacy of prednisolone in patients with pain and joint inflammation, of whom most reported a flare-up after withdrawal of pain medication, no data are available on whether other patients with hand osteoarthritis would benefit from this drug, although it is likely that joint inflammation is a prerequisite for its effectiveness. This hypothesis is also supported by findings from an open study,[24] showing that synovial thickening on ultrasound was the most important predictor for response to 120 mg intramuscular methylprednisolone in patients with inflammatory hand pain.

After tapering the study medication, symptoms resumed baseline levels, analogously to discontinuation of anti-inflammatory therapies in other rheumatic musculoskeletal diseases. Although the observed symptomatic effect at week 6 was substantial, it is unknown whether further improvement would have been achieved with continued treatment. It also remains to be seen whether timely suppression of inflammation can eventually alter the disease course. Future studies to investigate the optimal dosage and duration of treatment are warranted, possibly in trials employing treat-to-target strategies.

We found no safety signals for a short course of 10 mg prednisolone daily, but prolonged glucocorticoid treatment can lead to serious complications, the risk of which increases with increased dose and duration of therapy. A particularly relevant complication is the development of osteoporosis, since a large proportion of patients with hand osteoarthritis are (postmenopausal) women aged 50 years or older. Bone loss and increased vertebral and non-vertebral fracture risk can occur rapidly after initiation of glucocorticoid therapy.[25,26] A systematic literature review[27] found a dose-dependent increased risk of bone mineral density loss, osteoporosis, and vertebral and non-vertebral fractures with chronic, daily use of 7.5-30 mg of a prednisolone equivalent. Although the mean daily dose in these studies was comparable to that in the HOPE trial, their treatment duration and cumulative dose were substantially higher (1840-30240 mg *vs* 472.5 mg in the HOPE trial). Nevertheless, since our trial only provides evidence for the effectiveness of a 6-week course of 10 mg prednisolone daily, and in light of the risk of complications such as

glucocorticoid-induced osteoporosis, prescription of prednisolone for prolonged periods of time in patients with hand osteoarthritis should be discouraged. Notably, NSAIDs, which are widely used for symptom relief in patients with painful hand osteoarthritis, are also often unsuitable or, indeed, contraindicated, even for a short period of time, because of their established high risks of cardiac, gastrointestinal, and renal adverse events and because of drug-drug interactions with many other drugs, such as antihypertensive medication.[28-30]

Inclusion of a specific subset of patients (ie, with signs of active inflammation), is both a strength and a limitation of our study. Although it reduces the generalisability of the results to patients without this characteristic, it increased the likelihood of observing an effect of a targeted intervention. The heterogeneous nature of the disease necessitates clear patient stratification in clinical trials to identify patients who will most likely benefit from treatment. Liberal patient inclusion might have been a reason that previous trials in hand osteoarthritis produced negative results.

In conclusion, 6-week treatment with 10 mg prednisolone effectively improved signs and symptoms compared with placebo in patients with painful hand osteoarthritis and signs of synovial inflammation. The results of our study provide clinicians with a new short-term treatment option for patients with hand osteoarthritis who report a flare-up of their disease.

REFERENCES

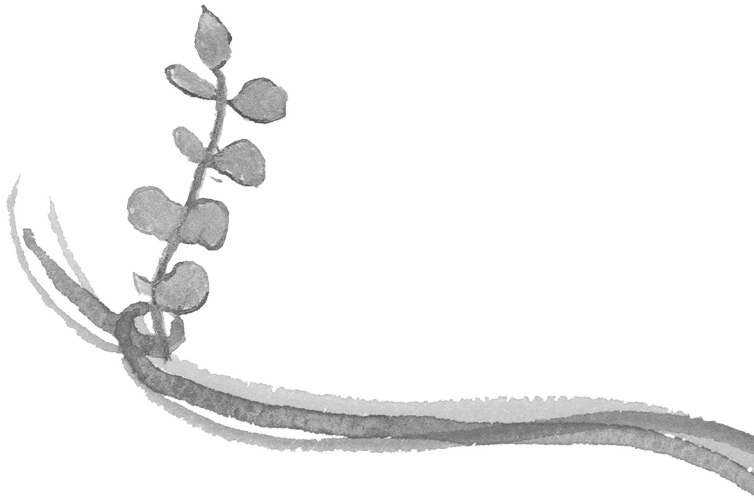
1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115-26.
2. Branco JC, Rodrigues AM, Gouveia N, et al. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt- a national health survey. *RMD Open* 2016;2:e000166.
3. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
4. Qin J, Barbour KE, Murphy LB, et al. Lifetime Risk of Symptomatic Hand Osteoarthritis: The Johnston County Osteoarthritis Project. *Arthritis Rheumatol* 2017;69:1204-12.
5. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
6. Marshall M, Watt FE, Vincent TL, et al. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. *Nat Rev Rheumatol* 2018;14:641-56.
7. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
8. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242-51.
9. Kroon FPB, Carmona L, Schoones JW, et al. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *RMD Open* 2018;4:e000734.
10. Kloppenburg M, Kroon FP, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019;78:16-24.
11. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
12. Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic review and meta-analysis. *Ann Rheum Dis* 2016;75:1971-8.
13. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
14. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308-20.
15. Keen HI, Lavie F, Wakefield RJ, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. *Ann Rheum Dis* 2008;67:651-5.
16. Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386-91.
17. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12:389-99.
18. Wenham CY, Hensor EM, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology (Oxford)* 2012;51:2286-94.
19. Kvien TK, Fjeld E, Slatkowsky-Christensen B, et al. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942-8.
20. Spolidoro Paschoal Nde O, Natour J, Machado FS, et al. Effectiveness of Triamcinolone Hexacetonide Intraarticular Injection in Interphalangeal Joints: A 12-week Randomized Controlled Trial in Patients with Hand Osteoarthritis. *J Rheumatol* 2015;42:1869-77.
21. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
22. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011;7:33-42.
23. Mitchell D, Collins J. Do corticosteroids really alter mood? *Postgrad Med J* 1984;60:467-70.
24. Karim Z, Quinn M, Wakefield R, et al. Response to intramuscular methyl prednisolone in inflammatory hand pain: evidence for a targeted clinical, ultrasonographic and therapeutic approach. *Ann Rheum Dis* 2007;66:690-92.
25. van Staa T, Leufkens H, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002;13:777-87.
26. Canalis E, Mazziotti G, Giustina A, et al. Gluococorticoid-induced osteoporosis:

pathophysiology and therapy. *Osteoporos Int* 2007;18:1319-28.
27. Duru N, van der Goes M, Jacobs J, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;72:1905-13.
28. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
29. Gabriel S, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.
30. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-79.



CHAPTER 6

Intra-articular therapies in the treatment of hand osteoarthritis: a systematic literature review



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ABSTRACT

Background. Local treatments to alleviate symptoms in hand osteoarthritis (OA) are preferred, especially in elderly patients with comorbidities. Therefore, we have summarized the benefits and harms of intra-articular (IA) therapies.

Methods. We conducted a systematic literature review until May 2015, including all controlled trials investigating efficacy or safety of any IA therapy in carpometacarpal (CMC) and interphalangeal (IP) OA compared with placebo or other treatments. Two authors independently selected trials and assessed risk of bias using the Cochrane tool. The main efficacy outcome was pain. We performed meta-analysis where appropriate.

Results. A total of 13 trials (864 patients) studying CMC (n=11) and IP OA (n=2) were included, comparing corticosteroids or hyaluronic acid (HA) versus placebo (n=4 and n=3), and corticosteroids versus HA (n=6). Single studies investigated infliximab, dextrose, and different HAs. The overall risk of bias was unclear or high in most trials. Meta-analysis of two trials comparing corticosteroids with placebo in CMC OA showed no improvement in pain (mean difference -3.56, 95% confidence interval (CI) -13.87 to 6.75, scale 0-100). HA also appeared not efficacious compared with placebo in CMC OA. One trial comparing corticosteroids with placebo in IP OA demonstrated significantly improved pain during movement. No convincing evidence for efficacy of corticosteroids or HA over the other or alternative therapies was found. Only local adverse events were reported. No specific IA therapy appeared more harmful than another.

Conclusion. Despite a beneficial short-term safety profile, IA corticosteroids or HA do not appear more effective than placebo in CMC OA. The suggestion that IA corticosteroids might be efficacious in IP OA requires confirmation.

INTRODUCTION

Hand osteoarthritis (OA) is a prevalent joint disorder with a high burden of disease, leading to pain, loss of function and a decreased quality of life.[1-3] The prevalence of symptomatic hand OA among men and women aged >70 years was estimated to be 13 and 26%, respectively, in a large population-based cohort study,[3] and the prevalence of radiographic hand OA is even higher, affecting up to 55 and 67% of men and women over the age of 55.[1]. No treatments are yet available to modify the disease course.[4] The main aim for therapies in hand OA is therefore to alleviate symptoms. For this purpose, non-pharmacological treatments (e.g. education, the use of assistive devices, and the application of splints for thumb base OA) as well as pharmacological treatment modalities [most importantly simple analgesics like paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)] are available. The European League Against Rheumatism (EULAR) recommends a combination of non-pharmacological and pharmacological treatment modalities for the optimal management of hand OA, with a preference of local treatments over systemic treatments.[5] Local treatment could be an attractive treatment modality, especially in elderly patients with more comorbidities.

A well-known, widely used form of local treatment is the injection of corticosteroids into the affected joint, particularly for patients with thumb-base OA.[6] The local anti-inflammatory effects of corticosteroid injections are hypothesized to decrease inflammation and consequently relieve the symptoms of OA. However, important side effects like infectious arthritis and cartilage damage have been described, although these adverse events are infrequent.[7] The EULAR 2007 recommendations advocate the use of intra-articular injection of corticosteroids to alleviate painful flares of OA, especially in thumb-base OA, based on expert opinion.[5] However, this recommendation was not supported by the 2012 American College of Rheumatology (ACR) recommendations for the management of OA, which "conditionally recommends not using intra-articular corticosteroids" in thumb-base OA.[8]

Another well-known intra-articular treatment is the injection of hyaluronic acid in the osteoarthritic joint (commonly called viscosupplementation). Viscosupplementation is based on the physiologic importance of hyaluronan in the synovial fluid, and it is hypothesized that this can restore the reduced viscoelasticity of the synovial fluid in osteoarthritic joints and thus decrease pain, improve mobility and restore the natural protective functions of hyaluronan in the joint.[9, 10] Reported side effects include local reactions, but also more serious side effects like pseudoseptic reactions and flare-ups of the disease.[11, 12] Experts do not yet agree on the usefulness of this form of intra-articular therapy, since EULAR guidelines specify that intra-articular hyaluronan may be useful in treating thumb-base OA, whereas ACR guidelines conditionally recommend not using intra-articular hyaluronates.[5, 8]

A recent systematic review assessing the efficacy of intra-articular injections of corticosteroids and hyaluronic acid in thumb-base OA concluded that intra-articular hyaluronic acid may be useful to increase functional capacity and that intra-articular corticosteroids can decrease pain in thumb OA after 24 weeks.[13] However, the authors

found large heterogeneity in the results of their meta-analysis. Moreover, they did not include other subsets of OA, e.g. interphalangeal (IP) OA and erosive OA, and excluded trials that assessed other intra-articular therapies besides corticosteroids or hyaluronic acid.

The aim of the present study was to assess the benefits and harms of all forms of intra-articular therapies in the treatment of hand OA, including all its subsets.

METHODS

We conducted a systematic literature review, including all published randomised controlled trials (RCTs) and quasi-RCTs (i.e. where allocation was not truly random), without language restrictions. We included trials of adults with hand OA, regardless of its subset (including thumb-base OA, IP OA and erosive OA), as determined by clinical diagnosis or fulfilment of the ACR criteria for hand OA.[14] Studies including participants with other diseases were only eligible if the results from participants with hand OA were presented separately. We included studies that compared any form of intra-articular therapy in the hand joints (including, but not restricted to, corticosteroids and hyaluronic acid) versus placebo; another intra-articular therapy; another pharmacological therapy; a non-pharmacological treatment; or different doses, frequency or duration of the same therapy. Studies that did not assess any efficacy or safety outcomes were not eligible for inclusion.

Search strategy

We searched the following databases up to May 2015: PubMed, Embase, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Academic Search Premier and ScienceDirect. The complete search strategy is provided in the Electronic Supplementary Material (ESM). Additionally, we searched three clinical trial registries to identify ongoing and recently finished studies [ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal and the International Standard Randomised Controlled Trial Number (ISRCTN) registry]. We contacted authors of completed but still unpublished trials that were identified in clinical trial registries to request more information about their study. We also screened conference abstracts of the EULAR, ACR and OsteoArthritis Research Society International (OARSI) annual conferences from the last 5years, as well as reference lists from included studies and other systematic reviews on the safety and efficacy of intra-articular therapies for hand OA. We contacted authors of eligible studies that were published only as a conference abstract for additional information, and excluded conference abstracts published more than 5 years ago.

Study selection and data collection

Two review authors (FK, RR) independently screened the retrieved titles and abstracts, and full-text papers were retrieved and read if necessary to determine inclusion. Disagreements between the authors were discussed in a consensus meeting. In case of non-consensus, a third

reviewer (MK) decided whether the study was eligible. One review author (FK) extracted data from each included study regarding study design, study duration, characteristics of the study population, interventions, outcome measures, timing of outcome assessment, co-interventions, results for outcomes of interest, losses to follow-up and funding. A second review author (RR) verified extracted data.

Assessment of risk of bias

Two review authors (FK, RR) independently assessed the risk of bias of each included study with regard to random sequence generation, allocation concealment, blinding (of participants, care provider and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias according to the Cochrane risk of bias tool.[15] Each criterion was judged as 'low risk of bias', 'high risk of bias' or 'unclear' (either lack of information or uncertainty over the potential for bias). In addition, an 'overall assessment' was formed for each study, based on the individual judgements for each risk of bias item. Items assessing selection bias and blinding were considered 'key domains', i.e. the most important domains in the risk of bias of a study. Studies were judged as having an overall high risk of bias if one or more items from the 'key domains' were judged as high risk. In cases where both key domains were judged as unclear risk, that study was rated as having an overall high risk of bias when more than two of the three remaining items were both rated high or unclear, and it was rated as having an overall unclear risk of bias when two of the remaining items were rated as low and unclear risk or if at least two items were both rated as low risk. In cases where both key domains were judged as low risk, that study was rated as having an overall unclear risk of bias when more than two remaining items were both rated high or unclear, and it was rated as having an overall low risk of bias when two of the remaining items were rated as low and unclear risk or if at least two items were rated as low risk. Disagreements were discussed, and in case of non-consensus a third review author (MK) made the final decision.

Outcome measures

All outcomes were assessed at baseline, week 4, week 12 and week 24. The main efficacy outcome was pain on a visual analogue scale (VAS) or a numerical rating scale (NRS). Other efficacy outcomes were self-reported physical function, patient global assessment, joint activity, health-related quality of life and hand strength, according to the core domains in clinical trials for hand OA proposed by Outcome Measures in Rheumatology (OMERACT).[16] The safety outcomes that were assessed included the number of withdrawals due to adverse events, the number of (local or systemic) adverse events and the number of serious adverse events.

Data analysis

Meta-analysis was only performed if the study data were clinically and statistically sufficiently homogeneous and/or the risk of bias was judged to be low enough to produce reliable results, using Review Manager 5.3 statistical software. For studies judged as clinically homogeneous with respect to intervention groups, control groups, timing of outcome assessment and outcome measures, the I^2 statistic was used to test for statistical heterogeneity. For continuous outcomes,

mean differences (MDs) with corresponding 95% confidence intervals (CIs) were calculated, unless different scales were used to measure the same conceptual outcome (e.g. pain), in which case the standardised mean difference (SMD) was calculated with corresponding 95% CIs. SMDs are calculated by dividing the MD by the standard deviation (SD), resulting in a unit-less measure of effect. For dichotomous outcomes the results were expressed as risk ratios (RRs) with corresponding 95% CIs. A random-effects model was used as the default option to be conservative in all analyses, independent of the I^2. The sample mean and SD was estimated from studies reporting only the median and (interquartile) range, using the appropriate approximation method proposed by Wan *et al*.[17] Studies that could not be included in the meta-analysis were described narratively.

RESULTS

Description of included studies

Database searching initially identified 2157 records, of which 24 qualified for full review, and 13 studies were finally included (figure 1).[18-31] We additionally identified 42 studies in clinical trial registries, of which two were eligible for inclusion. However, both trials were finally excluded as, upon request for more information from the authors, one trial appeared to be terminated prematurely due to adverse events in the intervention group, and the other trial was completed but results were not published because the pharmaceutical company did not pursue the indication. No additional records were found through other sources. All disagreements between the authors (FK, RR) on article selection (n=6) were resolved in a consensus meeting.

A total of 13 studies involving 864 participants (range 20-200, median 60), published between 2004 and 2014 were included. The mean age of participants was 62.8 years (reported in 12 trials). Four studies only included women, and in the other nine studies 84.5% of the participants were women. Most studies (n=11) only included participants with carpometacarpal (CMC) OA, and two trials only included participants with IP OA,[20, 30] of which one study specifically included participants with erosive OA.[20] In many studies (n=11), radiographic evidence of OA had to be present on top of clinical signs and symptoms.

Four trials compared corticosteroids with placebo; three trials compared hyaluronic acid with placebo; six studies compared corticosteroids with hyaluronic acid; and single studies compared infliximab with placebo, corticosteroids with dextrose, different frequencies of hyaluronic acid injections and hyaluronic acid with a low versus a high molecular weight (table 1). A total of 280 participants were treated with intra-articular corticosteroid injections: three trials used triamcinolone acetonide (dose range 10-40 mg in 0.5-1 ml, injected once in all studies),[18, 21, 24] two studies used triamcinolone hexacetonide (dose range 4-6 mg in 0.2-0.3 ml, injected once in both studies),[26, 30] two studies used betamethasone (3 mg in 0.5 ml injected three times in one trial, and a single injection of an unknown dose in 1 ml in the other),[22, 27] and two studies used methylprednisolone (40 mg in 0.5-1 ml injected once in both studies).[23, 31] Two trials added a small dose of lidocaine 2% to the injection fluid.[23, 30] A total of 360 participants were treated with intra-articular hyaluronate injections: three studies used Hylan G-F 20 (8 mg in 1

ml, injected once or twice),[19, 22, 24], six studies used sodium hyaluronate (dose range 5-15 mg in 0.5-1 ml, injected one to three times).[18, 21, 25, 27-29, 31] A total of 172 participants were treated with placebo, comprising a saline injection of 0.2-1 ml in four studies,[19, 20, 22, 26] or a local anaesthetic in two studies (0.1 ml lidocaine 2% or 0.5 ml bupivacaine 0.5%).[24, 30] Finally, 30 participants in one trial were treated with intra-articular dextrose 20% injections (0.5 ml, combined with 0.5 ml lidocaine 2%, injected three times monthly),[23] and ten participants were treated with intra-articular infliximab injections (0.2 ml, 0.1 mg/ml, injected 12 times monthly).[20]

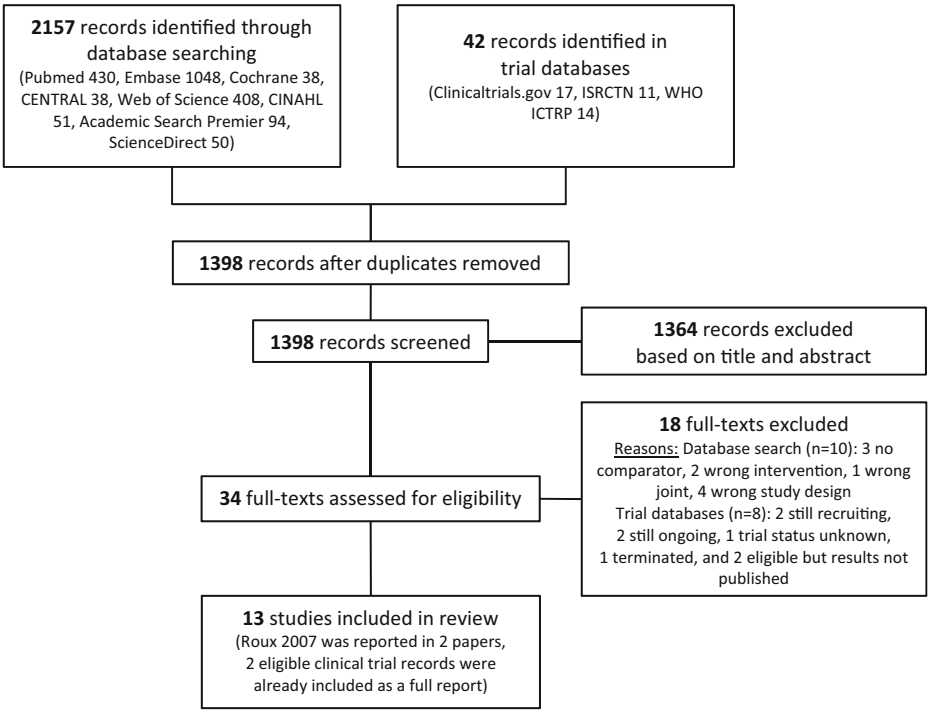


Figure 1. Study selection process. ICTRP, International Clinical Trials Registry Platform; ISRCTN, International Standard Randomised Controlled Trial Number; WHO, World Health Organization.

Table 1. Characteristics of included studies.

Study, **year**, **design**	**Important in/exclusion criteria**	**Intervention**	
		Group (name, dose, number of injections, frequency)	**Injection site**
Bahadir[18], 2009, RCT	Eaton stage II-III Women only No previous IAI in CMCJ	• CS (TA 20 mg/0.5 ml, 1x) • HA (SH 5 mg/0.5 ml, 3x, wkly)	Most painful CMCJ
Figen[19], 2009, RCT[a]	Eaton stage I-IV Women only Bilateral OA VAS >40mm Treatment fails No IAI in last 6 months	• HA (Hylan GF 20 8 mg/ 1 ml, 1x) • PL (saline 1ml, 1x)	CMCJ (HA, contralateral PL)
Fioravanti[20], 2009, CCT[a]	Central articular erosion in ≥1 IPJ VAS ≥40mm Treatment fails No IA CS in last 6 months	• IFX (0.02 mg/0.2 ml, 12x, mly) • PL (saline 0.2 ml, 12x, mly)	Each affected IPJ (worst side IFX, contra-lateral PL)
Fuchs[21], 2006, RCT	KL grade ≥ 1 VAS ≥ 40mm for ≥6 months No IA CS or GAGs in last 3 months No IA HA in last 6 months	• CS (TA 10 mg/1 ml, 3x, wkly) • HA (SH 10 mg/1 ml, 3x, wkly)	CMCJ
Heyworth[22], 2008, RCT	Eaton stage I-IV Improvement after prior IA CS at least mild-moderate Not >2x IA CS in target joint No IA CS in last 6 months	• CS (BM 1 ml, 1x PL + 1x CS, wkly) • HA (Hylan GF 20 8 mg/ 1 ml, 2x, wkly) • PL (saline 1 ml, 2x, wkly)	CMCJ
Jahangiri[23], 2014, RCT	Eaton stage ≥ II VAS >30 at least 3 months No IAI in last 6 months	• CS (MPA 40 mg/0.5 ml + LC 2% 0.5 ml, 2x PL + 1x CS, mly) • DX (100 mg/0.5 ml + LC 2% 0.5 ml, 3x, mly)	Most painful CMCJ
Mandl[24], 2012, RCT[b]	KL grade ≥1 VAS ≥35 mm No IA CS or HA in target joint in last 6 months No IA CS in last month	• CS (TA 40 mg/1 ml, 1x CS + 1x PL, wkly) • HA (Hylan GF 20 8 mg/1 ml, 2x, wkly) • PL (Bupivacaine 0.5% 1 ml, 2x, wkly)	CMCJ
Massarotti[25], 2013, RCT[b]	Women only	• HA low MW (SH MW 500-700 1 ml, 3x, wkly) • HA high MW (SH MW 800-1200 1 ml, 3x, wkly)	CMCJ
Meenagh[26], 2004, RCT	No previous IAI in either CMCJ	• CS (TH 5 mg/0.25 ml, 1x) • PL (saline 0.25 ml, 1x)	Most painful CMCJ
Monfort[27], 2014, RCT	KL grade 1-3 Complaints ≥3 months Routine use of analgesics or NSAIDs No IA CS in last 3 months	• CS (BM 3 mg/0.5 ml, 3x, wkly) • HA (SH 5 mg/0.5 ml, 3x, wkly)	CMCJ

	Guidance	N (finish)	Co-medication	Studied outcome	Industry funded
	No	• 20 (N/A) • 20 (N/A)	Splint allowed; no analgesics	Pain (VAS); function (DHI); grip and pinch strength; AEs	No
	No	• 33 (31) • 33 (31)	N/A	Pain (VAS); function (DFI); pinch strength; AEs	No
	No	• 10 (10)[c] • 10 (10)[c]	Rescue: PCM (max 1000 mg per day); no other treatments	Pain (VAS); pain on pressure (VAS); grip strength; morning stiffness; radiographic damage (VV); AEs	N/A
	No	• 28 (28) • 28 (28)	Prior therapies ceased 1 w before first IAI; rescue: PCM; no other analgesics	Pain (VAS, NRS); pain on pressure (VAS); pinch strength range of thumb motion; swelling; heat; crepitation; AEs	Yes
	No	• 22 (22) • • 20 (20) • • 18 (18)	NSAIDs stopped 2 w before start; everyone received splint after first IAI for 2 w, then splint and NSAIDs (400 mg ibuprofen every 4-6 h) as needed	Pain (VAS); function (DASH); grip and pinch strength; range of thumb motion; AEs	Yes
	No	• 30 (27) • • 30 (28)	No splints, analgesics, or physiotherapy allowed	Pain (VAS); function (HAQ-DI); pinch strength; pain on pressure (VAS); AEs	No
	No	• 65[d] • • 62[d] • • 61[d]	N/A	Pain (VAS); function (DASH); AEs	Yes
	No	• 40 (N/A) • 40 (N/A)	N/A	Pain (VAS); AEs	N/A
	X-ray	• 20 (17) • 20 (18)	Everyone received splint after IAI for 48 h	Pain (VAS); pain on pressure (NRS); morning stiffness; patient and physician global (NRS); AEs	N/A
	US	• 40 (N/A) • 48 (N/A)	Prior therapies ceased 1 w before first IAI; rescue: PCM (max 3000 mg per day) (use was recorded)	Pain (VAS); function (FIHOA); patient and physician global (%); quality of life (SF-36); AEs	N/A

Table 1. Continued

Study, **year**, **design**	**Important in/exclusion criteria**	**Intervention**	
		Group (name, dose, number of injections, frequency)	**Injection site**
Roux[28,29], 2007, RCT	KL grade 2-4 VAS >40 Treatment fails No treatment modifications in last 3 months	• HA (SH 10 mg/1 ml, 1x) • HA (SH 10 mg/1 ml, 2x, wkly) • HA (SH 1 0mg/1 ml, 3x wkly)	CMCJ
Spolidoro[30], 2013, RCT[b]	Osteophyte(s) in IPJ VAS 30-80 in ≥1 IPJ No treatment modifications in last 2 months No IA CS in target IPJ in last 3 months	• CS (TH 4mg/0.2ml (DIP) or 6mg/0.3ml (PIP) + LC 2% 0.1ml, 1x) • PL (LC 2% 0.1ml, 1x)	Most painful IPJ
Stahl[31], 2005, RCT	Eaton stage II	• CS (MPA 40mg/1ml, 1x) • HA (SH 15mg/1ml,1x)	CMCJ

ACR, American College of Rheumatology; AE, adverse event; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; BM, betamethasone; CCT, controlled clinical trial; CMCJ, carpometacarpal joint; CS, corticosteroid; DASH, Disabilities of the Arm Shoulder and Hand; DFI, Dreiser's Functional Index; DHI, Duruöz Hand Index; DIP, distal interphalangeal joint; DX, dextrose; EOA, erosive osteoarthritis; FIHOA, Functional Index for Hand Osteoarthritis; GAGs, glycosaminoglycans; h, hours; HA, hyaluronate; HAQ-DI, Health Assessment Questionnaire Disability Index; IA, intra-articular; IAI, intra-articular injection; IFX, infliximab; IPJ, interphalangeal joint; KL, Kellgren-Lawrence; LC, lidocaine; mly, monthly; MPA, methylprednisone acetate; MW, molecular weight; N/A, not available; NRS, numerical rating scale;

Risk of bias

Most trials were assessed as being at high or unclear risk of bias for multiple items (figure 2). In the overall assessment, only two studies were judged as having a low risk of bias.[26, 30] Four trials were at low risk of selection bias, as they described adequate sequence generation and allocation concealment; the risk of selection bias in the other trials was high (n=3) or unclear (n=6). One additional trial was at high risk of selection bias even though sequence generation and allocation concealment were performed using methods associated with a low risk of bias, since this study selectively included participants based on the probability of a positive treatment effect (judged as high risk of bias in the item 'other bias').[22] Participants were adequately blinded in five trials; however, in the remaining studies, participants were not blinded (n=4) or it was unclear whether participants were blinded (n=4), although most trials (n=8) adequately blinded the outcome assessor(s). One trial had unexplained incomplete outcome data and was assessed as being at high risk of attrition bias. The risk of attrition bias remained unclear in seven trials, for example because the number of participants finishing the study was not described (n=5). Many trials had a high risk of reporting bias (n=5), e.g. as they did not report all assessed outcomes at all time points or only reported p-values. Other potential sources of bias were identified in five trials and included inappropriate statistical analyses for the selected study design (n=2),[19, 20] exclusion of participants after inclusion[23] or after treatment allocation,[27] and selectively including patients based on probability of a positive treatment effect (n=2).[20, 22]

Guidance	N (finish)	Co-medication	Studied outcome	Industry funded
X-ray	• 14 (12) • 14 (13) • 14 (12)	Usual treatment continued during study	Pain (VAS); function (DFI); AEs	N/A
No	• 30 (N/A) • • 30 (N/A)	Injected IPJ in splint for 48 h; rescue: PCM (max 2250 mg per day)	Pain (VAS); function (Cochin, AUSCAN) grip and pinch strength; goniometry; swelling; AEs	No
No	• 25 (N/A) • 27 (N/A)	N/A	Pain (VAS); function performance (PPT); grip and pinch strength; AEs	Yes

NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PL, placebo; PCM, paracetamol; PIP, proximal interphalangeal joint; PPT, Purdue Pegboard Test; RCT, randomised controlled trial; SF-36, Short Form 36; SH, sodium hyaluronate; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide; US, ultrasound; VAS, visual analogue scale; VV, Verbruggen-Veys; w, week(s); wkly, weekly. [a]Each participant participated in both treatment groups (one hand in intervention group [random or worst hand], other hand in control group). [b]Study only published as a conference abstract. [c]Number of treated IP joints per group: n = 56 in IFX group, n = 34 in PL group. [d]No number available of N randomized per treatment group, reported number is the number of participants that finished in each treatment group ('completers').

Effects of interventions

Most studies were clinically too heterogeneous to compare, did not provide data eligible for meta-analysis (e.g., data only presented in figures or presentation of point estimates without a measure of variance), and/or the risk of bias was judged to be too high to produce reliable results. Only results of two studies, comparing corticosteroid injections versus placebo in participants with CMC OA, could be pooled.[24, 26] The remaining studies are discussed narratively under each relevant comparison. A summary of the most important findings is presented in table 2.

Intra-articular corticosteroids versus placebo

Three studies (n=206) compared a corticosteroid injection with placebo in participants with CMC OA.[22, 24, 26] Pooled results from two studies (n=166, unclear and low risk of bias) for our primary outcome measure pain on VAS showed no difference up to 26 weeks between intra-articular corticosteroids and placebo [MD -3.56 (95% CI -13.87 to 6.75) on a 100-mm VAS; figure 3]. The third study (n=40, unclear risk of bias) concluded that both groups showed a decrease in pain compared with baseline, although there were no significant between-group differences at any of the time points up to 26 weeks (data only presented graphically). Also, for the other reported efficacy outcomes [i.e. function (two trials), grip strength (one trial), pinch strength (one trial), pain on joint palpation (one trial), joint stiffness (one trial), patient global assessment (one trial), physician global assessment (one trial) and range of motion (one trial)],

no between-group differences up to 26 weeks were found by any study in this comparison. No adverse events were observed in any of the treatment groups in two trials, although one trial[24] observed adverse events in both treatment groups [9/65 the corticosteroid group (all local adverse events such as pain, swelling and skin or nail abnormalities) and 3/61 in the placebo group (of which two were local adverse events and one case of surgery unrelated to study medication)].

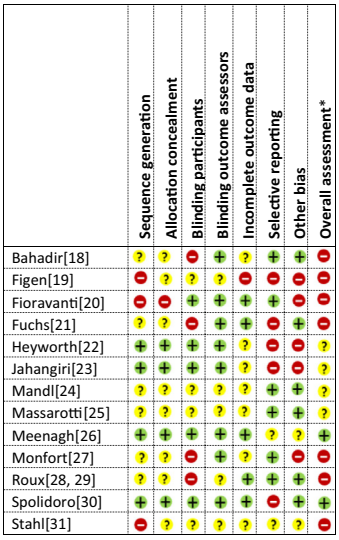


Figure 2. Risk of bias summary: review author's judgement about each risk of bias item for each included study (+ indicates low risk of bias, – indicates high risk of bias, ? indicates unclear risk of bias, *indicates overall assessment based on the individual judgements for each risk of bias item).

Spolidoro *et al*[30] (n=60, low risk of bias) studied participants with IP OA and found a decrease in pain compared with baseline for both groups, although there were no between-group differences for pain at rest at any of the time points up to 12 weeks. However, pain during joint movement improved more in the corticosteroid group than in those receiving placebo after 12 weeks [mean (SD) score on a 10-cm VAS after 12 weeks of 2.2 (2.9) vs. 4.0 (3.2), respectively]. Also, a significant decrease in joint swelling was found in the corticosteroid-treated group compared with the placebo group [1.1 (1.2) vs. 2.0 (1.3), respectively, on a 10-cm VAS]. For the other reported efficacy outcomes (i.e. function [measured with both the Cochin questionnaire and the Australian/Canadian hand osteoarthritis index (AUSCAN)], grip strength, pinch strength and goniometry), no between-group differences were identified. The authors reported that no severe adverse events were observed in either treatment group.

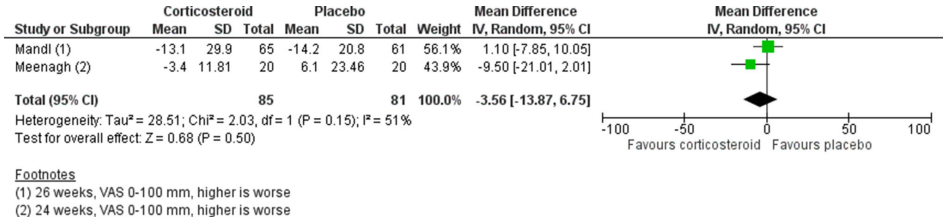


Figure 3. Forest plot: comparison of intra-articular corticosteroids versus placebo in participants with thumb-base OA, outcome pain on VAS. The studies included in the forest plot were Mandl *et al*[24] and Meenagh *et al*.[26] CI, confidence interval; df, degrees of freedom; IV, inverse variance; mm, millimetres; SD, standard deviation; VAS, visual analogue scale.

Intra-articular hyaluronic acid versus placebo

Three studies (n=196) investigated an injection with hyaluronic acid compared with placebo in participants with CMC OA.[19, 22, 24] One trial investigated the same participants in both treatment groups by including one CMC joint in the intervention group and the contralateral joint in the placebo group.[19] All studies [risk of bias: high (n=1) and unclear risk of bias (n=2)] showed a decrease in pain compared with baseline in both groups, but no significant between-group differences were found up to 26 weeks in two studies, while one study did not formally investigate between-group differences. Furthermore, no between-group differences were reported for the other efficacy outcomes [i.e. function (three trials), grip strength (one trial), pinch strength (two trials) and range of motion of the thumb (one trial)]. No adverse events were observed in any of the treatment groups in two trials, although one trial[24] observed adverse events in both treatment groups [5/62 in the hyaluronic acid group (three local adverse events and two cases of surgery unrelated to study medication) and 3/61 in the placebo group (two local adverse events and one case of surgery unrelated to study medication)].

Table 2. Summary of most important results.

OA type	Participants (n)	Visit	Risk of bias[a]	Outcome
Intra-articular corticosteroids vs. placebo				
CMCJ	N=206[22,24,26]	26 wk	Low (n=1), unclear (n=2)	Pain (VAS)
				AEs
IPJ	N=60[30]	12 wk	Low	Pain in rest (VAS)
				Pain during movement (VAS)
				AEs
Intra-articular hyaluronic acid vs. placebo				
CMCJ	N=196[19,22,24]	26 wk	Unclear (n=2), high (n=1)	Pain (VAS)
				AEs
Intra-articular corticosteroids vs. hyaluronic acid				
CMCJ	N=405[18,21 22,24,27,31]	26 wk	Unclear (n=2), high (n=4)	Pain (VAS)
				AEs

AEs, adverse events; BL, baseline; CI, confidence interval; CMCJ, carpometacarpal joint; CS, corticosteroid; HA, hyaluronic acid; IPJ, interphalangeal joint; MD, mean difference; OA, osteoarthritis; PL, placebo; wk, weeks; VAS, visual analogue scale.

Intra-articular corticosteroids versus hyaluronic acid

Six studies (n=405) investigated a corticosteroid injection compared with hyaluronic acid in participants with CMC OA.[18, 21, 22, 24, 27, 31] For the primary outcome – pain on VAS – all trials showed an improvement in both treatment groups. Four trials [risk of bias: high (n=2) and unclear (n=2)] showed no between-group difference in pain on VAS up to 26 weeks,[22, 24, 27, 31] one trial (high risk of bias) described a transitory superior effect of corticosteroids at 1 and 6 months,[18] and one trial (high risk of bias) concluded that the corticosteroid group initially displayed a better and faster pain relief up to 3 weeks but that hyaluronic acid was 'non-inferior' to corticosteroids thereafter.[21] Three studies [risk of bias: high (n=1) and unclear (n=2)] reported no between-group differences in self-reported function after 26 weeks,[22, 24, 27] although one trial (high risk of bias) reported temporarily more improvement in function in the corticosteroid group at 12 months of follow-up.[18] Three of four trials assessing self-reported function reported an improvement in function in both intervention groups.[18, 22, 27] No between-group differences were found for most other reported efficacy parameters [i.e. grip strength (one trial), pinch strength (one trial), range of motion of the thumb (one trial), joint pain on pressure (one trial), quality of life (one trial) and joint crepitation (one trial)]. However, single

Results	Comments
• CS and PL groups both improve vs. BL • No between-group difference (pooled MD -3.56 [95% CI -13.87 to 6.75] on 100-mm VAS)	Pooled result from two studies,[24, 26] see figure 3
• One study: same amount of AEs in both groups[b] • No AEs in other studies	Local AEs[c] and one surgery case (unrelated)[24]
• CS and PL groups both improve vs. BL • No between-group differences	
• CS and PL groups both improve vs. BL • CS better than PL (mean [SD] 2.2 [2.9] vs. 4.0 [3.2] on 10-cm VAS)	
• 'No severe AEs' in either group	
• HA and PL groups both improve vs. BL • No between-group differences	Between-group differences only assessed in two studies[22, 24]
• One study: same amount of AEs in both groups[b] • No AEs in other studies	Local AEs[c] and 3 surgery cases (unrelated)[24]
• HA and CS groups both improve vs. BL • No consistent beneficial effect of CS or HA over the other	
• Three studies: same amount of AEs in both groups[b] • No AEs in other studies	Local AEs[c], unrelated AEs and 2 surgery cases (unrelated)[21,24,27]

[a]The risk of bias in this table represents the 'overall assessment' for each study. [b]Based on non-significant results of Pearson's chi-squared test (defined as p[0.05) using data provided in the individual trial reports. [c]Local AEs include pain, swelling, and skin or nail abnormalities.

studies reported temporarily more improvement in grip strength in the corticosteroid-group at 1 month of follow-up,[18] and transitory better relief of joint swelling in the corticosteroid group.[21] In contrast, single studies also reported (transitory) beneficial effects in favour of hyaluronic acid injections in the outcomes pinch strength (temporarily more improvement after 12 weeks[22] and 24 weeks[21]), range of motion of the thumb (overall more improvement in the hyaluronic acid group[21]) and joint warmth (overall better relief of warmth in the hyaluronic acid group[21]). One trial only reported effects within each treatment group without formally comparing the two interventions for the outcomes function performance, grip strength and pinch strength.[31]

Three trials reported adverse events in both treatment groups, although numbers were relatively low and equal in both groups [corticosteroid vs. hyaluronic acid groups: 4/28 vs. 4/28 (Fuchs *et al*,[21] not related to study medication), 5/40 vs. 5/48 (Monfort *et al*,[27] minor side effects, including pain and local swelling following the injection), 9/65 vs. 5/62 (Mandl *et al*,[24] local side effects such as pain, swelling and skin and nail abnormalities, and few cases of surgery unrelated to study medication)], although no adverse events were observed in any of the treatment groups in the remaining three studies in this comparison.

Other comparisons

One study (n=20, high risk of bias) investigated intra-articular infliximab injections compared with placebo in a non-randomised pilot study in participants with erosive IP OA.[20] From each participant, the hand with the most severely affected finger joints was assigned to the intervention group; the other hand served as a control. Pain on VAS had significantly improved in the infliximab group after 12 months compared with baseline [mean (SD) 32.5 (15.1) vs. 75.3 (10.2), respectively, on a 100-mm VAS] and not in the placebo group [62.5 (20.4) vs. 50.5 (13.0)]. A formal between-group comparison was not possible due to the (known) baseline differences between the intervention and placebo group. Pain on pressure also improved only in the infliximab group, although no differences between groups were found for the other reported efficacy outcomes (i.e. grip strength, morning stiffness and radiological score). No side effects, neither local nor systemic, were observed during the study.

One study (n=60, unclear risk of bias) investigated intra-articular dextrose injections compared with corticosteroid injections in participants with CMC OA.[23] Pain during movement on VAS improved in both groups, with better pain relief 24 weeks after the last injection in the dextrose group compared with the corticosteroid group [mean (SD) score on a 10-cm VAS after 24 weeks of 1.2 (1.6) vs. 2.4 (1.8), respectively]. The outcomes function and joint pain on pressure also improved more in the dextrose group than in the corticosteroid group [function after 24 weeks: 1.6 (1.3) vs. 2.6 (1.5) on the Health Assessment Questionnaire Disability Index (scale 0-9, higher is worse); results for pain on pressure were only presented graphically]. No between-group differences were found for pinch strength. Three participants experienced minor adverse events (increase in joint pain, which subsided in several days), although which treatment these participants had received is unclear.

Two studies compared different frequencies or different forms of hyaluronic acid with each other in participants with CMC OA. The first study (n=42, high risk of bias) compared a single injection of hyaluronic acid with either 2- or 3-weekly injections.[28, 29] Pain on VAS improved only in both groups with multiple injections and not in the group with a single injection, although no between-group differences were found after 12 weeks [mean (SD) score on a 100-mm VAS after 12 weeks of 43.1 (22.8) vs. 39.5 (28.6) vs. 29.8 (21.9), respectively, for one, two or three injections]. Minor adverse events were observed in 30% of participants in all treatment groups, involving local pain, swelling, heat and/or redness, which subsided within several hours to days. The second study (n=80, unclear risk of bias) compared hyaluronic acid with a low molecular weight to that with a high molecular weight.[25] Pain on VAS improved in both treatment groups, although no between-group differences were found after 12 weeks [mean (SD) score on a 10-cm VAS after 12 weeks of 4.23 (2.90) vs. 4.03 (2.56), respectively, for the low versus high molecular weight fluid]. Minor side effects were observed in both groups, including mild pain and/or ecchymosis in the injection site (exact numbers per treatment group not specified).

DISCUSSION

Based upon trials of variable quality, both intra-articular corticosteroid injections and intra-articular hyaluronic acid injections appear not to be more efficacious than placebo in participants with CMC OA. A pooled analysis of two trials (low and unclear risk of bias) comparing corticosteroid with placebo injections in participants with CMC OA demonstrated no between-group difference in pain up to 26 weeks. However, one trial with a low risk of bias showed that intra-articular corticosteroid injections might be more effective than placebo in relieving both pain during joint movement and joint swelling in participants with IP OA. This between-group difference also reached clinical significance with a minimal clinically important difference (MCID) of 0.9 cm on a 10-cm VAS, based on studies in participants with OA of the lower extremities, in the absence of an MCID based on studies with patients with hand OA.[12] This finding possibly suggests different effects of intra-articular corticosteroid injections in different subsets of hand OA, although this needs confirmation since – to our knowledge – only one study to date has investigated intra-articular corticosteroids in IP OA. It is well-known that CMC and IP OA are associated with a separate risk factor profile, which underlines the different nature of these two subsets of hand OA and thus the possibility of different effects of the same intervention.[32] It is possible that inflammation plays a bigger role in IP OA than it does in CMC OA, in which mechanical loading is known to be an important factor, explaining why corticosteroids might be more effective in IP OA. Several trials in this review, all with a high or unclear risk of bias, compared corticosteroid versus hyaluronic acid injections in participants with CMC OA, but no consistent beneficial effect of one intervention over the other could be demonstrated. Single studies, all judged to have a high or unclear risk of bias, investigated alternative intra-articular therapies, including infliximab versus placebo (possible beneficial effect of infliximab, although no formal comparison could be made), dextrose versus corticosteroid injections (more improvement of pain during movement, pain on pressure and function in the dextrose group), single versus two or three hyaluronic acid injections (no between-group differences) and low versus high molecular weight hyaluronic acid (no between-group differences).

Apart from local adverse events at the injection site, including local pain, swelling and skin and/or nail abnormalities, no important adverse events were reported in any of the trials, indicating that the intra-articular therapies studied in this review appear to be relatively safe. Based on the included studies, none of the intra-articular therapies appeared to be more harmful than another. However, studies were small and possibly underpowered to assess adverse events. A large meta-analysis investigating the benefits and harms of viscosupplementation for knee OA found a clinically important increase in the risk for serious adverse events, withdrawals because of adverse events, and local adverse events associated with the use of intra-articular hyaluronic acid.[12] However, dosages of hyaluronic acid used in studies in hand OA (range 5-15 mg per injection) were generally significantly lower than the dosage commonly used in the treatment of knee OA (usually 20-40 mg per injection), possibly decreasing the risk of adverse events. A network meta-analysis investigating all pharmacological interventions in knee OA reported more withdrawals due to adverse events in oral treatments (i.e. acetaminophen and NSAIDs) than in intra-articular therapies.[33] The most commonly reported adverse events among intra-

articular therapies for knee OA were similar to those found in this review, i.e. transient local reactions, with similar events reported in different intra-articular therapies (corticosteroids and hyaluronic-acid). Since all included studies were of a short duration, we cannot draw conclusions on long-term safety and/or potential side effects associated with repeated intra-articular injections in the finger joints.

Studies systematically evaluating the benefits and harms of intra-articular therapies in hand OA are scarce, although many studies have been performed in knee OA, with conflicting results.[9, 12, 34-37] A recently published network meta-analysis comparing the effects of all available treatments in knee OA showed that intra-articular therapies were the most effective form of treatment.[33] The authors of this meta-analysis also found that intra-articular injection with placebo had an effect on pain similar to that of an (oral) NSAID, both with an effect size of 0.3. The intra-articular delivery mode itself thus appears to have a large positive treatment effect, which could be a true placebo response or possibly a physiological effect after injecting a fluid into a joint with a needle. The positive treatment effect of intra-articular injections in general was also confirmed by our finding that, in all placebo-controlled studies, not only the intervention group, but also the placebo group improved over time.

One of the strengths of our study was the use of a rigorous search strategy, minimizing the risk of missing eligible studies. In an attempt to reduce the risk of publication bias, we also searched for unpublished literature. This yielded two additional potentially relevant trials for inclusion, but both trials were eventually excluded, since one trial (hyaluronic acid vs. corticosteroids in CMC OA) was prematurely terminated due to adverse events in the hyaluronic acid group (trial registration number ISRCTN63038599), and results from the other (hyaluronic acid vs. placebo in CMC OA) were unobtainable because the pharmaceutical company funding the trial did not pursue the indication (trial registration number NCT00423371). Furthermore, through database searching we retrieved a trial comparing a thumb splint alone versus a single intra-articular corticosteroid injection in the CMC joint in addition to a thumb splint, which did not fulfil our inclusion criteria since it was only presented as an abstract at a conference meeting more than 5 years ago.[38] In this trial, no sustained benefit from a corticosteroid injection in addition to wearing a thumb splint could be demonstrated. Despite rigorous searching, no full trial report of this study could be identified. The exclusion of the three above-mentioned trials has possibly introduced a risk of publication bias. However, we believe it is unlikely that including these three studies would have led to major implications for the conclusions of our review, since we found no clear positive effect of any of the intra-articular therapies studied.

An important limitation is the poor methodological quality of many of the included trials, which is (partly) reflected by the fact that many of the included studies were judged as having an overall high risk of bias. Moreover, many studies did not provide data eligible for meta-analysis (e.g. authors presented data only in figures or presented point estimates without a measure of variance). We decided only to perform meta-analysis if the data of the studies were clinically and statistically sufficiently homogeneous and/or the risk of bias was judged to be low enough to produce reliable results. This decision was made based on previous reports that different forms of bias can have a major impact on the estimates of treatment benefits in osteoarthritis trials.[39-41] Consequently, pooled analysis was only possible in the comparison of corticosteroid

injections versus placebo in participants with CMC OA. Although this comparison consisted of three trials, only two of these were included in the meta-analysis, since the third trial only presented data in figures and its trial population was also too different from that of the other two studies (i.e. participants were only included when they had previously experienced at least a mild to moderate improvement after a corticosteroid injection in the CMC joint). However, we believe that further studies with higher methodological quality are not likely to substantially change the conclusions of this review. Confounding from biases across studies would have likely favoured the intra-articular treatment, and correcting for these biases is thus unlikely to change the direction of results towards a benefit of intra-articular treatment with corticosteroids or hyaluronic acid for hand OA compared with placebo. Our decision not to include all available studies in a meta-analysis is likely the explanation why our findings differ slightly from those of a recently published systematic review evaluating the effectiveness of intra-articular corticosteroids and hyaluronic acid in participants with thumb-base OA.[13]

It is known that generalizing results from the specialized and highly controlled setting of an RCT to real-life settings can sometimes be troublesome, and it could be argued that (the lack of) treatment effects found in the trials in our review might not be consistent with experiences from clinical practice. However, we believe that evidence from RCTs, provided that such a study is well-executed, is the most reliable form of evidence we have, since it accounts for several important forms of bias. Reasons that clinicians might see a treatment effect of any form of intra-articular therapy despite it not being found in the studies in this review, are, for example, a 'regression to the mean' effect because patients come to their treating physician when complaints are at the maximum level, and the placebo effect.

We aimed to include all possible intra-articular therapies for hand OA in this review, and our extensive database search also retrieved a few studies investigating prolotherapy in hand OA. Prolotherapy is a form of treatment in which repeated injections with an irritating substance are given around the joint (peri-articular). A commonly used substance for this purpose is dextrose, which is the compound that is also studied by one of the included studies.[23] However, since most studies investigating prolotherapy did not clearly indicate whether the solution was only injected peri-articularly, or whether it entered the intra-articular space, we excluded studies investigating prolotherapy unless they clearly specified that the investigated solution was injected intra-articularly. This led to the exclusion of one RCT comparing dextrose prolotherapy (n=13) versus placebo (n=14) in participants with finger and thumb OA, reporting that pain at rest and with grip improved more in the dextrose group, although not significantly, and pain with movement as well as finger flexion improved significantly more in the dextrose group.[42]

CONCLUSIONS

For patients with CMC OA, intra-articular injections with corticosteroids or hyaluronic acid do not seem to be more effective than placebo, although in the short term these treatments are probably not associated with important adverse events other than local side effects. Despite the apparent beneficial safety profile of intra-articular treatments, at least in short-term use, which would suggest an interesting treatment option for clinicians treating elderly patients, the lack of efficacy discourages the use of these treatments for hand OA. More well-performed studies investigating these therapies in this patient group are unlikely to substantially change this conclusion. Findings from one well-performed study suggested that intra-articular corticosteroid injections might be effective compared with placebo for patients with IP OA, although this finding needs to be confirmed in future studies.

REFERENCES

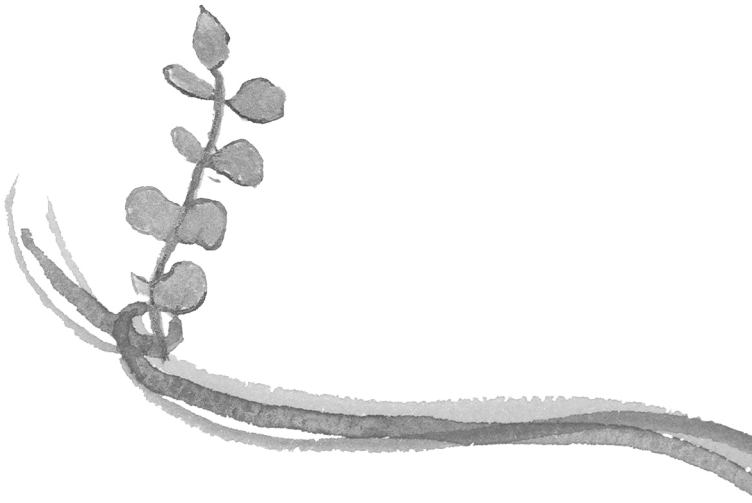
1. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
2. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
3. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
4. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242-51.
5. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:377-88.
6. Wolf JM, Delaronde S. Current trends in nonoperative and operative treatment of trapeziometacarpal osteoarthritis: a survey of US hand surgeons. *J Hand Surg Am* 2012;37:77-82.
7. Grillet B, Dequeker J. Intra-articular steroid injection. A risk-benefit assessment. *Drug Safety* 1990;5:205-11.
8. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthrit Care Res* 2012;64:465-74.
9. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;2:CD005321.
10. Fam H, Bryant JT, Kontopoulou M. Rheological properties of synovial fluids. *Biorheology* 2007;44:59-74.
11. Hunter DJ. Viscosupplementation for osteoarthritis of the knee. *N Engl J Med* 2015;372:1040-7.
12. Rutjes AW, Jüni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:180-91.
13. Trellu S, Dadoun S, Berenbaum F, et al. Intra-articular injections in thumb osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Joint Bone Spine* 2015, Mar 14. doi: 10.1016/j.jbspin.2015.02.002. [Epub ahead of print].
14. Altman RAG, Appelrouth D, Bloch D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
15. Higgins JPT, Sterne JAC. Assessing risk of bias in included studies. In: *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration. 2011. http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. [Accessed June 2015].
16. Kloppenburg M, Bøyesen P, Visser W, et al. Report from the OMERACT hand osteoarthritis workshop: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015, Jul 1. doi: 10.3899/jrheum.141017. [Epub ahead of print].
17. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135-47.
18. Bahadir C, Onal B, Dayan VY, et al. Comparison of therapeutic effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint osteoarthritis. *Clin Rheumatol* 2009;28:529-33.
19. Figen AF, Ustun N. The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up. *Clin Rheumatol* 2009;28:535-41.
20. Fioravanti A, Fabbroni M, Cerase A, et al. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. *Rheumatol Int* 2009;29:961-5.
21. Fuchs S, Monikes R, Wohlmeiner A, et al. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. *Osteoarthritis Cartilage* 2006;14:82-8.
22. Heyworth BE, Lee JH, Kim PD, et al. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. *J Hand Surg Am* 2008;33:40-8.
23. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. *J Orthop Sci* 2014;19:737-43.
24. Mandl LA, Wolfe S, Daluiski A, et al. A randomized controlled trial of hylan G-F 20 for the treatment of carpometacarpal osteoarthritis. *Arthritis Rheum* 2012;64:S475-S6.
25. Massarotti M, Crotti C, Ughi N, et al. Comparison of two different intra-articular hyaluronic acid compounds for carpo-metacarpal joint osteoartrhitis. *Ann Rheum Dis* 2013;71:695.

26. Meenagh GK, Patton J, Kynes C, et al. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004;63:1260-3.
27. Monfort J, Rotes-Sala D, Segales N, et al. Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: results of a 6-month single-masked randomized study. *Joint Bone Spine* 2015;82:116-21.
28. Roux C, Fontas É, Breuil V, et al. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. *Joint Bone Spine* 2007;74:368-72.
29. Roux C, Fontas É, Breuil V, et al. (Injection of intra-articular sodium hyaluronate into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis: a prospective evaluation of efficacy). (French) *Rev Rhum* 2007;74:660-5.
30. Spolidoro NDO, Machado FS, Oliveira HAV, et al. Interphalangeal intra-articular injection with triamcinolone hexacetonide: Assessment of effectiveness in hand osteoarthritis. *Arthritis Rheum* 2013;65:2141.
31. Stahl S, Karsh-Zafrir I, Ratzon N, et al. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. *J Clin Rheumatol* 2005;11:299-302.
32. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2012;8(1):22-31.
33. Bannuru R, Schmid C, Kent D, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis. *Ann Intern Med* 2015;162:46-55.
34. Bellamy N, Campbell J, Robinson V, et al. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;2:CD005328.
35. Lo GH, LaValley M, McAlindon T, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003;290:3115-21.
36. Wang CT, Lin J, Chang CJ, et al. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004;86-A:538-45.
37. Wang F, He X. Intra-articular hyaluronic acid and corticosteroids in the treatment of knee osteoarthritis: A meta-analysis. *Exp Ther Med* 2015;9:493-500.
38. Negi A, Wilding J, Kallarackal G, et al. Primary osteoarthritis of base of the thumb: A randomised controlled trial of intra-articular steroid vs thumb splint. *Rheumatology (Oxford)* 2006;45:I74-I.
39. Nüsch E, Reichenbach S, Trelle S, et al. The importance of allocation concealment and patient blinding in osteoarthritis trials: a meta-epidemiologic study. *Arthritis Rheum* 2009;61:1633-41.
40. Nüsch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009;339:b3244.
41. Nüsch E, Trelle S, Reichenbach S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;341:c3515.
42. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *J Altern Complem Med* 2000;6:311-20.



CHAPTER 7

In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis



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ABSTRACT

Objective. Osteoarthritis in thumb base joints (first carpometacarpal (CMC-1), scaphotrapeziotrapezoid (STT)) is prevalent and disabling, yet focussed studies are scarce. Our aim was to investigate associations between ultrasonographic and magnetic resonance imaging (MRI) inflammatory features, radiographic osteophytes, and thumb base pain in hand osteoarthritis patients.

Design. Cross-sectional analyses were performed in cohorts with MRI (n=202) and ultrasound measurements (n=87). Pain upon thumb base palpation was assessed. Radiographs were scored for CMC-1/STT osteophytes. Synovial thickening, effusion and power Doppler signal in CMC-1 joints were assessed with ultrasound. MRIs were scored for synovitis and bone marrow lesions (BMLs) in CMC-1 and STT joints using OMERACT-TOMS. Associations between ultrasound/MRI features, osteophytes, and thumb base pain were assessed. Interaction between MRI features and osteophytes was explored.

Results. In 289 patients (mean age 60.2, 83% women) 139/376 thumb bases were painful. Osteophyte presence was associated with pain (MRI cohort: odds ratio (OR) 5.1 (2.7-9.8)). Ultrasound features were present in 25-33% of CMC-1 joints, though no associations were seen with pain. MRI-synovitis and BMLs grade ≥2 were scored in 25% and 43% of thumb bases, and positively associated with pain (OR 3.6 (95% CI 1.7-7.6) and 3.0 (1.6-5.5)). Associations attenuated after adjustment for osteophyte presence. Combined presence of osteophytes and MRI-synovitis had an additive effect.

Conclusions. Ultrasonographic and MRI inflammatory features were often present in the thumb base. Osteophytes were more strongly associated with thumb base pain than inflammatory features, in contrast to findings in finger OA studies, supporting thumb base osteoarthritis as a distinct phenotype.

INTRODUCTION

The thumb base is a unique complex of articulations within the hand, consisting of several joints, including the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints. The STT joint is one of the intercarpal joints and involves multiple articulations, including those between the scaphoid and trapezium bone, and between the scaphoid and trapezoid bone. In contrast to the other finger joints, the CMC-1 joint is a saddle joint, allowing a high range of motion, yet at the cost of joint stability.[1,2] Moreover, biomechanical studies have shown that the forces on this joint are high, and that the load on the CMC-1 joint is significantly higher compared to more distally located finger joints.[3,4]

Osteoarthritis (OA) often affects the thumb base, causing pain and functional disability.[5] Previous studies have shown that involvement of the CMC-1 joint contributes considerably to the disease burden of hand OA patients.[6] Thumb base OA has been hypothesized to comprise a separate hand OA subset, since it is associated with different risk factors and outcomes than interphalangeal OA.[5] For example, studies have shown that mechanical factors seem to constitute a far more important factor in thumb base OA development, with associations of CMC-1 subluxation, higher maximal grip strength, and hypermobility to CMC-1 but not (distal) interphalangeal joint OA.[7-10] However, much is still unknown about the pathophysiology of thumb base OA, and possible distinctions with interphalangeal OA.

Structural abnormalities on radiographs, including osteophytes, subchondral bone sclerosis, and joint space narrowing (JSN), are a hallmark of the disease. An overview of studies assessing the association between structural damage and clinical signs and symptoms, concluded that a positive association between radiographic hand OA and hand pain existed, although the association was rather weak.[11] A more recent study found similar associations.[12] Yet studies assessing this relationship on joint level, taking into account patient effects, have reported strong dose-response associations.[13,14]

Magnetic resonance imaging (MRI) and ultrasound (US) studies from the recent past have further increased our insights in hand OA, by providing the opportunity to assess other structures than bone, such as the cartilage, synovium and subchondral bone. In US studies it was shown that inflammatory signs such as grey-scale synovitis and power Doppler signal (PDS) are frequently present in the finger joints of hand OA patients,[15] and that these are associated with pain. MRI studies also showed an association between synovitis and bone marrow lesions (BMLs) and pain.[16,17] Moreover, Liu *et al* found that after adjustment for synovitis and BMLs, structural damage (defined as Kellgren-Lawrence grade 2 or more) was no longer statistically significantly associated with pain, while the point estimate of both MRI features barely changed.[17] In the study by Haugen *et al* osteophytes were also no longer statistically significantly associated with pain after adjustment for other MRI features, including synovitis and BMLs.[16] Thus far, however, imaging studies have focussed on the interphalangeal joints or investigated all hand joints without differentiating between different joint groups.

Studies aimed specifically at thumb base OA, are lacking. The objective of this study therefore, was to investigate the associations between US and MRI inflammatory features, structural damage and pain in the thumb base of hand OA patients, taking advantage of the newly developed OMERACT thumb base OA MRI scoring system (TOMS).[18]

METHODS

Patients

Cross-sectional data from hand OA patients from three distinct cohorts were used in this study. Analyses exploring associations with MRI features were performed in patients from the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort including consecutive patients from the outpatient clinic of the Leiden University Medical Center (LUMC) with primary hand OA diagnosed by their treating rheumatologist. Participants who underwent MRI of the right thumb base at baseline were included in the present study (n=202, in this paper referred to as 'MRI cohort'). Analyses exploring associations with US features were performed in patients participating in the EChography in Hand OA (ECHO, n=63) and the Etanercept in Hand OA (EHOA, n=24) study at the Leiden University Medical Center (in total n=87, together referred to as 'US cohort'). Patients from the US cohort were required to fulfil the American College Rheumatology criteria for hand OA.[19] Local medical ethics committee approval was obtained for the three cohorts. All participants gave written informed consent. Details on recruitment and selection of the three cohorts have been published elsewhere.[15,20,21]

Clinical assessment

All patients underwent physical examination by trained research nurses, who assessed presence of pain upon palpation in the thumb base (absent/present). Clinical assessment was performed on the same day as the MRI or US assessment. Patients also indicated whether their thumb base was currently painful on a standardized hand diagram (self-reported thumb base pain, yes/no), the amount of current hand pain on a visual analogue scale (VAS, 0-100 mm) and completed the Australian/Canadian Osteoarthritis Hand Index (AUSCAN).[22]

Imaging

MRI

MRIs of the base of the thumb were acquired on a 1.5T extremity MRI unit (GE, Wisconsin, USA) using a 100 mm coil. A general wrist acquisition was used. MRIs were acquired according to standard protocol, including T1-weighted (T1w) fast spin echo (FSE) images in coronal and axial planes (TR/TE 575/11.2 ms, slice thickness (ST) 2.0 and 3.0 mm, slice gap (SG) 0.2 and 0.3 mm), and T2w FSE images with frequency-selective fat-saturation (fs) in coronal and axial planes (TR/TE 3000/61.8 ms and 3000/60 ms, ST 2.0 and 3.0 mm, SG 0.2 and 0.3 mm). Synovitis and BMLs were scored in the CMC-1 and STT joint (grade 0-3) by two well-trained readers (FK, SB) according to the OMERACT TOMS.[18] In absence of post-contrast images, synovitis was evaluated on T2w-fs images, as advised in the original publication.[12] BMLs were evaluated in proximal and distal joint parts separately, so the proximal part of the first metacarpal bone and distal half of the trapezium were evaluated for the CMC-1 (range 0-6), and for the STT the proximal half of the trapezium and trapezoid and the distal half of the scaphoid were scored (range 0-9). Intraclass correlation coefficients (ICCs; average measure, mixed-effect, absolute agreement) were calculated to assess inter-reader reliability, which was moderate for synovitis (CMC-1: 0.65, STT: 0.58) and excellent for BMLs (CMC-1: 0.92, STT: 0.91). A consensus score was reached when one reader had scored

synovitis grade 0-1 (absent/minimal) while the other had scored 2-3 (moderate/severe) (n=41 cases). The two readers re-assessed these cases together, and decided on a consensus score. At all times, readers were blinded for clinical characteristics and radiographic scores. The average score of the two readers, or the consensus score if applicable, was used for all analyses. An aggregated thumb base synovitis score was also calculated (synovitis grade 0-1 in both thumb base joints vs synovitis grade 2 or higher in at least one joint), and similarly for BMLs.

Ultrasound

US was performed by two ultrasonographers, who scored together in consensus during the examination, using a Toshiba Applio scanner (Toshiba medical systems, Tustin, California) with a 10-14 MHz linear array transducer. Settings were optimised by an application specialist of the manufacturer, and were identical and maintained stable throughout both studies.[15,23] The CMC-1 joint of both hands was evaluated on a semi-quantitative scale (0-3) for synovial thickening effusion and PDS as described previously.[15] Intra-observer reliability has been published before and was good to excellent in both studies (ICC 0.62-0.91).[15,23] The ultrasonographers were blinded for clinical characteristics and radiographic scores. Due to the low prevalence of joints with grade 3 synovial thickening, effusion or PDS grade, grades 2 and 3 were combined in the analyses.

Hand radiographs

Dorso-volar hand radiographs were scored for osteophytes and JSN in the CMC-1 (0-3) and STT (0-1) joints according to the Osteoarthritis Research Society International (OARSI) atlas by a single reader in each separate study.[24] Intra-reader reliability of all readers was good to excellent (ICCs 0.73-0.94).[13,25] Readers were blinded for clinical characteristics and US or MRI features.

Statistical analyses

Associations between US or radiographic features and pain on palpation of the thumb base were assessed on joint level using generalized estimating equations (GEE), accounting for the assessment of two CMC-1 joints per patient. In the MRI cohort, associations between synovitis, BMLs or osteophytes and pain were analysed using logistic regression. Interaction between MRI abnormalities and radiographic osteophytes were subsequently explored by stratifying for absence/presence osteophytes. Analyses were adjusted for relevant confounders (sex, body mass index (BMI)). Analyses were performed using SPSS version 23.0 and Stata SE version 14.1.

RESULTS

Study population

Demographic and clinical characteristics of the 289 patients included in this study are presented in table 1, split by imaging modality. Overall, patients in the US and MRI cohorts had similar characteristics, and reflect a typical hand OA population from secondary care. In the cohort with MR imaging, the prevalence of thumb base joints painful on palpation was somewhat higher (42% compared to 31%).

Imaging features in the thumb base

In table 1 the imaging characteristics of the thumb base joints are presented. Imaging features of the patients with US on patient level are presented in supplementary table 1. Around 25% of CMC-1 joints in the US cohort presented with synovial thickening and/or positive PDS, while 15% of CMC-1 joints in the MRI cohort had moderate to severe MRI-synovitis. In both cohorts, the prevalence of CMC-1 osteophytes was higher than of inflammatory features in that joint. MRI-synovitis in the STT joint had a similar prevalence as in the CMC-1 (13%), while osteophytes were less commonly seen (9%). Synovitis in both joints was uncommon (7/202 thumb bases). BMLs were more prevalent than synovitis, although higher scores were not common. In general, inflammatory features were predominantly seen in thumb bases with osteophytes (e.g., 38 of 51 thumb bases with MRI-synovitis also had a CMC-1 or STT osteophyte, and 34 of 46 thumb bases with US-synovial thickening also had an osteophyte).

Associations between imaging features and pain

No association was observed between inflammatory US features and pain upon palpation of the thumb base (table 2). Synovitis and BMLs on MRI were positively associated with pain upon palpation (odds ratios (OR) 3.6 (95% confidence interval (CI) 1.7-7.6) and 3.0 (1.6-5.5), respectively). Radiographic osteophytes, however, were more strongly associated with pain upon palpation in both cohorts, and in the participants with US there was an indication of a dose-response relation (table 2). JSN showed similar positive associations with pain upon palpation (US cohort: OR 1.9 (0.8-4.9) for grade 1, up to OR 4.2 (0.8-23.2) for grade 3; MRI cohort: OR 2.2 (1.2-4.0) for JSN present vs absent). Since osteophytes and inflammatory MRI features were often present simultaneously, and both were associated with pain upon palpation, we subsequently performed analyses in which we adjusted for the presence of osteophytes. After adjustment for osteophytes, the association between MRI-synovitis or BMLs and pain upon palpation attenuated (table 2). Additional adjustment for presence of JSN did not change the point estimates (OR for MRI-synovitis of 2.2 (0.9-5.5) and for BMLs 1.2 (0.5-2.7)). Analyses with self-reported thumb base pain in the MRI cohort, which was present in 57% of patients, revealed similar results (e.g., ORs for association between MRI-synovitis and self-reported pain of 4.7 (2.1-10.3) and 2.7 (1.1-6.4) before and after adjustment for presence of osteophytes).

Interaction between inflammatory features and osteophytes

To explore the interaction between inflammatory features and radiographic damage in relation to pain upon palpation in the thumb base, analyses stratified for absence/presence of osteophytes were performed. As shown in table 3, the association of MRI-synovitis with pain upon palpation in thumb base joints without osteophytes (OR 2.7 (0.7-10.1)) was weaker than the association of isolated osteophytes and pain upon palpation (OR 4.8 (2.2-10.6)). Combined presence of osteophytes and MRI-synovitis had an additive effect. BMLs showed a similar interaction with osteophytes, although there the additive effect was small (table 3). Analyses with self-reported thumb base pain again yielded similar results (data not shown). The fraction of pain upon palpation attributable to interaction between MRI-synovitis and osteophytes was thus (9.1-6.5)/9.1 = 29%, and, similarly, the interaction between BMLs and osteophytes accounted for 8%.

Table 1. Clinical characteristics of 289 hand osteoarthritis patients (376 thumb bases).

	Patients with US (n=87)	**Patients with MRI (n=202)**
Women, n (%)	71 (81)	169 (84)
Age, years, mean (SD)	60.3 (8.8)	60.1 (8.4)
BMI, kg/m^2, mean (SD)	27.2 (4.5)	27.6 (5.0)
Fulfilling ACR criteria, n (%)	87 (100)	181 (89.6)
AUSCAN pain, 0-20, mean (SD)	9.5 (4.6)	9.1 (4.2)
VAS hand pain, 0-100, mean (SD)	47 (21.7)	36.2 (21.0)
	Thumb bases with US (n=174)	**Thumb bases with MRI (n=202)**
Pain upon palpation, n (%)	54 (31)*	85 (42)†
US features, n (%)		
Synovial thickening	46 (26)‡	
Effusion	57 (33)‡	
Power Doppler signal	44 (25)‡	
MRI features, n (%)		
Synovitis CMC-1 joint§		
Grade 0-1		167 (83)
Grade 2-3		31 (15)
Synovitis STT joint‖		
Grade 0-1		170 (84)
Grade 2-3		27 (13)
Synovitis thumb base‖		
CMC-1 and STT grade 0-1		146 (72)
CMC-1 or STT grade 2-3		51 (25)
Bone marrow lesions CMC-1 joint‖		
Grade 0-1		128 (63)
Grade 2-3		37 (18)
Grade 4-6		32 (16)
Bone marrow lesions STT joint‖		
Grade 0-1		140 (69)
Grade 2-3		42 (21)
Grade 4-9		15 (7)
Bone marrow lesions thumb base‖		
CMC-1 and STT grade 0-1		110 (54)
CMC-1 or STT grade ≥2		87 (43)
Radiographic features, n (%)		
Osteophyte CMC-1 joint		
Absent	78 (45)	111 (55)¶
Grade 1	56 (32)	51 (25)¶
Grade 2	25 (14)	22 (11)¶
Grade 3	15 (9)	17 (8)¶
Osteophyte STT joint		18 (9)¶

ACR, American College of Rheumatology; AUSCAN, Australian/Canadian osteoarthritis hand index; BMI, body mass index; CMC-1, first carpometacarpal joint; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid joint; US, ultrasonography. *3 joints with missing data on pain. †1 joint with missing data on pain. ‡1 joint with missing US data. §4 MRIs not evaluable for this feature. ‖5 MRIs not evaluable for this feature. ¶1 radiograph not available.

Table 2. Associations of US, MRI and radiographic features with pain upon palpation of the thumb base of hand osteoarthritis patients.

	Pain* yes/no, n	**Associations** OR (95% CI)	**Associations, adjusted for osteophytes** OR (95% CI)
Ultrasound cohort			
US features			
Synovial thickening			
Absent	40/85	1	
Grade 1	10/22	1.1 (0.5-2.6)	
Grade 2+3	4/10	1.2 (0.3-4.6)	
Effusion			
Absent	35/79	1	
Grade 1	13/25	0.9 (0.4-2.2)	
Grade 2+3	6/13	1.0 (0.3-3.1)	
Power Doppler signal			
Absent	41/86	1	
Grade 1	8/24	0.9 (0.4-2.7)	
Grade 2+3	5/7	1.5 (0.6-3.9)	
Radiographic features			
Osteophyte CMC-1 joint			
Absent	18/58	1	
Grade 1	16/40	1.2 (0.5-2.6)	
Grade 2	11/13	1.5 (0.5-4.5)	
Grade 3	9/6	5.3 (1.1-23.2)	
MRI cohort			
MRI features			
Synovitis†			
CMC-1 and STT grade 0-1	53/93	1	1
CMC-1 or STT grade 2-3	30/21	3.6 (1.7-7.6)	2.1 (0.9-4.7)
Bone marrow lesions†			
CMC-1 and STT grade 0-1	35/75	1	1
CMC-1 or STT grade ≥2	49/38	3.0 (1.6-5.5)	1.3 (0.6-2.7)
Radiographic features			
Osteophyte CMC-1 or STT‡			
Absent	28/78	1	
Present	57/38	5.1 (2.7-9.8)	

Presented ORs were adjusted for sex and BMI. AUSCAN, Australian/Canadian osteoarthritis hand index; BMI, body mass index; CMC-1, first carpometacarpal joint; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid joint; US, ultrasonography**.** *3 joints with missing data on pain. †5 MRIs not evaluable for this feature. ‡1 radiograph not available.

Table 3. Number of thumb base joints painful upon palpation (yes/no) and associations (OR (95% CI)) of MRI-synovitis or BMLs with pain upon palpation, stratified for osteophytes (n=196)*.

		Osteophyte CMC-1 or STT			
		Absent		Present	
Synovitis	**Absent**†	23/70	1	30/22	4.8 (2.2-10.6)
	Present‡	5/8	2.7 (0.7-10.1)	25/13	9.1 (3.6-23.0)
BMLs	**Absent**†	21/64	1	14/10	5.7 (2.0-16.5)
	Present‡	7/14	1.4 (0.5-4.1)	42/24	6.6 (3.1-14.0)

Presented ORs were adjusted for sex and BMI. BMI, body mass index; BML, bone marrow lesion; CMC-1, first carpometacarpal; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid. *196/202 patients had evaluable MRI for synovitis/BMLs and radiographs available. †Defined as CMC-1 and STT grade 0-1. ‡Defined as CMC-1 or STT grade ≥2.

DISCUSSION

This study reports on the prevalence of inflammatory features on US and MRI in thumb base joints of a large cohort of patients with hand OA, and their association with pain in comparison with radiographic damage. The prevalence of synovial thickening, effusion and PDS on US, as well as MRI-synovitis and BMLs, was similar to what has previously been reported in studies of OA finger joints.[15-17]

Positive, dose-response associations between different inflammatory US features and pain have been reported in a study that included all hand joints in the analysis.[15] MRI studies have consistently shown positive associations of synovitis and BMLs and pain in interphalangeal joints, independent of radiographic damage, with similar effect sizes as for US.[16,17] In contrast, we show that the association of US and MRI inflammatory features with pain in the thumb base is less evident than in finger joints of hand OA patients. Moreover, we found an association between radiographic damage and pain in the thumb base as expected, yet in contrast to finger OA studies this association seemed more important in predicting pain than the inflammatory features that were assessed.

In our study, associations of MRI-detected inflammation with pain were found, but this association was no longer significant after adjustment for osteophytes. US-detected inflammation showed no association with pain. This difference in results may be due to small differences in patient characteristics of the cohorts, or due to differences between the imaging modalities. For example, US and MRI do not measure exactly the same aspect of inflammation, supported by moderate agreement between these modalities found in previous studies comparing synovitis on US and MRI.[23,26] US of the CMC-1 could also be hampered by the location of the joint (i.e., on MRI, both the radial and ulnar side of the joint can be visualized).

The observed differences between the results of our study and previous finger OA studies could indicate a difference in the underlying pathogenesis of finger and thumb base OA. In the thumb base, mechanical influences likely play a prominent role, while inflammation may be relatively more important in the pathogenesis of interphalangeal OA. The different

role of mechanical influences may be due to the different joint types and associated range of motion (saddle joint with multidirectional movements versus hinge joint with unidirectional movements), and the higher load on the thumb base than on the interphalangeal joints.[3,4] The hypothesis of thumb base OA as a distinct hand OA subset is also supported by studies showing associations with different risk factors and outcomes than interphalangeal OA.[5] Furthermore, trials investigating the effect of intra-articular injections of the CMC-1 joint with corticosteroids have shown conflicting results, and a recent meta-analysis demonstrated that intra-articular corticosteroid injections did not result in more pain relief than placebo injections.[27] In contrast, one placebo-controlled double-blind trial of intra-articular corticosteroid injections for interphalangeal OA did show positive results, although to date no trials have been performed to confirm this finding.[28]

To our knowledge, this is the first large cohort of hand OA patients with MRI of the thumb base, besides two small studies (n=9 and n=12) assessing cartilage visualization on thumb base MRIs.[29,30] It is also the first study to date investigating the role of inflammation in the thumb base joints of hand OA patients separately from the other finger joints. Some limitations have to be acknowledged. In this cohort, contrast-enhanced MR images were not available, and therefore MRI-synovitis was assessed on T2w-fs images. The disadvantage of T2w-fs images is that it is not possible to distinguish between synovitis and effusion, which may have led to an underestimation of the association between synovitis and pain. However, the inflammatory features on US even showed no associations with pain, making it less likely that we underestimated the association. Furthermore, we did not have data of patients who underwent both US and MRI examination, yet the observation that our results are similar in three different cohorts, using two different imaging modalities, also strengthens our findings. However, the US protocol did not include assessment of the STT joint, and therefore we cannot compare the findings of the US and MRI for the STT. In the analyses of the MRI cohort, the CMC-1 and STT joint were combined, since the outcome (pain on palpation of the thumb base) was assessed for the thumb base and not the separate joints, and the number of participants in each subgroup would become too small to draw robust conclusions. In this study, other, less common, radiographic features of structural damage, such as erosions, cysts and sclerosis, were not evaluated, and inclusion of these in future studies would be of interest. Finally, this is a cross-sectional study, precluding the assessment of causal relationships, or of the effect of fluctuation of the assessed inflammatory features over time.

In conclusion, in this study we have confirmed that inflammatory features on US and MRI are also present in the thumb base of hand OA patients, yet we found that radiographic osteophytes were more strongly associated with thumb base pain than these inflammatory features. Our findings are in contrast to previous studies in finger OA, supporting thumb base OA as a distinct hand OA phenotype. Future studies are warranted to further elucidate the different role of structural damage and inflammation in thumb base and interphalangeal OA, and possible consequences of these differences for treatment of hand OA patients.

REFERENCES

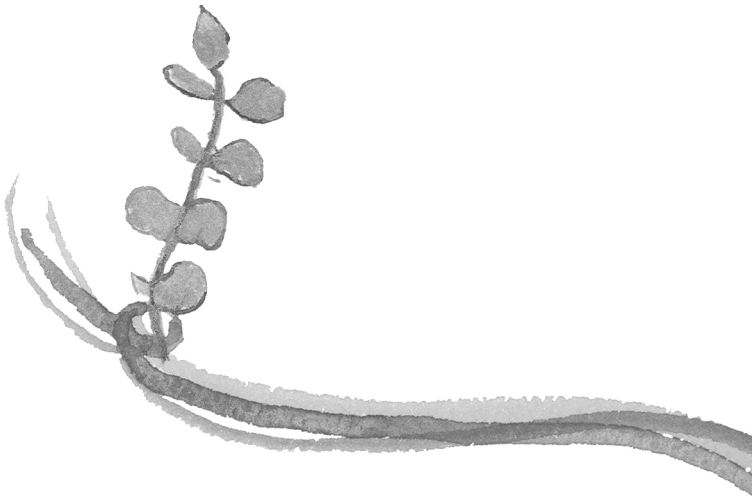
1. Anakwe RE, Middleton SD. Osteoarthritis at the base of the thumb. *BMJ* 2011;343:d7122.
2. Ladd AL, Crisco JJ, Hagert E, et al. The 2014 ABJS Nicolas Andry Award: the puzzle of the thumb: mobility, stability, and demands in opposition. *Clin Orthop Relat Res* 2014;472:3605-22.
3. Cooney WP, Chao EY. Biomechanical analysis of static forces in the thumb during hand function. *J Bone Joint Surg Am* 1977;59:27-36.
4. Goislard de Monsabert B, Vigouroux L, Bendahan D, et al. Quantification of finger joint loadings using musculoskeletal modelling clarifies mechanical risk factors of hand osteoarthritis. *Med Eng Phys* 2014;36:177-84.
5. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
6. Bijsterbosch J, Visser W, Kroon HM, et al. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. *Ann Rheum Dis* 2010;69:585-7.
7. Hunter DJ, Zhang Y, Sokolove J, et al. Trapeziometacarpal subluxation predisposes to incident trapeziometacarpal osteoarthritis (OA): the Framingham Study. Osteoarthritis Cartilage 2005;13:953-7.
8. Chaisson CE, Zhang Y, Sharma L, et al. Grip strength and the risk of developing radiographic hand osteoarthritis: results from the Framingham Study. *Arthritis Rheum* 1999;42:33-8.
9. Jonsson H, Valtysdottir ST. Hypermobility features in patients with hand osteoarthritis. Osteoarthritis Cartilage. *Osteoarthritis Cartilage* 1995;3:1-5.
10. Jonsson H, Valtysdottir ST, Kjartansson O, et al. Hypermobility associated with osteoarthritis of the thumb base: a clinical and radiological subset of hand osteoarthritis. *Ann Rheum Dis* 1996;55:540-3.
11. Dahaghin S, Bierma-Zeinstra SM, Hazes JM, et al. Clinical burden of radiographic hand osteoarthritis: a systematic appraisal. *Arthritis Rheum* 2006;55:636-47.
12. Marshall M, van der Windt D, Nicholls E, et al. Radiographic thumb osteoarthritis: frequency, patterns and associations with pain and clinical assessment findings in a community-dwelling population. *Rheumatology (Oxford)* 2011;50:735-9.
13. Kortekaas MC, Kwok WY, Reijnierse M, et al. Osteophytes and joint space narrowing are independently associated with pain in finger joints in hand osteoarthritis. *Ann Rheum Dis* 2011;70:1835-7.
14. Ding H, Solovieva S, Vehmas T, et al. Finger joint pain in relation to radiographic osteoarthritis and joint location--a study of middle-aged female dentists and teachers. *Rheumatology (Oxford)* 2007;46:1502-5.
15. Kortekaas MC, Kwok WY, Reijnierse M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367-9.
16. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
17. Liu R, Damman W, Reijnierse M, et al. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. *Osteoarthritis Cartilage* 2017;25:1093-9.
18. Kroon FP, Conaghan PG, Foltz V, et al. Development and reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System. *J Rheumatol* 2017;44:1694-98.
19. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
20. Damman W, Liu R, Kroon FPB, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand Osteoarthritis in Secondary Care Cohort. *J Rheumatol* 2017, Sep 15. doi: 10.3899/jrheum.170208. [Epub ahead of print].
21. Kloppenburg M, Ramonda R, Kwok WY, et al. Randomized, placebo-controlled trial to evaluate clinical efficacy and structure modifying properties of subcutaneous etanercept (ETN) in patients with erosive inflammatory hand osteoarthritis (OA). *Ann Rheum Dis* 2016;75:90-1.
22. Bellamy N, Campbell J, Haraoui B, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthritis Cartilage* 2002;10:863-9.
23. Kortekaas MC, Kwok WY, Reijnierse M, et al. Magnetic resonance imaging in hand osteoarthritis: intraobserver reliability and criterion validity for clinical and structural characteristics. *J Rheumatol* 2015;42:1224-30.
24. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15:A1-56.
25. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-7.

26. Wittoek R, Jans L, Lambrecht V, et al. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. *Ann Rheum Dis* 2011;70:278-83.
27. Kroon FP, Rubio R, Schoones JW, et al. Intra-articular therapies in the treatment of hand osteoarthritis: a systematic literature review. *Drugs Aging* 2016;33:119-33.
28. Spolidoro Paschoal N, Natour J, Machado FS, et al. Effectiveness of triamcinolone hexacetonide intraarticular injection in interphalangeal joints: a 12-week randomized controlled trial in patients with hand osteoarthritis. *J Rheumatol* 2015;42:1869-77.
29. Williams A, Shetty SK, Burstein D, et al. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) of the first carpometacarpal (1CMC) joint: a feasibility study. *Osteoarthritis Cartilage* 2008;16:530-32.
30. Saltzherr MS, Coert JH, Selles RW, et al. Accuracy of magnetic resonance imaging to detect cartilage loss in severe osteoarthritis of the first carpometacarpal joint: comparison with histological evaluation. *Arthritis Res Ther* 2017;19:55.



CHAPTER 8

Two-year changes in MRI-features and pain in thumb base osteoarthritis



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ABSTRACT

Objectives. To investigate the two-year course of pain and osteoarthritic magnetic resonance imaging (MRI) features in the thumb base.

Methods. Patients of the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort who underwent hand radiography, MRI and clinical examination of the right thumb base at baseline and two-year follow-up were studied. Pain on palpation of the thumb base (0-3) was assessed. MRI were scored with the OMERACT thumb base osteoarthritis MRI scoring-system (TOMS) for synovitis, bone marrow lesions (BMLs), subchondral bone defects (SBDs), cartilage space loss, osteophytes, and subluxation. Radiographs were assessed for osteophytes and joint space narrowing. We studied associations of changes in synovitis and BMLs with changes in pain with logistic regression, adjusted for radiographic damage.

Results. Of 165 patients (83.0% women, mean 60.7 years) 65 had thumb base pain at baseline. At two-year follow-up, pain had decreased in 32 and increased in 33 patients. MRI-features remained stable in most patients. Structural MRI-features generally deteriorated, while synovitis and BMLs improved in some and deteriorated in others. Change in radiographic osteophytes rarely (n=10) occurred. Increased synovitis (OR 3.4 (95% CI 1.3-9.3)) and increased BMLs (OR 5.1 (2.1-12.6)) were associated with increased pain. Decreased BMLs were associated with decreased pain (OR 2.7 (0.8-8.9)), but synovitis decrease occurred too infrequently to calculate associations.

Conclusion. Over two years, thumb base pain fluctuated, while MRI-features changed in a minority of hand osteoarthritis patients. Changes in synovitis and BMLs were associated with changes in pain, even after adjustment for radiographic damage.

INTRODUCTION

Hand osteoarthritis (OA) is a polyarticular disease, affecting the interphalangeal joints and the thumb base, a joint complex which includes the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints. The thumb base has certain unique qualities, such as a high range of motion and the capability to bear high loads, which sets it apart from other hand joints.[1-3] Thumb base OA is associated with different clinical and imaging outcomes than interphalangeal OA, and was therefore considered to be a separate hand OA subset.[2-4] Most research in hand OA has focussed on the hand as a whole or the interphalangeal joints specifically, and American College of Rheumatology (ACR) classification criteria do not distinguish between interphalangeal and thumb base OA. Therefore, our knowledge on this hand OA subset and its natural course is limited.

Alongside structural joint damage – a hallmark of the disease – inflammatory features visible on magnetic resonance imaging (MRI), including synovitis and bone marrow lesions (BMLs), are often present in interphalangeal and thumb base OA.[5-7] Cross-sectional studies have shown that in interphalangeal joints, synovitis and BMLs are associated with pain on palpation, and more strongly so than structural damage.[5,6] Yet, in a study investigating these aspects in thumb base OA, the opposite was seen: while synovitis and BMLs were associated with pain, structural damage was found to be its most important determinant.[7]

Longitudinal imaging studies of interphalangeal OA have shown that a change in MRI inflammation was associated with a change in pain levels.[8,9] In thumb base OA, however, no longitudinal imaging studies have been performed thus far. Hence, the natural course of osteoarthritic MRI-features is unknown, as is the relation between changes in these features and clinical outcomes. Therefore, our aim was to investigate the two-year course of pain and MRI-features in thumb base OA, and their association.

METHODS

Study design

We used longitudinal data of the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort of consecutive patients from our outpatient clinic, who were included after being diagnosed with primary hand OA by their treating rheumatologist. Patients with secondary hand OA or with hand symptoms due to another cause were excluded. More details on recruitment and selection have been published elsewhere.[10]

Participants with baseline and two-year follow-up data available were included in this analysis (supplementary figure S1). Written informed consent was obtained from all participants. The study was approved by the Leiden University Medical Center medical ethics committee.

Demographics and clinical assessment

Demographics and clinical characteristics were collected by standardized questionnaires, including self-reported thumb base pain and stiffness during the last month (absent/present), the Australian/Canadian hand OA index (AUSCAN),[11] self-reported hand pain on

a visual analogue scale (VAS, range 0-100 millimeter). Trained research nurses examined the thumb bases for pain upon palpation on a semi-quantitative scale (0-3),[12] and bony swelling (absent/present).

MRI acquisition and scoring

MR images of the right CMC-1 and STT joints were obtained at baseline and two-year follow-up visits using an MSK-Extreme 1.5 T extremity MR imaging scanner (GE, Wisconsin, USA). The following sequences were acquired: coronal T1-weighted (T1-w) fast spin echo (FSE) images (repetition time [TR]/echo time [TE] 575/≤ 11 ms), axial T1-w FSE images (TR/TE 575/≤ 10.5 ms), coronal T2-w FSE images with frequency selective fat saturation (fat sat) (TR/TE 3000/61.8 ms), and axial T2-w FSE fat sat images (TR/TE 3000/60 ms). 18 coronal slices (slice thickness 2 mm, slice gap 0.2 mm) and 20 axial slices (slice thickness 3 mm, slice gap 0.3 mm) were obtained. No intravenous contrast was administered.

Images were scored pairwise in chronological order by two readers (SvB; FPBK), who scored independently while blinded for clinical and radiography data, using TOMS.[13-15] Synovitis, BMLs, subchondral bone defects (SBDs), cartilage space loss and osteophytes were scored 0-3 for the CMC-1 and STT joints, and CMC-1 subluxation was scored dichotomously. Osteophytes, SBDs and BMLs were scored for distal and proximal joint parts separately, adding up to a sum score of 6 (CMC-1) and 9 (STT). For changes in synovitis, SBDs and BMLs half-point increments were used to indicate within-grade changes. Interrater reliability was moderate/good for all baseline features (mixed model, exact agreement, average measure, ICCs 0.59-0.92, CMC-1 subluxation prevalence-adjusted bias-adjusted kappa [PABAK] 0.77) and change scores (mixed model, exact agreement, average measure, ICCs 0.53-0.81, CMC-1 subluxation PABAK 0.88).[16]

Radiograph acquisition and scoring

Postero-anterior hand radiographs were obtained at baseline and two-year follow-up. Images were scored paired in chronological order by two readers (SvB; HMK), who scored in consensus while blinded for clinical and MRI data. Osteophytes and joint space narrowing (JSN) in CMC-1 (0-3) and STT (absent/present) joints, and erosions and cysts in CMC-1 joint (absent/present) were scored according to the OARSI atlas.[17] Intraobserver reliability based on a subset of 20 randomly selected patients was excellent (prevalence-adjusted bias-adjusted kappa [PABAK] values of 0.8–0.9 for baseline and 0.9–1.0 for change scores).

Statistical analysis

A previous cross-sectional analysis of the associations between inflammatory MRI-features, pain and radiographic damage using baseline data of this cohort was taken as the starting point for the current study.[7] To ascertain that those findings also applied to the present study, which concerns a selection of the study population with follow-up data available (supplementary figure S1) in which different readers scored the radiographs, we first repeated the cross-sectional analyses of associations between baseline synovitis, BMLs and radiographic osteophytes (determinants) and presence of pain on palpation (outcome).

Next, we determined the smallest detectable change (SDC) for use as a threshold for increase and decrease in MRI-scores.[18] Since pain was assessed for the thumb base as a whole, change scores of CMC-1 and STT joints were combined, comparing no change in both joints (i.e. 'stable') with an increase or decrease in at least one joint. A thumb base was also classified as 'stable', when one joint increased while the other decreased. Radiographic baseline scores of CMC-1 and STT joints were combined and dichotomized similarly: absent in CMC-1 and STT versus present in CMC-1 or STT.

Using logistic regression, we then investigated the associations between imaging features (determinants), and change in pain on palpation (outcome), expressed as odds ratios (ORs) with 95% confidence intervals (CI).

First, we assessed whether baseline imaging features (synovitis, BMLs, or radiographic damage) were associated with increase in pain on palpation (excluding thumb bases with maximum pain at baseline, figure 1) or decrease in pain on palpation (excluding thumb bases without pain at baseline, supplementary figure S2) over two years.

Second, we assessed whether a two-year increase in the imaging features (synovitis, BMLs or radiographic damage) was associated with an increase in pain on palpation. For this, we excluded thumb bases with maximum score in the imaging feature or maximum pain at baseline (supplementary figure S2). Thumb bases with stable or decreased imaging features served as the reference category.

Third, we examined the reverse situation for the MRI-features, excluding thumb bases without synovitis or BMLs and without pain at baseline (supplementary figure S2). Thumb bases with stable or increased MRI-features served as the reference category.

All analyses were done in univariable and multivariable models, adjusting for the other imaging features. Selection of covariates was based on proven or hypothesized associations with both the exposure and the outcome, which were then verified in our dataset.

To explore possible interaction between structural damage and MRI-features in relation to the course of pain, we also performed analyses assessing the association of increase in synovitis or BMLs with increased pain stratified for presence or absence of baseline radiographic osteophytes. The attributable proportion was estimated, which reflects the proportion of the odds ratio for the doubly exposed group attributable to interaction.[19,20]

Since baseline radiographic osteophyte scores may not fully account for the structural damage in a joint, we performed two sets of sensitivity analyses, in which we (1) replaced the osteophytes scores by JSN scores, and (2) added JSN scores as an additional covariate to the models.

Data were analysed using SPSS for Windows, version 23.0 (IBM SPSS statistics, New York, USA). Area Proportional Euler diagrams were drawn using eulerAPE, version 3.0.0 (freely available at http://www.eulerdiagrams.org/eulerAPE/).[21]

RESULTS

Study population

In the HOSTAS cohort, 202 patients underwent MRI of the right thumb base at baseline, of whom 166 also did at two-year follow-up (supplementary figure S1). One patient was excluded due to prior joint anatomy-altering thumb base surgery. The majority of the included 165 patients fulfilled the ACR criteria, were middle-aged and female (table 1). Baseline characteristics (including imaging scores) of patients included in the analyses were not different from those who only underwent baseline MRI.

Pain and imaging features at baseline

At baseline, 93 (56.4%) of the patients indicated to frequently have had pain in the right thumb base in the previous month, and 65 (39.4%) had pain on palpation during physical examination, of whom 11 had maximum pain.

MRI-features were highly prevalent at baseline, with a total of 81.6% of patients having at least one thumb base joint (CMC-1 or STT) with synovitis or BMLs (table 1). All MRI-features were more prevalent in the CMC-1 than in the STT joint. Generally, scores were low, which can be appreciated from the medians and interquartile ranges in table 1. Osteophytes were the most frequently observed structural feature on MRI (86% of CMC-1 joints and 52% of STT joints). Radiographic osteophytes were present in 74 thumb bases (45%), primarily in the CMC-1 joints.

As expected, we reaffirmed previous findings in this cohort that, cross-sectionally, pain on palpation was strongly associated with the presence of radiographic osteophytes (OR 7.4, 95% CI 3.47–15.7), and that the association of inflammatory MRI-features with pain (synovitis: 3.05 [1.35–6.9], BMLs: 2.50 [1.28–4.9]) attenuated after adjustment for osteophytes (synovitis: 1.63 [0.66–4.0], BMLs: 1.10 [0.49–2.46]).[7]

Pain and imaging features at two-year follow-up

Frequencies and dimensions of changes in pain and imaging features are presented in table 2. At the two-year follow-up visit, pain on palpation had decreased or resolved in 32 patients (19.4%) and increased or developed in 33 patients (20%).

The majority of patients had no change in MRI scores beyond the smallest detectable change. Structural MRI-features generally increased, while in inflammatory features, such as synovitis and BMLs, both increased and decreased scores were observed.

Synovitis most often only changed in one joint (n=44, 81.5%; figure 1), and in fewer cases the CMC-1 and STT joints both increased (n=6), decreased (n=2), or changed in opposite directions (n=2). Likewise, a change in BMLs in only one joint (n=44, 64.7%; figure 2) was more common than a paired increase (n=11), decrease (n=8), or CMC-1 and STT changing in opposing directions (n=5). Change in MRI inflammation (synovitis or BMLs) was seen equally often in the CMC-1 and STT joints (41.4% versus 43.1%).

Table 1. Baseline characteristics of n=165 patients with hand osteoarthritis (OA).

			Baseline	
Demographics				
Sex, n (%) female			137	(83.0)
Age, years			60.7	(8.3)
Fulfilling ACR criteria for hand OA, n (%)			151	(91.5)
Clinical assessment				
Body mass index*, kg/m^2			27.5	(5.1)
VAS right hand pain, (0–100 mm scale)			36	(21)
Self-reported pain of right thumb base, n (%)			93	(56.4)
Self-reported stiffness of right thumb base, n (%)			58	(35.2)
Pain on palpation of right thumb base present, n (%)			65	(39.4)
Bony swelling of right thumb base, n (%)			74	(44.8)
AUSCAN hand pain, (0–20 scale)			10	(6–12)
AUSCAN hand physical function, (0–36 scale)			16	(10–22)
Self-reported use of acetaminophen, n (%)			85	(51.5)
Self-reported use of NSAIDs, n (%)			50	(30.3)
Self-reported use of thumb base splint, n (%)			11	(6.7)
Radiography† (right hand)				
CMC-1				
OARSI osteophyte present, n (%)			74	(45.1)
OARSI joint space narrowing present, n (%)			61	(37.2)
STT				
OARSI osteophyte present, n (%)			9	(5.5)
OARSI joint space narrowing present, n (%)			32	(19.5)
MR Imaging (right hand)	**present, n**	**(%)**	**median**	**(IQR)**
CMC-1				
Synovitis‡, (0–3 scale)	69	(42.3)	0	(0–1)
Bone marrow lesions‡, (0–6 scale)	79	(48.5)	0	(0–2)
Subchondral bone defects, (0–6 scale)	95	(57.6)	1	(0–1)
Cartilage space loss, (0–3 scale)	81	(49.1)	0	(0–1)
Osteophytes, (0–6 scale)	141	(85.5)	2	(1–4)
Subluxation, (absent/present)	30	(18.2)		
STT				
Synovitis‡, (0–3 scale)	65	(39.9)	0	(0–1)
Bone marrow lesions‡, (0–9 scale)	77	(47.2)	0	(0–1)
Subchondral bone defects, (0–9 scale)	87	(52.7)	1	(0–1)
Cartilage space loss, (0–3 scale)	68	(41.2)	0	(0–1)
Osteophytes, (0–9 scale)	86	(52.1)	1	(0–1)

Mean (SD) or median (IQR) unless stated otherwise. AUSCAN, Australian/Canadian osteoarthritis hand index; CMC-1, first carpometacarpal joint; MR, magnetic resonance; NSAIDs, non-steroidal anti-inflammatory drugs; STT, scaphotrapeziotrapezoid joint. *Weight or height was not recorded for five patients, †one baseline radiograph was missing, and ‡two baseline scores were missing due to unreadable MR images.

Compared with MRI, radiography less frequently showed an increase in osteophyte scores (6.1% versus 24.2% of thumb bases), JSN scores (13% versus 19.4% of thumb bases) and erosion/cyst scores (3.7% versus 16.4% of CMC-1 joints).

Associations between baseline imaging features and change in pain

Baseline synovitis and BML scores were not associated with an increase in pain after two years (ORs 1.13 [0.83–1.53] and 1.11 [0.96–1.27], respectively). Similarly, baseline scores of these features were not associated with a decrease in pain after two years (synovitis: 0.84 [0.60–1.19], BMLs: 0.95 [0.80–1.12]). Baseline radiographic osteophyte scores were not associated with change in pain after two years, when adjusted or stratified for change in MRI-features (table 3 and 4).

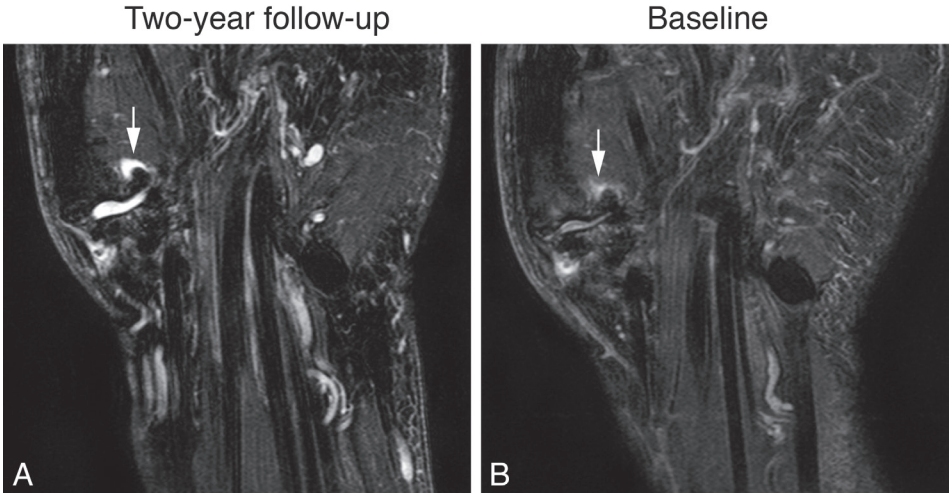


Figure 1. Coronal fat saturated T2-weighted FSE MR imaging showing increase in synovitis in the CMC-1 joint (*arrows*) at the two-year follow-up visit (A) compared to baseline (B).

Associations between change in inflammatory MR features and change in pain

An increase in synovitis or BMLs was associated with increased pain, also after adjustment for the presence of baseline radiographic osteophytes (table 3). Increases in radiographic osteophytes or JSN were not associated with increased pain (ORs 0.95 [0.19–4.7] and 0.87 [0.27–2.81], respectively).

Likewise, a decrease in BMLs seemed to be associated with a decrease in pain, although confidence intervals included no effect (table 3). Decrease of synovitis in patients with baseline pain was rare (n=7), therefore associations were not computed.

In sensitivity analyses, with radiographic JSN to reflect structural damage, effect estimates of the associations of change in MRI-features with course of pain did not change (supplementary table S1).

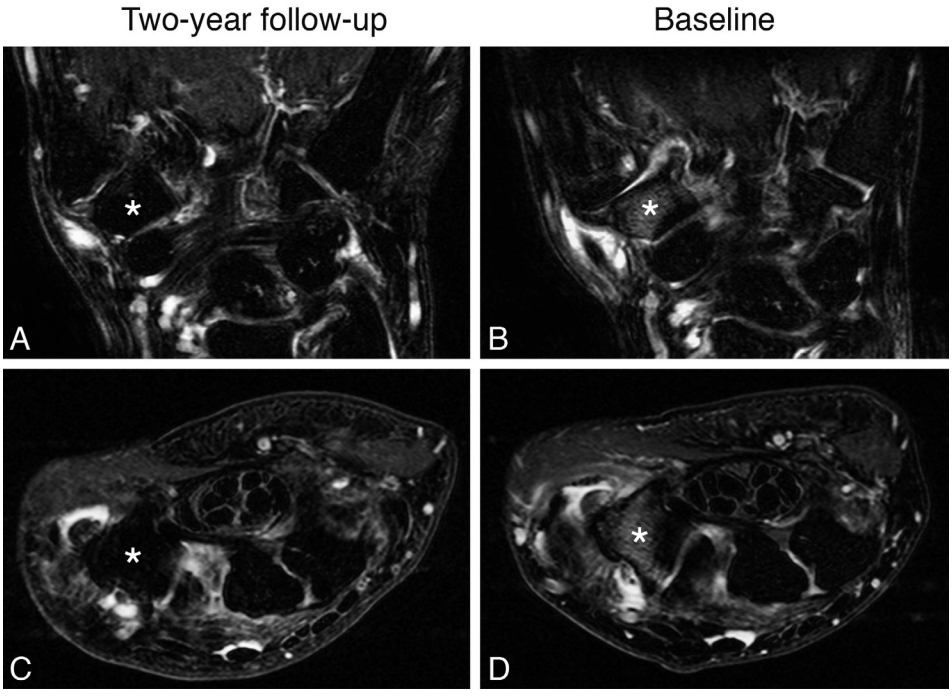


Figure 2. Coronal (A, B) and axial (C, D) fat saturated T2-weighted FSE MR imaging showing decrease in bone marrow lesions in the trapezium bone (*asterisks*) at the two-year follow-up visit (A, C) compared to baseline (B, D).

Interaction between osteophytes and change in inflammatory MR features

To explore whether the association between an increase in inflammatory MRI-features and an increase in pain was different in thumb bases with radiographic damage at baseline, we stratified these analyses for the presence of radiographic osteophytes at baseline. Due to low numbers, synovitis and BMLs were assessed together in these analyses. As shown in table 4, in joints without baseline osteophytes, an increase in inflammatory MRI-features (synovitis or BMLs) was associated with increased pain (OR 4.3 [1.25–14.8]). However, when osteophytes were present at baseline, the association between an increase in MRI inflammation and increased pain was stronger than expected from the combination of separate effects (OR 11.0 [3.35–36.1]). The proportion of this association attributable to interaction is (11.0–1–3.3–0.24)/11.0 = 59% [95% CI 12%–100%]. Sensitivity analyses in which we stratified for the presence of baseline JSN instead of osteophytes, and in which we additionally adjusted for baseline JSN scores revealed similar results (supplementary tables S2 and S3).

Table 2. Two-year changes in pain and MR features of the right thumb base in n=165 patients

		Decrease			Stable				Increase			
		N	Median			N	Median			N	Median		
			min.		max.		min.		max.		min.		max.
Pain													
Thumb base													
Self-reported pain		26				121				18			
Self-reported pain/stiffness		23				124				18			
Pain on palpation		32	-3	-1	-1	100	n/a	0	n/a	33	1	1	2
MR features	**SDC**												
CMC-1													
Synovitis*	0.40	11	-1.00	-0.50	-0.50	134	-0.25	0	0.25	18	0.50	0.63	1.00
Bone marrow lesions†	0.93	17	-2.50	-1.25	-1.00	115	-0.75	0	0.75	30	1.00	1.38	4.50
Subchondral bone defects	0.60	0	n/a	n/a	n/a	130	-0.50	0	0.50	35	0.75	1.00	2.25
Cartilage space loss	0.35	6	-0.50	-0.50	-0.50	139	0	0	0	20	0.50	0.50	1.50
Osteophytes	0.46	1	n/a	-0.50	n/a	138	0	0	0	26	0.50	0.50	1.00
Subluxation	0.24	0				159				6			
STT													
Synovitis‡	0.39	15	-3.00	-0.50	-0.50	124	-0.25	0	0.25	21	0.50	1.00	1.00
Bone marrow lesions*	0.79	23	-3.00	-1.50	-1.00	117	-0.75	0	0.75	23	1.00	1.50	3.50
Subchondral bone defects	0.53	4	-1.25	-1.00	-0.75	134	-0.50	0	0.50	27	0.75	1.00	2.25
Cartilage space loss	0.37	6	-2.50	-1.00	-0.50	137	0	0	0	22	0.50	0.50	1.50
Osteophytes	0.31	1	n/a	-0.50	n/a	147	0	0	0	17	0.50	0.50	1.00
CMC-1 and/or STT													
Synovitis‡		22	-3.00	-0.50	-0.50	108	-0.50	0	0.25	30	0.25	1.00	2.00
Bone marrow lesions†		27	-5.50	-2.00	-0.25	99	-1.50	0	1.25	36	0.50	1.63	7.50
Subchondral bone defects		4	-1.25	-1.00	-0.75	109	-0.75	0	0.75	52	0.25	1.25	3.50
Cartilage space loss		10	-2.50	-0.50	-0.50	123	0	0	0.50	32	0.50	0.50	2.00
Osteophytes		2	-0.50	-0.50	-0.50	123	0	0	0	40	0.50	0.50	1.50

Two/ †three/ ‡five change scores were missing due to unreadable MR images. CMC-1, first carpometacarpal joint; MR, magnetic resonance; STT, scaphotrapeziotrapezoid joint.

Table 3. Longitudinal associations between change in MRI-defined synovitis or BMLs and change in thumb base pain in 165 patients with hand OA after two-year follow-up

	Change in pain		Crude	Adjusted*
	yes	/no, n	OR (95% CI)	OR (95% CI)
Associations with increased pain				
(in joints without maximum pain, n=154)				
Delta synovitis†				
Stable/decrease	20	/101	1	1
Increase	12	/16	3.70 (1.49 – 9.2)	3.44 (1.28 – 9.3)
Delta bone marrow lesions‡				
Stable/decrease	16	/102	1	1
Increase	15	/18	5.1 (2.15 – 12.1)	5.1 (2.10 – 12.6)
Baseline radiographic osteophytes§				
Absent	13	/73	1	1
Present	20	/47	2.11 (0.94 – 4.7)	1.73 (0.73 – 4.1)
Associations with decreased pain				
(in joints with baseline pain, n=65)				
Delta synovitis†‖				
Stable/Increase	18	/19	-	-
Decrease	4	/3	-	-
Delta bone marrow lesions‡¶				
Stable/Increase	11	/17	1	1
Decrease	12	/7	2.65 (0.80 – 8.8)	2.67 (0.80 – 8.9)
Baseline radiographic osteophytes				
Absent	11	/9	1	1
Present	21	/24	0.72 (0.25 – 2.06)	0.78 (0.26 – 2.28)

BMLs, bone marrow lesions; CI, confidence interval; OR, odds ratio. *Adjustments were made for the other imaging scores of features in this table. †Five/‡three missing change scores due to unreadable MR images and §one missing baseline radiograph. ‖Synovitis or ¶BMLs had to be present at baseline to study decrease resulting in n<65.

Table 4. Number of thumb base joints with increased pain (yes/no) and associations of increased MR inflammatory features (synovitis or BMLs) with increased pain, stratified for baseline radiographic osteophytes, in 154 patients without maximum thumb base pain at baseline.

		Delta inflammatory MR features			
		Stable/decrease		Increase	
BL osteophytes	Absent	5/51	1	8/19	4.3 (1.25 – 14.8)
	Present	4/33	1.24 (0.31 – 4.9)	14/13	11.0 (3.35 – 36.1)

Associations are presented as odds ratios (95% CI). BL, baseline; CI, confidence interval; MR, magnetic resonance. Seven patients were excluded due to missing data on at least one imaging feature.

DISCUSSION

In this study, we describe the two-year natural course of pain and osteoarthritic MRI-features in the thumb base, and their associations in patients with hand OA.

While thumb base pain levels fluctuated over time, MRI-features and radiographic damage remained stable in the majority of patients. In those in whom MRI-features did change, structural features, such as SBDs, cartilage space loss and osteophytes, generally deteriorated, while in inflammatory features, including synovitis and BMLs, changes in either direction were seen. MRI-features in the CMC-1 and the STT joints had a comparable course over the two-year follow-up.

Baseline MRI inflammation was not associated with change in pain. However, an increase in synovitis or BMLs was strongly associated with increased pain, also after adjustment for radiographic damage. Likewise, a decrease in BMLs appeared to be associated with decreased pain, although less markedly. The number of joints with a decrease in synovitis was too small to estimate associations with a decrease in pain. All associations between imaging features and pain were on a thumb base level, since pain on palpation was inevitably examined for the thumb base as a whole, due to the close proximity of CMC-1 and STT joints to each other.

Few studies have investigated the longitudinal relation between inflammatory MRI-features and pain in hand OA. Previous studies have shown that in interphalangeal OA an increase in synovitis was associated with more pain, that less synovitis was associated with less pain, and also that fluctuation in BMLs amplified this effect of synovitis on change in pain.[8,9] These studies also suggest that BMLs mainly have an additive effect when accompanying synovitis, and that synovitis is the main driver of pain.[5,9] Our study shows that a longitudinal association between inflammatory MRI-features and pain is also present in thumb base OA. However, in our study, associations with BMLs appeared somewhat stronger than with synovitis, which may suggest that in thumb base OA BMLs do not merely amplify the effect of synovitis. However, the small number of patients in whom a change in synovitis and BMLs occurred in this study precluded formal assessment of interaction between synovitis and BMLs. Further study is warranted to investigate whether associations between synovitis, BMLs and pain are different in the thumb base compared to the interphalangeal joints.

In a previous cross-sectional analysis in this hand OA cohort,[7] we showed that radiographic damage was a more important determinant of pain in the thumb base than synovitis or BMLs were, which contrasted findings of studies in interphalangeal OA.[5,6] The same study demonstrated that the combined presence of inflammation and structural damage in the thumb base had an additive effect on pain. We now show that a change in synovitis and BMLs was associated with a change in pain, even after adjustment for radiographic damage. Subsequently, stratified analyses revealed that this association was strongest in joints where radiographic damage was present at baseline. Taking the results of these two studies together, radiographic damage seems to be the most important feature associated with pain in thumb base OA cross-sectionally, but a change in inflammatory features may still have a relevant effect on the course of pain.

The role of inflammation in the pathogenesis of osteoarthritic joint pain was already discussed in an excellent seminar published in the Lancet over a decade ago.[22] Recently, a review by different authors in the same journal corroborates the proposed mechanisms, though definite proof is yet to be found.[23] Peripheral nociceptive pain could arise from ongoing tissue injury or inflammation of innervated tissues such as the subchondral bone, periosteum and synovium. The cartilage itself is aneural, but can still be involved by releasing cytokines and other signaling molecules that can sensitize pain pathways at the peripheral, spinal or cortical compartment. Pain sensitization might also explain why associations between decreased MRI-features and decreased pain, are smaller compared to increased MRI-features and increased pain, as pathways can still remain sensitized after the inflammation subsides.[22,23]

The relatively low number of thumb base joints with radiographic progression after two-year follow-up is in line with results from a previous study in 172 hand OA patients, of whom merely 8 (4.7%) had osteophyte progression and even less (n=5, 2.9%) had JSN progression in the CMC-1 joints after two years.[24] After six-year follow-up, still only a small proportion of CMC-1 and STT joints showed radiographic osteophyte (16.5% and 1.5%) or JSN (10.5% and 6.2%) progression.[25] Although radiographic progression did not appear to affect pain levels in this study, the low number of joints progressing hampers strong conclusions, and a longer follow-up may be needed to investigate this relationship.

In our study, increase in structural damage was more often seen on MRI than on radiography. The higher sensitivity of MRI to detect structural damage was also shown in a recent cross-sectional study.[26] Currently, structural damage assessed on radiographs is considered the gold standard. Whether (an increase in) structural damage on MRI, not visible on radiography, is clinically relevant, should be investigated in future studies.

To our knowledge, this is the first study describing the course of clinical and MRI parameters in thumb base OA in a study with a considerable sample size. This cohort, recruited from a rheumatology outpatient clinic in a secondary and tertiary referral center, is a good representation of hand OA patients that are in need of and could benefit from treatment, but might be different from a primary care population, hence results should be extrapolated with caution. As a result of including patients with hand OA, but not necessarily thumb base OA, our cohort consisted of patients with a wide variety of thumb base OA disease stages. An important limitation of this study is the low number of patients in whom a change in pain, MRI-features or structural damage occurred, which demonstrates that the natural course of thumb base OA is a slow process. As a consequence, the estimated associations are less accurate, which is reflected by wide CIs, especially for the stratified analyses. Future studies of the longitudinal relation between pain, MR-defined inflammation and radiographic damage with a large group size and longer follow-up are therefore warranted. In addition, analyses in the setting of a positive clinical trial would provide more insight in associations with improvement in pain. Another limitation might be the possible usage of over-the-counter analgesics and thumb base splints in this observational cohort. However, in general, the efficacy of analgesics for treating OA pain is small,[27,28] and even though a recent meta-analysis showed positive effects of thumb base splinting on pain,[29]

there is no evidence that these interventions influence MRI-features. Therefore, we believe these interventions might only have introduced additional noise in the studied associations, but did not introduce bias.

Besides providing more insight in the course and prognosis of thumb base OA, this study suggests inflammation in the thumb base could be explored as a potential treatment target. This may seem to contrast negative findings of clinical trials of intra-articular glucocorticoid injections in the thumb base,[30] though the lack of trials with positive outcomes could also be related to the inclusion of patients without inflammation. Therefore, trials selecting patients based on the presence of thumb base inflammation, and not primarily radiographic damage as has been done before, may generate different results. Indeed, a recently published trial of prednisolone in interphalangeal OA that only included patients with objectifiable inflammation of at least one interphalangeal joint showed significant and clinically meaningful results,[31] whereas previous trials of glucocorticoids in hand OA without confirmed inflammation at baseline were inconclusive.[32]

In conclusion, over the course of two years, thumb base pain fluctuated. Osteoarthritic MRI-features in the thumb base changed in a minority of patients with hand OA, in whom structural features mostly deteriorated and inflammatory features changed in either direction. Changes in synovitis and BMLs were associated with changes in pain, mainly in patients with radiographic damage. Therefore, while radiographic damage may be the main determinant of pain in thumb base OA, this study shows that a change in inflammatory features in the thumb base may still be relevant effect on pain.

REFERENCES

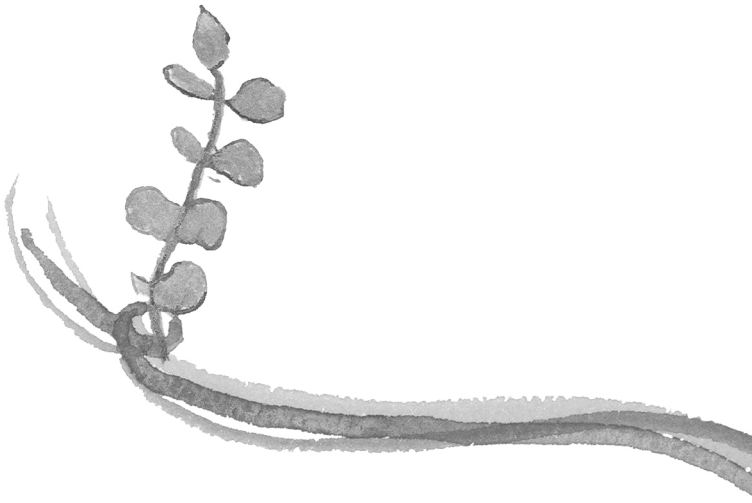
1. Goislard de Monsabert B, Vigouroux L, Bendahan D, et al. Quantification of finger joint loadings using musculoskeletal modelling clarifies mechanical risk factors of hand osteoarthritis. *Med Eng Phys* 2014;36:177-84.
2. Li ZM, Tang J. Coordination of thumb joints during opposition. *J Biomech* 2007;40:502-10.
3. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
4. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
5. Liu R, Damman W, Reijnierse M, et al. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. *Osteoarthritis Cartilage* 2017;25:1093-9.
6. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
7. Kroon FPB, van Beest S, Ermurat S, et al. In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis. *Osteoarthritis Cartilage* 2018;26:1196-202.
8. Haugen IK, Christensen BS, Bøyesen P, et al. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Ann Rheum Dis* 2016;75:702–8.
9. Van Beest S, Damman W, Liu R, et al. In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study. *Osteoarthritis Cartilage* 2019;27:1048-56.
10. Damman W, Liu R, Kroon FPB, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand Osteoarthritis in Secondary care cohort. *J Rheumatol* 2017;44:1659-66.
11. Bellamy N, Campbell J, Haraoui B, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthritis Cartilage* 2002;10:863-9.
12. Bijsterbosch J, Wassenaar MJE, le Cessie S, et al. Doyle Index is a valuable additional pain measure in osteoarthritis. *Osteoarthritis Cartilage* 2010;18:1046-50.
13. Kroon FPB, Conaghan PG, Foltz V, et al. Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging ccoring system. *J Rheumatol* 2017;44:1694-8.
14. Kroon FPB, Peterfy CG, Conaghan PG, et al. Atlas for the OMERACT thumb base osteoarthritis MRI scoring system (TOMS). *RMD Open* 2018;4:e000583.
15. Kroon FPB, van Beest S, Gandjbakhch F, et al. Longitudinal reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system (TOMS). *J Rheumatol* 2019; 46:1228-31.
16. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993;46:423-9.
17. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15 Suppl A:A1-56.
18. Bruynesteyn K, Boers M, Kostense P, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179-82.
19. Rothman KJ. *Epidemiology: An Introduction*. Second Edition. Oxford, New York: Oxford University Press; 2012.
20. Hosmer DW, Lemeshow S. Confidence Interval Estimation of Interaction. *Epidemiology* 1992;3:452-6.
21. Micallef L, Rodgers P. EulerAPE: Drawing area-proportional 3-venn diagrams using ellipses. *PLoS One* 2014;9:e101717.
22. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965-73.
23. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393:1745-59.
24. Botha-Scheepers S, Riyazi N, Watt I, et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. *Ann Rheum Dis* 2009;68:1260-4.
25. Bijsterbosch J, Meulenbelt I, Watt I, et al. Clustering of hand osteoarthritis progression and its relationship to progression of osteoarthritis at the knee. *Ann Rheum Dis* 2014;73:567-72.
26. Van Beest S, Kroon FPB, Kroon HM, et al. Assessment of osteoarthritic features in the thumb base with the newly developed OMERACT magnetic resonance imaging scoring system is a valid addition to standard radiography. *Osteoarthritis Cartilage* 2019;27:468-75.
27. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*

2015;162:46-54.
28. Da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017;390:e21–33.
29. Buhler M, Chapple CM, Stebbings S, et al. Effectiveness of splinting for pain and function in people with thumb carpometacarpal osteoarthritis: a systematic review with meta-analysis. *Osteoarthritis Cartilage* 2019;27:547-59.
30. Kroon FPB, Rubio R, Schoones JW, et al. Intra-articular therapies in the treatment of hand osteoarthritis: a systematic literature review. *Drugs Aging* 2016;33:119-33.
31. Kroon FPB, Kortekaas MC, Boonen A, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. Lancet 2019;394:1993-2001.
32. Kroon FPB, Carmona L, Schoones JW, et al. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. RMD Open 2018;4:e000734.



CHAPTER 9

The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis



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ABSTRACT

Objectives. To investigate associations of leptin and adiponectin levels with knee and hand osteoarthritis, and explore whether these mediate the association between adiposity and osteoarthritis.

Methods. This is a cross-sectional analysis of baseline data from the population-based Netherlands Epidemiology of Obesity study. Adiposity was assessed with body mass index (BMI) and percentage total body fat (%TBF). Osteoarthritis, defined as hand or knee osteoarthritis, was determined using American College of Rheumatology criteria. Fasting serum adipokine levels were measured using immunoassays. Associations between adiposity and osteoarthritis were examined with logistic regression, adjusted for age, sex, ethnicity and education, and additionally for leptin and adiponectin as potential mediators.

Results. In 6408 participants (56% women, median age 56 years), prevalence of osteoarthritis was 22% (10% isolated knee and 8% isolated hand osteoarthritis). Leptin levels were positively associated with osteoarthritis, while adiponectin levels were not. Leptin partially mediated the association of adiposity with osteoarthritis (OR 1.40 (95% CI 1.30; 1.52) attenuated to 1.38 (1.24; 1.54) per 5 units BMI and OR 1.25 (1.17; 1.35) to 1.20 (1.10; 1.32) per 5 units %TBF, representing 4% and 17% mediation, respectively). Larger proportion mediation by leptin was found in knee (13%/27%) than in hand osteoarthritis (9%/18%). Sex-stratified analyses generally showed stronger associations between adiposity, leptin and osteoarthritis in women than in men.

Conclusions. Serum leptin levels were associated with osteoarthritis, and partially mediated the association between adiposity and osteoarthritis, while adiponectin levels were not associated with osteoarthritis. These findings provide evidence for systemic effects of adipose tissue in osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is one of the most common musculoskeletal disorders in the developed world, and a leading cause of disability among elderly.[1] Besides a substantial individual disease burden, OA is associated with a significant socioeconomic burden.[2]

Obesity is an important risk factor for OA. While this association has often been reported for weight-bearing joints, studies have also suggested a relation in non-weight-bearing joints.[3,4] However, the underlying mechanism of this association is topic of debate. While the increased mechanical stress across weight-bearing joints is thought to result in joint damage, this paradigm fails to explain the association of obesity with OA in non-weight-bearing joints.[5] It has therefore been suggested that the systemic metabolic effects of obesity also have detrimental effects on joint tissue.[6] The presence of systemic metabolic effects in OA is supported by a study in which surrogates for systemic processes (metabolic syndrome) were associated with OA, particularly in hand OA,[7] although a recent study refuted the association between metabolic syndrome and hand OA.[8] In fact, adipose tissue is a known source of several bioactive factors, including adipokines, cytokines, chemokines, and complement factors.[9] Of these, adipokines have been postulated as a potential link between obesity and OA.[10,11] Leptin and adiponectin are among the most often studied, and have been detected in synovial fluid and the infrapatellar fat pad of knee OA patients.[10,12,13] Studies of the association of adipokines with OA, however, have led to contradictory conclusions. Most evidence is available for an association between leptin and knee OA.[14-22] Associations with adiponectin[14,15,18,21,23] or hand OA[24-27] are less consistent. However, most studies are small, and mediation is not often formally assessed.

Our aim was therefore to investigate the association of leptin and adiponectin levels with knee and hand OA, and to explore whether these adipokines play a mediating role in the association between adiposity and OA.

METHODS

Study design and population

A cross-sectional analysis of baseline measurements of the Netherlands Epidemiology of Obesity (NEO) study was performed. The NEO study is a population-based cohort study, designed to investigate pathways that lead to obesity-related diseases, which recruited individuals aged 45-65 years with a self-reported body mass index (BMI) ≥27 kg/m^2 living in the greater area of Leiden (the Netherlands) between September 2008-2012.[28] Additionally, all inhabitants aged 45-65 years from the Leiderdorp municipality were invited to participate irrespective of their BMI, to allow for a reference BMI distribution, resulting in 6671 participants in total. The study was approved by the medical ethics committee of the Leiden University Medical Centre. All participants provided written informed consent.

After exclusion of participants with missing data for determination of OA (n=17), adipokine measurements (n=61) or %TBF (n=31), and those with inflammatory rheumatic diseases (n=154), data from 6408 participants were analysed.

Data collection

All participants completed questionnaires on demographic and clinical data, and attended the study centre for baseline measurements, including blood sampling and physical examination. Questionnaires included questions on ethnicity (eight categories; regrouped into Caucasian vs other), educational level (ten categories; regrouped into high (higher vocational education, university degree, and postgraduate education) vs low), presence of self-reported inflammatory rheumatic diseases (including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and ankylosing spondylitis), and self-reported pain or stiffness of hands or knees on most days of the preceding month.

BMI (kg/m^2) was calculated from measured body weight and height. Bioelectrical impedance analysis (Tanita TBP-300 Body Composition Analyser) was used to estimate percentage total body fat (%TBF). Physical examination of knees and hands was performed by trained research nurses. In the knees, presence of tenderness of the bony margins, bony enlargement, movement restriction, crepitus and palpable warmth were assessed. In the hands, presence of bony swelling, soft swelling and deformities of the distal interphalangeal, proximal interphalangeal, metacarpophalangeal and first carpometacarpal joints were assessed. Participants were classified as having OA, defined as having hand or knee OA, according to clinical American College of Rheumatology criteria.[29,30] Participants with a knee prosthesis were classified as having knee OA.

Serum adipokine levels were measured in fasting blood samples using a latex particle-enhanced turbidimetric immunoassay (Cat A0299, Randox Laboratories Ltd) for adiponectin, and a human competitive radio-immunoassay (Cat HL-81HK, Merck Millipore, Darmstadt, Germany) for leptin. The lowest detectible levels were 0.7 mg/L (adiponectin) and 0.8 ug/L (leptin). Observations below this level (adiponectin n=4, leptin n=14) were recorded in the database with a value of 0.5, as recommended by the NEO study group.

Statistical analyses

To correctly represent distributions and associations in the general population,[31] adjustments for oversampling of individuals with BMI ≥27 kg/m^2 were made by weighting towards the BMI distribution of participants from the Leiderdorp municipality (n=1671),[32] whose BMI distribution was similar to the general Dutch population.[33] All results were based on weighted analyses. Consequently, results apply to a population-based study without oversampling of individuals with BMI ≥27 kg/m^2.

To investigate whether adipokines mediate the association between adiposity and OA, sequential regression analyses were performed according to the Baron and Kenny framework (figure 1).[34] In this framework, pathway C represents the total effect of the exposure (adiposity) on the outcome (OA). This effect can be divided in the direct effect (pathway C'), and the indirect effect via the potential mediator (through pathway A and B). Mediation was suspected when four assumptions of the Baron-Kenny framework were satisfied: (1)adiposity was associated with OA, (2)adiposity was associated with serum adiponectin/leptin, (3)serum adiponectin/leptin was associated with OA, and (4)the association between adiposity and OA attenuated after inclusion of adiponectin/leptin into the model. Satisfaction of the first three assumptions was based on the size of the effect estimate in the regression analysis.

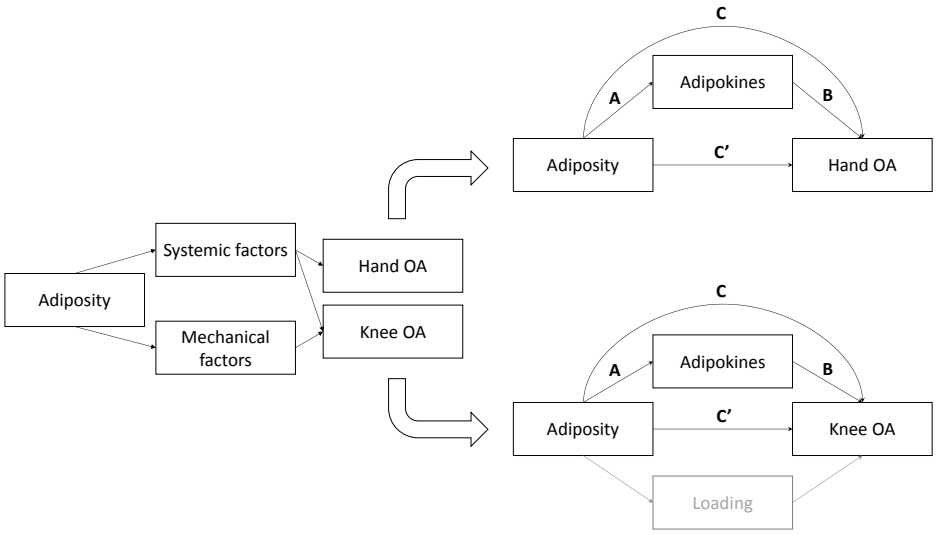


Figure 1. Hypothesized associations between adiposity, OA and adipokines, and the Barron and Kenny framework.

Logistic regression analysis was used for dichotomous endpoints. Linear regression analysis was used for continuous endpoints. Associations, expressed as ORs or betas with 95% CI, were estimated for participants with OA (knee or hand), isolated knee OA and isolated hand OA, using participants without OA as the reference group. BMI was used as measure of adiposity, and analyses were repeated using %TBF. All associations were calculated per 5 units of BMI, %TBF and adiponectin, and per 10 units of leptin. Notably, since a 5 unit increase in BMI or %TBF is not of comparable size, the point estimates of these analyses should not be directly compared and are not indicative of the relative importance of BMI or %TBF.

When the four assumptions for mediation were fulfilled, the proportion of the association between adiposity and OA mediated by the adipokine was calculated. For this, the indirect effect was estimated as the product of the regression coefficients of pathway A and B, with corresponding standard errors calculated according to the Sobel method.[35] The percentage mediation was subsequently calculated by dividing the indirect effect by the total effect (pathway C). In case not all assumptions of the Baron-Kenny framework were fulfilled, percentage mediation was not calculated. The presence of exposure-mediator interaction was explored by adding an interaction term to the model of pathway C'. No evidence of exposure-mediator interaction was found, based on statistical significance of the interaction term ($p<0.05$), and was thus assumed absent in subsequent analyses.

In analogy with previous studies of adipokines in OA, many comparing obese to non-obese persons, and also to evaluate the robustness of our estimation of the percentage mediation, we performed sensitivity analyses, estimating the percentage mediation for BMI and %TBF high vs low. Here, besides the Sobel method, we also used the *medeff* package in Stata, which estimates mediation effects on an additive scale.[36] The cut-off was set at a BMI of 27.5 kg/m^2 or %TBF above or below the median (determined for men and women separately).

All analyses were adjusted for age, sex, ethnicity and education. Since load plays an important role in the relation between adiposity and knee OA (figure 1), these analyses were repeated stratified by body weight (<75 vs 75-90 vs >90 kg). We also performed sex-stratified analyses to explore differences between men and women. Analyses were performed using Stata 14 (StataCorp LP, Texas, USA).

RESULTS

Population characteristics

Baseline characteristics are presented in table 1. In total, 22% had OA of the knee or hands (10% knee OA, 8% hand OA, 4% both knee and hand OA). OA prevalence was higher in women than in men (11% vs 9% with knee OA, 10% vs 5% hand OA, and 7% vs 1% combined OA). Adipokine levels were higher in participants with OA than in those without. On average women had higher serum leptin (mean (SD) 23.4 (18.1) vs 9.1 (7.4)) and adiponectin levels (11.3 (5.1) vs 6.6 (3.1)) than men.

Table 1. Characteristics of the study population (n=6408), stratified by OA presence.

	No OA (78%)	**OA (22%)***			
			Knee OA (10%)	Hand OA (8%)	Knee and hand OA (4%)
Age, years	55.1 (6.1)	57.6 (5.1)	57.0 (5.2)	58.1 (5.2)	58.3 (4.6)
Sex, % women	52	71	61	74	87
Education, % high	49	38	37	40	36
Ethnicity, % Caucasian	95	94	95	94	92
BMI, kg/m^2	26.0 (4.2)	27.3 (5.1)	27.8 (5.3)	26.6 (4.7)	27.5 (5.0)
Total body fat, %	30.7 (8.4)	34.9 (8.6)	34.2 (9.3)	34.5 (7.8)	37.5 (7.4)
Adiponectin levels, mg/L	9.0 (4.8)	10.1 (5.2)	9.6 (5.3)	10.4 (5.5)	10.7 (4.6)
Leptin levels, ug/L	15.7 (14.5)	22.3 (19.9)	22.2 (20.9)	21.0 (17.6)	24.8 (21.1)

Results were based on analyses weighted towards the BMI distribution of the general population. Numbers represent mean (standard deviation) unless otherwise specified. BMI, body mass index; OA, osteoarthritis. *Defined as having knee or hand OA.

Associations between adipokines and OA

Table 2 presents the associations between adiposity, OA and leptin or adiponectin. From left to right this table presents the association between adiposity (BMI or %TBF) and OA, the association between adiposity and the adipokine (leptin or adiponectin), the association between the adipokine and OA, and the associations with OA from the multivariable model including both adiposity and the adipokine.

First, we assessed the associations between adiposity, both adipokines and OA presence in knees or hands. While leptin levels were positively associated with OA (OR 1.16, 95% CI 1.11 to 1.22, per 10 units; table 2), adiponectin levels were not (table 2).

Table 2. Associations between adiposity, OA* and leptin or adiponectin.

Independent variable	Dependent variable				Mediation
	OA OR (95% CI)	**Leptin** β (95% CI)	**OA** OR (95% CI)	**OA** OR (95% CI)†	%
BMI	1.40 (1.30; 1.52)	1.16 (1.11; 1.20)		1.38 (1.24; 1.54)	4
Leptin			1.16 (1.11; 1.22)	1.01 (0.95; 1.07)	
%TBF	1.25 (1.17; 1.35)	0.75 (0.72; 0.78)		1.20 (1.10; 1.32)	17
Leptin			1.16 (1.11; 1.22)	1.05 (1.00; 1.11)	
	OA OR (95% CI)	**Adiponectin** β (95% CI)	**OA** OR (95% CI)	**OA** OR (95% CI)†	
BMI	1.40 (1.30; 1.52)	-0.23 (-0.26; -0.20)		1.44 (1.32; 1.56)	N/A
Adiponectin			1.02 (0.92; 1.13)	1.11 (1.00; 1.24)	
%TBF	1.25 (1.17; 1.35)	-0.17 (-0.19; -0.14)		1.28 (1.19; 1.37)	N/A
Adiponectin			1.02 (0.92; 1.13)	1.10 (0.99; 1.23)	

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated per 5 units, associations with leptin were calculated per 10 units, associations with adiponectin were calculated per 5 units. BMI, body mass index; CI, confidence interval; N/A, not applicable; OA, osteoarthritis; OR, odds ratio; %TBF, percentage total body fat. *Defined as having knee or hand OA. †OR from multivariate analysis with both the adiposity measure and the adipokine included in the model.

Mediating effect of leptin

As shown in table 2, after additionally including leptin in the model, the observed association between adiposity and OA attenuated. This represented a mediating effect of leptin of 4% of the association of 5 units BMI with OA, and 17% of the association of 5 units %TBF with OA. A summary of the total, indirect and direct effects is presented in supplementary table 1.

Next, we explored whether the relationship between adiposity, leptin and OA differed for different OA localisations, by comparing participants with knee OA vs those with hand OA. In this analysis, participants with both knee and hand OA were not taken into account. Table 3 shows that adiposity and leptin were both more strongly associated with knee than with hand OA. While mediation by leptin in the association between adiposity and OA was found for both OA localisations, the effect in knee OA (13% and 27% per 5 units BMI and %TBF, respectively) was larger than in hand OA (9% and 18%).

In an attempt to account for the effect of adiposity on knee OA through increased loading, knee OA analyses were repeated stratified for weight categories. After stratification, an association between BMI and knee OA was found in the highest and the lowest weight category. However, the mediating effect of leptin on the association between BMI and knee OA only remained present in the lowest weight category. In this subgroup, the association between adiposity and knee OA was OR 1.92 (95% CI 1.22 to 3.02, per 5 units BMI; pathway C), which attenuated after inclusion of leptin into the model to 1.51 (95% CI 0.87 to 2.61; pathway C'), with an estimated 35% mediation.

Table 3. Associations between adiposity, OA and leptin for different OA localisations.

Independent variable	Dependent variable				Mediation %
	Knee OA OR (95% CI)	**Leptin** β (95% CI)	**Knee OA** OR (95% CI)	**Knee OA** OR (95% CI)*	
BMI	1.48 (1.34; 1.64)	1.16 (1.11; 1.20)		1.41 (1.22; 1.62)	13
Leptin			1.20 (1.14; 1.27)	1.04 (0.97; 1.12)	
%TBF	1.30 (1.18; 1.43)	0.75 (0.72; 0.78)		1.20 (1.07; 1.35)	27
Leptin			1.20 (1.14; 1.27)	1.10 (1.03; 1.17)	
	Hand OA OR (95% CI)	**Leptin** β (95% CI)	**Hand OA** OR (95% CI)	**Hand OA** OR (95% CI)*	
BMI	1.22 (1.09; 1.38)	1.16 (1.11; 1.20)		1.20 (1.02; 1.41)	9
Leptin			1.09 (1.03; 1.16)	1.02 (0.93; 1.11)	
%TBF	1.15 (1.04; 1.27)	0.75 (0.72; 0.78)		1.12 (0.98; 1.27)	18
Leptin			1.09 (1.03; 1.16)	1.03 (0.95; 1.12)	

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated per 5 units, associations with leptin were calculated per 10 units, associations with adiponectin were calculated per 5 units. BMI, body mass index; CI, confidence interval; OA, osteoarthritis; OR, odds ratio; %TBF, percentage total body fat. *OR from multivariate analysis with both the adiposity measure and leptin included in the model.

Adiposity as a binary variable

Table 4 presents the total, indirect and direct effects, and the percentage mediation of the sensitivity analyses where adiposity was treated as a binary variable. The estimated percentage mediation was larger than when adiposity was entered in the model per 5 units. Substantial mediation by leptin was shown for OA in general, and in both OA localisations separately. Again, the associations and estimated mediation were larger in knee OA than in hand OA. Estimation of the proportion mediation by the two different calculation methods (i.e., Sobel method vs using the *medeff* command in Stata) revealed similar results, except for the estimate of the analyses of %TBF and hand OA, likely due to a smaller number of participants in this subgroup.

Sex differences

Sex-stratified analyses (supplementary tables 2 and 3) showed that the association between adiposity and leptin levels was somewhat stronger in women than in men. Moreover, the interrelation between adiposity, leptin levels and OA, and as a consequence the mediating effect of leptin, was stronger in women, particularly in OA in general and in the knee OA subset. The subgroups of participants with isolated hand OA were even smaller, so definite conclusions on sex differences could not be drawn from these analyses.

Adiponectin

In contrast to leptin, adiponectin levels were not associated with OA (OR 1.02, 95% CI 0.92 to 1.13, per 5 units). Stratification by OA localisation revealed no differences for knee (OR 1.02, 95% CI 0.89 to 1.17) and hand OA (OR 1.03, 95% CI 0.88 to 1.21). In absence of an association between adiponectin levels and OA, we did not further explore mediation of the association of adiposity with OA by adiponectin.

Table 4. Sensitivity analysis: mediation by leptin on the association of adiposity with OA, treating adiposity as a binary variable (high vs. low).

	Measure of adiposity	Total effect β (SE)	Indirect effect β (SE)	Direct effect β (SE)	Mediation	
					Sobel method %	*medeff* method % (95% CI)
OA						
	BMI	0.53 (0.08)	0.14 (0.04)	0.37 (0.09)	27	28 (22; 39)
	%TBF	0.37 (0.10)	0.17 (0.03)	0.17 (0.11)	48	51 (34; 106)
Knee OA						
	BMI	0.60 (0.11)	0.21 (0.05)	0.37 (0.12)	35	35 (26; 52)
	%TBF	0.42 (0.13)	0.23 (0.04)	0.17 (0.14)	55	58 (36; 149)
Hand OA						
	BMI	0.39 (0.12)	0.07 (0.06)	0.31 (0.14)	18	18 (11; 45)
	%TBF	0.11 (0.14)	0.14 (0.05)	-0.04 (0.16)	119	66 (-993; 2070)

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated for high vs. low (binary), associations with leptin were calculated per 10 units. BMI, body mass index; CI, confidence interval; OA, osteoarthritis; SE, standard error; %TBF, percentage total body fat.

DISCUSSION

In this study, we investigated the role of systemic adipokines in OA, to gain more insight in systemic mechanisms connecting adiposity and OA. Increased leptin levels were associated with higher odds of OA, while adiponectin levels were not associated with OA. Leptin levels appeared to partially mediate the association between adiposity and OA, with larger effects in knee than in hand OA. Generally, effects were more pronounced in women than in men.

The absence of an association between adiponectin levels and OA is in accordance with most previous studies.[14,15,18,21,23,24] Only one study found a protective effect of adiponectin in a hand OA cohort of 164 patients, with a 70% decreased risk for joint space narrowing in those with the highest adiponectin levels compared to the lowest.[25] Important aspects which reduce comparability with our study include the differences in setting (population-based vs hand OA cohort) and outcome definition (presence of clinical OA vs progression of radiographic OA).

The association we found between leptin levels and OA also corresponds to previous reports. Most studies have been done in knee OA.[14-22] Fewer studies investigated the role of leptin in hand OA, and results are conflicting. The population-based Michigan SWAN study including 543 women also found a positive association between serum leptin levels and presence of radiographic hand OA, with an OR of 1.06 (1.01-1.12) per 5 ng/mL increase.[26] However, in the NHANES-III cohort, no differences were found in leptin levels between men or women with symptomatic (n=90), asymptomatic (n=376), and no hand OA (n=590).[27] Also in a hand OA cohort (n=164) baseline leptin levels were not associated with hand OA progression after six-year follow-up.[25] Smaller sample size, use of different outcome definitions, and differences in setting may partly explain the divergent results.

Only one previous report assessed mediation by adipokines. In a population-based study (n=635) mediation by leptin in the relationship between BMI and knee OA was investigated.[22] In women, they estimated that leptin mediates approximately 49% of the total adverse effect of a high BMI on knee OA, which is similar to our finding of approximately 50% mediation in women in knee OA in the binary model. Interestingly, they found no association between leptin and knee OA in men, which corresponds to the sex-differences found in our study. Despite the resembling results, their study was tenfold smaller, comprised an elderly population (aged 70 and over), did not include measures of body composition, and did not adjust for mechanical effects of adiposity. We found no previous studies assessing mediation by adipokines in hand OA.

In an attempt to account for the mechanical component of adiposity in knee OA, we explored the effect of body weight on the analyses of leptin in knee OA, and found that the mediating effect of leptin only remained present in the lowest weight category. This may imply that in individuals with a higher weight, the detrimental effect of increased load is the most important determinant of knee OA. In contrast, in individuals with a lower weight this biomechanical effect may be smaller, and systemic effects may play a larger role, partially mediated by leptin. Since the only previous report of mediation analyses did not take body weight into account, future studies need to replicate this finding.[22]

In-vitro studies have shown that human chondrocytes express functional leptin receptors.[37] It has also been shown that leptin is overexpressed in cartilage and osteophytes of OA patients, and that it can induce synthesis of growth factors in cartilage.[10] More in-vivo support for a link between leptin and OA pathogenesis comes from a study in which female leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice developed extreme obesity, while the incidence of knee OA did not increase.[38] The authors of that study conclude that leptin signalling is necessary for obesity-induced OA to develop.

Most studies investigating adipokines in OA used a female study population,[14,16,17,24,26] adjusted for sex or lacked power to stratify by sex.[15,18-23,25] Therefore, sex differences in the adipokine-OA relation have not often been explored. In accordance with our findings, a previous analysis in the NHANES-III cohort reports that leptin was more strongly associated with knee OA in women than in men.[39] A possible explanation for the sex differences found in the associations with and mediating effect of leptin could be that the aetiology of knee OA in men is more biomechanical in nature, whereas the aetiology in women has a larger systemic or inflammatory component. This hypothesis is in line with a previous report showing that in men skeletal muscle mass was more strongly associated with knee OA, while in women fat mass was a more important determinant.[40] This is further supported by the finding that work-related trauma were more strongly related to knee OA in men.[41] However, the separate analyses in men and women should be interpreted with caution, especially in the participants with hand OA, due to the small size of the subgroups.

Although we found evidence for mediation by systemic leptin levels, these are likely not the sole systemic mechanisms by which adiposity contributes to OA. Rather, the systemic effects of adiposity on OA probably stem from a combination of factors, including adipokines, but also for example hypertension and dyslipidemia.[6,8,42,43] This is supported by our finding of partial, and not complete, mediation.

Notable strengths of this study include the size of the study population and its population-based design, extensive characterization of participants, and the availability of information of both weight-bearing (knee) and non-weight-bearing (hand) joints. However, there are few limitations that need to be acknowledged. The lower prevalence of OA in men resulted in less precise effect estimates in some analyses. The study had a cross-sectional design, and inherent to this design, reverse causation cannot be excluded, hampering causal inference. While we adjusted for multiple potential confounding factors, another limitation of our study design is that residual confounding by (an) unmeasured variable(s) related both to the exposure and the outcome may remain present, which may have introduced biased results. Therefore, longitudinal studies are warranted to draw more definite conclusions about the mediating role of leptin in OA. Moreover, adipokines were measured systemically, and this may not necessarily reflect intra-articular adipokine levels.[44]

In conclusion, in this population-based study we demonstrated that serum leptin levels were associated with OA, and partially mediated the association adiposity and OA, while adiponectin levels were not associated with OA. These findings support the growing body of evidence for systemic effects of adipose tissue in OA.

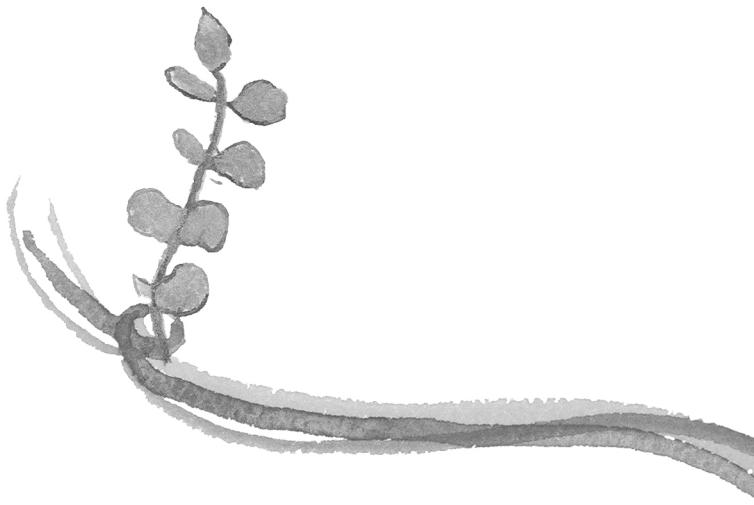
REFERENCES

1. Murray CJL, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145-91.
2. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437-41.
3. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:507-15.
4. Yusuf E, Nelissen RG, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* 2010;69:761-5.
5. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. *Med Clin North Am* 2009;93:1-24, xv.
6. Berenbaum F, Griffin TM, Liu-Bryan R. Review: Metabolic Regulation of Inflammation in Osteoarthritis. *Arthritis Rheumatol* 2017;69:9-21.
7. Visser AW, de Mutsert R, le Cessie S, et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Ann Rheum Dis* 2015;74:1842-7.
8. Strand MP, Neogi T, Niu J, et al. Association Between Metabolic Syndrome and Radiographic Hand Osteoarthritis: Data From a Community-Based Longitudinal Cohort Study. *Arthritis Care Res* 2018;70:469-74.
9. Neumann E, Junker S, Schett G, et al. Adipokines in bone disease. *Nat Rev Rheumatol* 2016;12:296-302.
10. Dumond H, Presle N, Terlain B, et al. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* 2003;48:3118-29.
11. Berry PA, Jones SW, Cicuttini FM, et al. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. *Arthritis Rheum* 2011;63:700-7.
12. Klein-Wieringa IR, Kloppenburg M, Bastiaansen-Jenniskens YM, et al. The infrapatellar fat pad of patients with osteoarthritis has an inflammatory phenotype. *Ann Rheum Dis* 2011;70:851-7.
13. Schaffler A, Ehling A, Neumann E, et al. Adipocytokines in synovial fluid. *JAMA* 2003;290:1709-10.
14. Calvet J, Orellana C, Gratacos J, et al. Synovial fluid adipokines are associated with clinical severity in knee osteoarthritis: a cross-sectional study in female patients with joint effusion. *Arthritis Res Ther* 2016;18:207.
15. de Boer TN, van Spil WE, Huisman AM, et al. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. *Osteoarthritis Cartilage* 2012;20:846-53.
16. Karvonen-Gutierrez CA, Harlow SD, Jacobson J, et al. The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. *Ann Rheum Dis* 2014;73:883-9.
17. Karvonen-Gutierrez CA, Harlow SD, Mancuso P, et al. Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women. *Arthritis Care Res* 2013;65:936-44.
18. Martel-Pelletier J, Raynauld JP, Dorais M, et al. The levels of the adipokines adipsin and leptin are associated with knee osteoarthritis progression as assessed by MRI and incidence of total knee replacement in symptomatic osteoarthritis patients: a post hoc analysis. *Rheumatology (Oxford)* 2016;55:680-8.
19. Staikos C, Ververidis A, Drosos G, et al. The association of adipokine levels in plasma and synovial fluid with the severity of knee osteoarthritis. *Rheumatology (Oxford)* 2013;52:1077-83.
20. Stannus OP, Cao Y, Antony B, et al. Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. *Ann Rheum Dis* 2015;74:82-8.
21. Van Spil WE, Welsing PM, Kloppenburg M, et al. Cross-sectional and predictive associations between plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. *Osteoarthritis Cartilage* 2012;20:1278-85.
22. Fowler-Brown A, Kim DH, Shi L, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. *Arthritis Rheumatol* 2015;67:169-75.
23. Zheng S, Xu J, Xu S, et al. Association between circulating adipokines, radiographic changes, and knee cartilage volume in patients with knee osteoarthritis. *Scand J Rheumatol* 2016;45:224-9.
24. Choe JY, Bae J, Jung HY, et al. Serum resistin level is associated with radiographic changes in hand osteoarthritis: cross-sectional study. *Joint Bone Spine* 2012;79:160-5.
25. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. *Ann Rheum Dis* 2011;70:1282-4.

26. Karvonen-Gutierrez CA, Manusco P, Jiang Y, et al. Association of leptin levels with radiographic hand ostearthritis and severity among a cohort of midlife women. *Osteoarthritis Cartilage* 2017;25:S196.
27. Massengale M, Reichmann WM, Losina E, et al. The relationship between hand osteoarthritis and serum leptin concentration in participants of the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther* 2012;14:R132.
28. de Mutsert R, den Heijer M, Rabelink T, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol* 2013;28:513-23.
29. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
30. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1029-49.
31. Korn EL, Graubard BL. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health* 1991;33:1166-73.
32. Lumley T. Analysis of complex survey samples. 2004. http://www.jstatsoft.org/v09/i08/paper.
33. Ministerie van VWS. Hoeveel mensen hebben overgewicht? 2013. www.rivm.nl/nldemaat.
34. Baron R, Kenny D. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173-82.
35. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt, ed. *Sociological methodology*. Washington DC: American Sociological Association; 1982:290-312.
36. Hicks R, Tingley D. Causal mediation analysis. *The Stata Journal* 2011;11:1-15.
37. Figenschau Y, Knutsen G, Shahazeydi S, et al. Human articular chondrocytes express functional leptin receptors. *Biochem Biophys Res Commun* 2001;287:190-7.
38. Griffin TM, Huebner JL, Kraus VB, et al. Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis. *Arthritis Rheum* 2009;60:2935-44.
39. Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. *Osteoarthritis Cartilage* 2012;20:614-21.
40. Visser AW, de Mutsert R, Loef M, et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. *Osteoarthritis Cartilage* 2014;22:197-202.
41. Kellgren JH, Lawrence JS. Osteo-arthrosis and disk degeneration in an urban population. *Ann Rheum Dis* 1958;17:388-97.
42. Li S, Felson DT. What is the evidence to support the association between metabolic syndrome and osteoarthritis? - A systematic review. *Arthritis Care Res* 2018, Jul 12. doi: 10.1002/acr.23698 [epub ahead of print].
43. Niu J, Clancy M, Aliabadi P, et al. Metabolic Syndrome, Its Components, and Knee Osteoarthritis: The Framingham Osteoarthritis Study. *Arthritis Rheumatol* 2017;69:1194-203.
44. Presle N, Pottie P, Dumond H, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. *Osteoarthritis Cartilage* 2006;14:690-5.

PART III

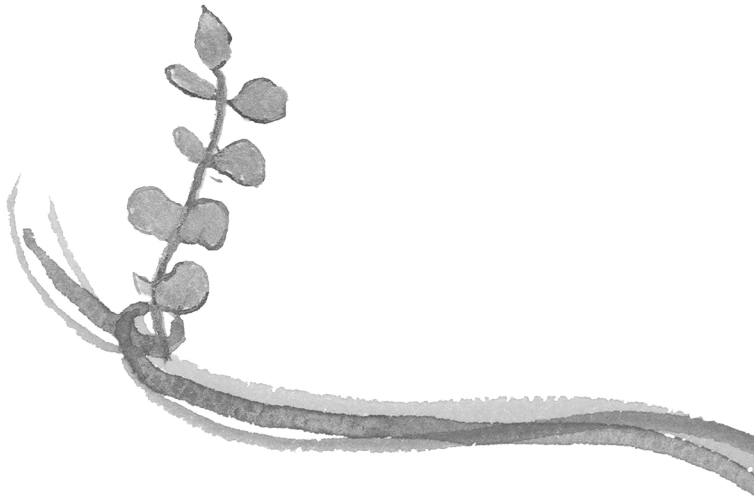
Outcome measurement





CHAPTER 10

Reference curves for the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) in the middle-aged Dutch population



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ABSTRACT

Objective. The aim was to establish reference curves of the Australian/Canadian Hand Osteoarthritis Index (AUSCAN), a widely used questionnaire assessing hand complaints.

Methods. Analyses were performed in a population-based sample, the Netherlands Epidemiology of Obesity study (n=6671, aged 45-65 years). Factors associated with AUSCAN scores were analysed with ordered logistic regression, because AUSCAN data were zero inflated, dividing AUSCAN into three categories (0 vs 1-5 vs >5). Age- and sex-specific reference curves for the AUSCAN (range 0-60; higher is worse) were developed using quantile regression in conjunction with fractional polynomials. Observed scores in relevant subgroups were compared to the reference curves.

Results. The median age was 56 [interquartile range (IQR): 50-61] years; 56% were women and 12% had hand OA according to ACR criteria. AUSCAN scores were low (median 1; IQR: 0-4). Reference curves where higher for women, and increased moderately with age: 95% percentiles for AUSCAN in men and women were, respectively, 5.0 and 12.3 points for a 45-year-old, and 15.2 and 33.6 points for a 65-year-old individual. Additional associated factors included hand OA, inflammatory rheumatic diseases, FM, socio-economic status and BMI. Median AUSCAN pain subscale scores of women with hand OA lay between the 75th and 90th centiles of the general population.

Conclusion. AUSCAN scores in the middle-aged Dutch population were low overall, and higher in women than in men. AUSCAN reference curves could serve as a benchmark in research and clinical practice settings. However, the AUSCAN does not measure hand complaints specific for hand OA.

INTRODUCTION

Hand complaints are frequent in the general population.[1] Hand OA is a common cause of hand complaints such as pain and functional disability.[2] Current treatment strategies for hand OA aim to alleviate symptoms, although their efficacy is limited.[3] Clinical trials aiming for disease modification have been conducted recently, or are still on-going.[3]

Assessment of patient-reported outcomes is important to evaluate treatment. The Australian/Canadian Hand Osteoarthritis Index (AUSCAN) is a widely used instrument, recognized by both Osteoarthritis Research Society International and OMERACT as a valid and reliable outcome in clinical trials for hand OA.[4-6] The interpretation of patient-reported outcomes such as the AUSCAN, however, depends on the availability of benchmarks, such as the patient acceptable symptom state (PASS). Recently, a PASS for the AUSCAN was established in a multinational sample of patients with OA.[7] A disadvantage of the PASS is that it is a cut-off value, which is not adjusted for age and sex. Population-based normative values can also serve as benchmarks. Previously, age- and sex-specific normative values for the AUSCAN were developed in an Australian population-based cohort.[8] Limitations of this study, however, were the limited availability of information on other characteristics of the studied population, and the definition of normative values solely based on descriptive analysis of observed scores.

The objective of this study was to investigate factors associated with AUSCAN scores in the middle-aged Dutch population, such as sex, BMI, socio-economic status and presence of hand OA or other (inflammatory) rheumatic diseases, and to establish reference curves for the AUSCAN taking associated factors in account.

METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort. Detailed information about study design and data collection are described elsewhere.[9] Men and women aged between 45 and 65 years with a self-reported BMI ≥27 kg/m^2 living in the greater area of Leiden (The Netherlands) were eligible to participate, resulting in 5000 participants. Additionally, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited, irrespective of their BMI, resulting in 1671 additional participants and allowing a reference distribution of BMI. The present study is a cross-sectional analysis of baseline measurements of the NEO study. The study was approved by the medical ethics committee of the Leiden University Medical Center, and all participants gave written informed consent. This study did not require additional approval or consent.

Data collection

All participants completed questionnaires on demographic and clinical data and visited the study centre for baseline measurements, including physical examination.

Questionnaires included standardized questions on ethnicity [self-identification in eight categories, which we grouped into white (reference) and other], education [the highest form of education from which the participant had graduated, which we grouped into poorly (none, primary school or lower vocational education; reference) vs highly educated], income (monthly net personal income, divided into seven categories ranging from less than €500 to more than €3000), the presence of self-reported rheumatic diseases (i.e. RA, SLE, gout, FM, PsA and AS) and self-reported hand pain and stiffness on most days of the prior month (present or absent). The AUSCAN was completed on a five-point Likert scale, with a total score ranging from 0 to 60, and scores from the three subscales pain, stiffness and function ranging from 0 to 20, 4 and 36 respectively (higher scores are worse). Physical examination of the hands was performed by trained research nurses, assessing bony and soft swellings, deformities and pain on palpation in the DIP, PIP, MCP and CMC-1 joints. Primary hand OA was defined as fulfilment of the ACR criteria for hand OA, without a concurrent inflammatory rheumatic disease (RA, SLE, gout, PsA or AS).[10] Pre-hand OA was defined as having hand pain and at least two bony swellings or deformities in the DIP, PIP or CMC-1 joints, without being classified as having primary hand OA or reporting an inflammatory rheumatic disease.

Statistical analyses

In the NEO study, there is an oversampling of persons with a BMI ≥27 kg/m^2. To represent distributions and associations in the general population correctly,[11] adjustments for the oversampling of individuals with a BMI ≥27 kg/m^2 were made. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality,[12] whose BMI distribution was similar to that of the general Dutch population.[13] All results were based on weighted analyses, using probability weights in Stata V14 (StataCorp LP, TX, USA). Consequently, results apply to a population-based study without oversampling.

Ordered logistic regression analyses were performed to examine factors associated with increasing AUSCAN scores. For this purpose, three categories of AUSCAN total (0 vs 1-5 vs >5) and each subscale (0 vs 1-2 vs >2 for pain and function, and 0 vs 1 vs >1 for stiffness) were created. Cut-offs for AUSCAN categories were chosen in a way that the upper two categories were approximately equal in size, and that the cut-off values of the subscales added up to the cut-off value of the total score. Ordered logistic regression was chosen, because AUSCAN data were heavily zero-inflated (reflecting absence of hand complaints in most individuals). Participants with missing data of all AUSCAN subscales or physical examination were excluded from these analyses. Analyses were stratified by sex. Associations were expressed as odds ratios (ORs) with 95% CIs, representing the OR of being in the highest compared to the middle or lowest AUSCAN category for a unit change in the determinant.

Age- and sex-specific reference curves were developed for the AUSCAN total and its subscales, except the stiffness subscale, because it is a single question. The curves were developed similar to the approach used for development of short form-36 population norms and children's growth curves, using data from all participants, that is, not excluding those with hand complaints. We applied a commonly used method to derive reference curves, based on fractional polynomials described by Royston and Wright.[14] Since a parametric approach was

not possible in our zero-inflated data, reference curves were derived using quantile regression in conjunction with fractional polynomials. This allows quantiles to be estimated as a smooth function of covariates without imposing parametric distributional assumptions, allowing the construction of reference curves on data that do not meet the assumptions of normality, linearity and constant variance.[15,16] The application of fractional polynomials provides the possibility of accounting for a curved relationship between the independent (i.e. age) and the dependent variable (i.e. AUSCAN score). The 75th, 90th, 95th, 97.5th and 99th centiles were derived. Powers for the fractional polynomial models were taken from a predefined set (S = {-2, -1, -0.5, 0, 0.5, 1, 2, 3}). Simple functions were preferred; more complicated functions were accepted only if the fit was substantially improved. Adjustments for other covariates assessed in the regression analyses were only made if deemed necessary, to improve feasibility in practical application. The goodness of fit of the regression line of the simple function was inspected visually first. If it was judged that the line did not fit the data well, the fit of the regression line of the more complicated function was visually inspected and the deviance of both models was compared [estimated as $n_{obs}{}^{*}log(\sum_{adev}/\sum_{rdev})$, where n_{obs} is the number of observations, $\sum_{adev}$ is the sum of absolute deviations and $\sum_{rdev}$ is the sum of raw deviations]. Only when the fit of the more complicated model was both visually and statistically significantly better ($p<0.05$), was the complex model adopted. The final percentile curves were compared with observed (unweighted) values of the AUSCAN in subgroups hypothesized to have high AUSCAN scores (e.g. individuals with primary hand OA).

Items from the questionnaire driving high scores were explored. Therefore, in the subgroup of participants with high pain or function subscale scores, defined as a score >2 for that subscale, histograms of the proportion of participants that scored positive on each item were made, as well as histograms of the proportion of participants with each possible score (0, 1, 2, 3 or 4) on each item. An item was flagged as a driver of high scores when the proportion of participants with a positive score on that item was higher, or the distribution of the participants' scores within that item was more skewed towards high scores than on the other items.

Data were analysed using Stata V14.

RESULTS

Population characteristics

After exclusion of individuals with missing data on all AUSCAN subscales (n=14) and physical examination (n=14), data from 6643 participants were analysed. Table 1 shows the participants' characteristics. The median [interquartile range (IQR)] age was 56 years (50 to 61), and 56% were women. Primary hand OA was present in 6% of men and 16% of women, and its prevalence increased with increasing age (2.4% in individuals aged 44-48 years, up to 16.3% in the age group 61-66 years). Median AUSCAN scores were low in both men and women, although scores were higher in women and increased slightly with age [median (IQR) 0 (0-2) in the age group 44-48 years, up to 1 (0-6.4) in the age group 61-66 years]. However, even in the highest age category, AUSCAN scores remained low.

Table 1. Characteristics of the study population, stratified by sex.

	Men	Women
Prevalence, %	44	56
Age, median (IQR), years	57 (51-62)	56 (50-61)
Ethnicity, % Caucasian	95.1	94.7
Education, % high	48.1	44.4
Income[a], %		
Less than €500 up to €1500	11.2	52.9
€1500 up to €2500	38.9	27.0
€2500 or more	39.7	5.4
Unknown	10.2	14.7
BMI, median (IQR), kg/m^2	26.4 (24.4-28.7)	25.1 (22.4-28.0)
Fulfilling ACR criteria for hand OA,[b] %	6.3	18.0
Primary hand OA,[c] %	5.5	16.3
Pre-hand OA,[d] %	3.3	7.9
Self-reported inflammatory rheumatic disease, %	4.6	3.9
RA	1.2	2.4
SLE	0.1	0.1
PsA	0.1	0.2
Gout	2.8	1.0
AS	0.4	0.2
Self-reported FM, %	0.3	3.0
AUSCAN total score, median (IQR), range 0-60	0 (0-1)	2 (0-8)
AUSCAN pain subscale, median (IQR), range 0-20	0 (0-0)	0 (0-2)
AUSCAN stiffness subscale, median (IQR), range 0-4	0 (0-0)	0 (0-1)
AUSCAN function subscale, median (IQR), range 0-36	0 (0-0)	1 (0-5)

Results are based on weighted analyses of the study population (n=6643). [a]Net monthly personal income. [b]As defined by Altman *et al.*[10] [c]Defined as fulfilment of the ACR criteria for hand OA, without a concurrent inflammatory rheumatic disease (RA, SLE, gout, PsA, or AS). [d]Defined as the presence of hand pain in combination with at least two bony swellings or deformities in the DIPs, PIPs or first CMC joints, and not being classified as having primary hand OA or reporting a concurrent inflammatory rheumatic disease. AUSCAN, Australian/Canadian Hand Osteoarthritis Index; IQR, interquartile range.

Associations with AUSCAN scores

We assessed associations of factors that were hypothesized to be related with AUSCAN scores in men and women with univariable followed by multivariable ordered logistic regression analyses (table 2). Regression analyses in the three subscales of the AUSCAN yielded similar results (data not shown). Associated factors were age, presence of primary hand OA, presence of self-reported inflammatory rheumatic diseases or FM, pre-hand OA, education (as a proxy for socio-economic status) and BMI. These associations were similar in men and women, although after correction for rheumatic diseases, BMI in men and education in women were no longer associated with AUSCAN.

Reference curves

Age- and sex-specific AUSCAN reference curves and associated percentiles are presented in figures 1A-F and table 3. No additional covariates were deemed essential to be taken into account for development of the curves. Most curves were derived using the simplest fractional polynomial function (i.e. a first degree fractional polynomial, introducing only one power in the function of the regression line), except the 99th percentile of the AUSCAN pain subscale in men, which was fitted with a second-degree fractional polynomial (introducing two powers in the function of the regression line). The function of the regression line for each percentile, an estimation example and a table with regression coefficients can be found in the supplementary data (supplementary data section Regression function of the reference curves and supplementary table S1). Reference curves for women were generally higher than those for men. For instance, the 95% percentiles for AUSCAN in men were 5.0 and 15.2 points for a 45- and a 65-year-old, respectively, whereas for women these were 12.3 and 33.6 points. Although AUSCAN scores increased moderately with age in both sexes, maximum scores were not reached, and the score plateaued at 40.

Subgroup-specific AUSCAN scores relative to reference curves

In figure 2A and 2B, reference curves of AUSCAN pain are plotted over boxplots of observed AUSCAN scores of women with primary hand OA and self-reported FM, respectively. The median AUSCAN pain score of women with primary hand OA lay between the 75th and 90th percentile curves of the general population. Scores of women with self-reported FM were even higher (between the 90th and 95th percentiles). Moreover, AUSCAN pain scores of women with primary hand OA did not seem to increase markedly with age. A similar figure of women with inflammatory rheumatic diseases showed comparable results as the figure with primary hand OA (not shown).

Items driving high AUSCAN scores

In participants with a high pain subscale (>2), especially the items assessing pain during activities (grabbing, lifting, turning and squeezing objects) were scored positive by many (88-96%). For the function subscale, the most important items appraised difficulty with opening jars and grabbing large or heavy objects (94 and 83% scored these items positive), and, to a lesser extent, difficulty in carrying objects with one hand and squeezing a cloth (62 and 63% with positive score). Results for men and women were similar (not shown).

Table 2. Factors associated with AUSCAN total scores, stratified by sex.

	Univariable OLR (OR (95% CI))	
	Men	**Women**
Age, years	1.03 (1.01 to 1.05)	1.07 (1.05 to 1.08)
Education (high vs other)	0.75 (0.61 to 0.93)	0.76 (0.63 to 0.91)
BMI, kg/m^2	1.03 (1.00 to 1.05)	1.04 (1.02 to 1.05)
Primary hand OA	14.11 (9.42 to 21.14)	9.55 (7.09 to 12.87)
Pre-hand OA[a]	9.81 (6.10 to 15.75)	5.51 (3.72 to 8.17)
Inflammatory rheumatic disease[b]	2.44 (1.55 to 3.85)	4.78 (2.95 to 7.74)
FM	246.76 (29.84 to 2040.97)	20.13 (9.73 to 41.64)

Results are based on weighted analyses of the study population. [a]Defined as the presence of hand pain in combination with at least two bony swellings or deformities in the DIPs, PIPs or first CMC joints, and not being classified as having primary hand OA or reporting a concurrent inflammatory rheumatic disease. [b]Including RA, SLE, gout, PsA or AS. AUSCAN, Australian/Canadian Hand Osteoarthritis Index; OLR, ordered logistic regression; OR, odds ratio.

Table 3. Calculated age- and sex-specific percentiles for Australian/Canadian Hand Osteoarthritis Index total, pain and function.

		Men				
Measure	**Age**, years	**75th**	**90th**	**95th**	**97.5th**	**99th**
AUSCAN total	45	0.9	3.4	5.0	11.0	17.9
	50	1.0	3.9	9.6	15.9	22.3
	55	1.1	4.6	11.1	18.1	25.6
	60	1.5	5.7	11.8	19.4	28.4
	65	2.1	7.0	12.3	20.3	30.9
AUSCAN pain	45	0	1.7	5.0	5.0	7.5
	50	0	1.8	5.0	7.4	11.8
	55	0	2.2	5.0	7.8	11.8
	60	0	2.9	5.0	8.0	10.7
	65	0	4.0	5.0	8.0	9.3
AUSCAN function	45	0	1.8	3.0	5.4	10.2
	50	0.1	2.0	5.0	7.6	13.5
	55	0.2	2.3	5.7	9.3	16.0
	60	0.6	3.0	6.0	10.7	18.1
	65	1.1	4.0	6.2	12.0	20.0

Results are based on weighted analyses of the study population.

Multivariable OLR (OR (95% CI))	
Men	**Women**
1.02 (1.00 to 1.04)	1.04 (1.02 to 1.06)
0.79 (0.62 to 1.00)	0.95 (0.77 to 1.17)
0.99 (0.96 to 1.02)	1.01 (1.00 to 1.03)
18.37 (11.94 to 28.27)	12.37 (8.92 to 17.15)
15.39 (9.24 to 25.62)	9.64 (6.28 to 14.81)
3.15 (1.85 to 5.37)	8.78 (5.22 to 14.78)
228.00 (23.64 to 2198.82)	13.67 (6.23 to 30.00)

Women				
75th	**90th**	**95th**	**97.5th**	**99th**
1.9	6.1	15.2	23.4	39.3
5.6	15.1	23.1	32.3	39.8
8.5	20.4	27.8	35.3	40.0
10.9	24.2	31.0	36.8	40.1
13.0	27.1	33.6	37.7	40.1
0	2.0	7.2	8.6	12.2
1.3	6.0	9.6	11.0	13.0
2.5	7.7	10.4	11.8	13.8
3.8	8.8	10.8	12.2	14.7
5.0	9.5	11.1	12.4	15.5
1.3	3.5	7.0	14.0	22.8
3.8	9.0	14.0	19.3	24.4
5.3	12.3	17.1	21.6	25.0
6.4	14.6	18.9	23.0	25.3
7.2	16.4	20.2	24.0	25.4

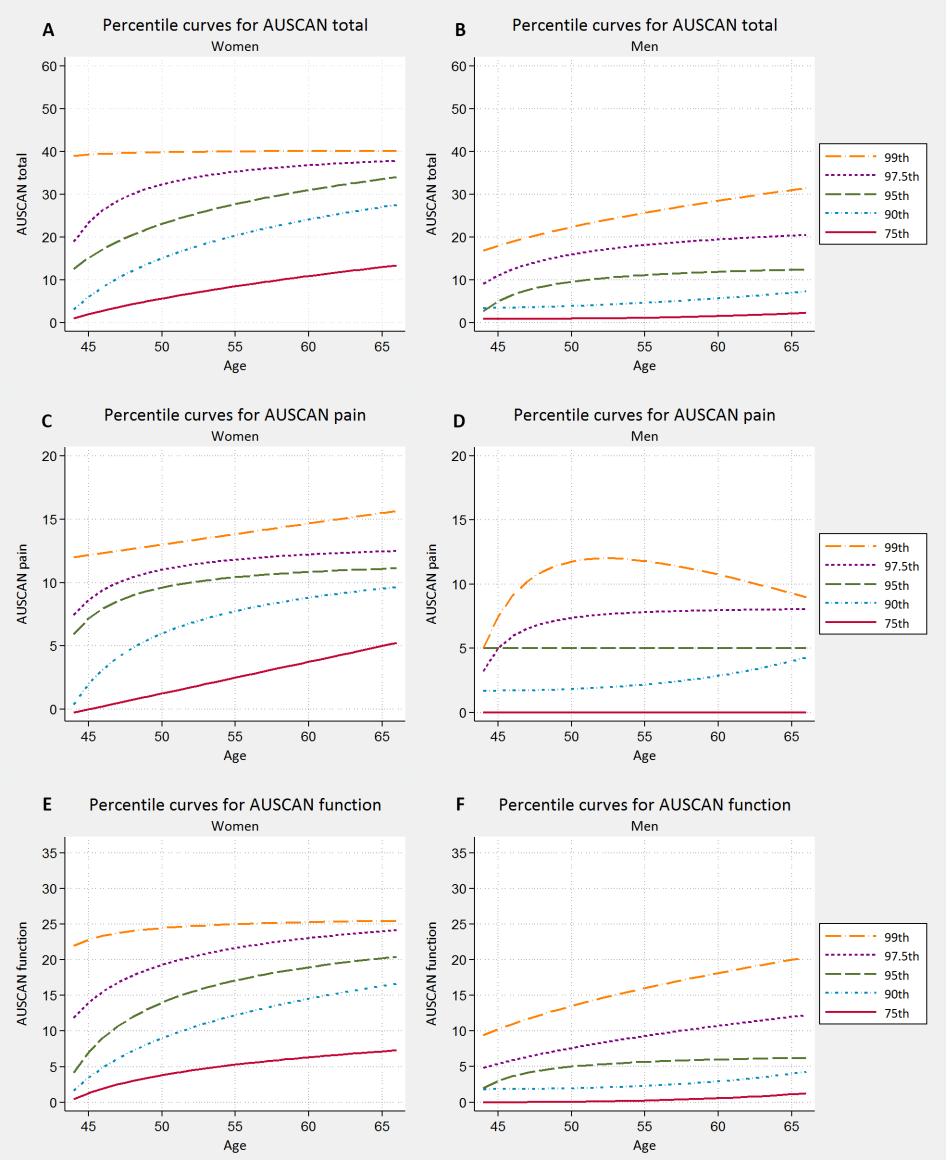


Figure 1. Age- and sex-specific reference curves for AUSCAN total, AUSCAN pain and AUSCAN function in women (A, C, E) and men (B, D, F). AUSCAN, Australian/Canadian Hand Osteoarthritis Index.

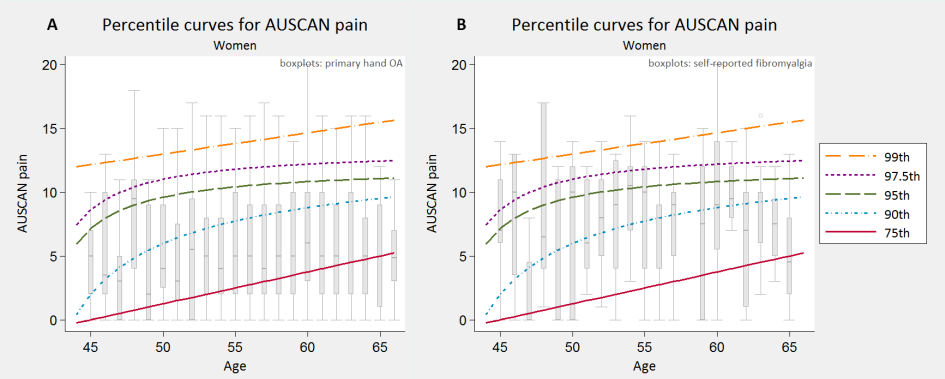


Figure 2. Reference curves for AUSCAN pain plotted over boxplots of the observed (unweighted) values of the AUSCAN scores of women with primary hand OA (A) and self-reported fibromyalgia (B).

Each box represents the interquartile range, with the median represented by a horizontal line within the box. Whiskers represent the smallest and largest value within 1.5 interquartile range, and dots depict outliers. AUSCAN, Australian/Canadian Hand Osteoarthritis Index.

DISCUSSION

In this study, we developed age- and sex-specific reference curves for the AUSCAN in the middle-aged Dutch population. Overall, AUSCAN scores were low, and women reported more hand complaints than men. This gender difference is explained in part by a higher prevalence of hand OA in women. Besides, it is possible that women report hand complaints more readily than men do.[17] Furthermore, many participants had a score of zero, and the percentile curves plateaued at a score of 40 on the AUSCAN total. This might indicate that there is a lack of items assessing mild symptoms or relatively easy tasks. We saw that mainly squeezing and turning motions led to pain and functional limitation, and perhaps other items depart from normal only in extreme situations (e.g. end-stage disease of hand OA).

Previously described normative values in an Australian population-based sample also showed increasing hand complaints with increasing age and similar differences between men and women.[8] However, AUSCAN scores reported in that cohort did not clearly plateau and were higher overall than what we observed. This may be explained by cultural differences, as previous studies have highlighted important differences across countries in the assessment of patient-reported outcomes,[18] or the occurrence of selection bias in the Australian study (i.e. individuals with more complaints might have been more inclined to return the mailed questionnaire). A different percentage of participants with hand OA or other rheumatic diseases could also explain the discrepancies, but this information is not available for the Australian cohort. Moreover, the authors applied different statistical analyses, using empirical centiles based on descriptive analysis to define normative values for different age categories.

Empirical centiles can be biased in small samples, and estimates are known to be inefficient and have large variance.[19] Reference curves for outcome measures are preferably developed using regression models, adjusting for important factors (e.g. age), as has been done for the well-known and extensively used growth curves.[14,20]

An important limitation of our study is the age range of included participants, limiting the age range for which reference curves could be developed. However, the included age range is the most relevant, because it is the time frame in which the prevalence of symptomatic as well as radiological hand OA increases steeply and, as a consequence, it can be expected that the prevalence of hand complaints increases too.[2,21] Besides, we used self-reported data on other rheumatic diseases other than hand OA, without validating these in medical records, although a recent review suggested that the accuracy of self-reported RA is acceptable for large-scale studies.[22] Furthermore, the low prevalence of rheumatic diseases sometimes led to excessively large ORs and corresponding CIs, such as for FM, resulting in an inaccurate estimate of the true size of the association between AUSCAN and these diseases. Finally, a disadvantage of the AUSCAN is that it is not freely available (copyrighted), but nevertheless it was used for this study because it is the most widely used hand-specific questionnaire with evidence of good metric properties.[23]

An important strength of the NEO study is its large sample size and the availability of extensive demographic and clinical data, with few missing data. Another strength of our study was the solid methodology used for the statistical analysis, based on the methodology used for the development of paediatric growth curves by the World Health Organization.[20] Given that a parametric approach was not possible, we adopted a modified approach (i.e. quantile regression in conjunction with fractional polynomials). A similar method was used previously to develop reference curves for radiographic damage in RA patients.[16] Quantile regression is robust and flexible, and an important advantage is that it allows age to remain a continuous variable,[24] which enables the computation of a value for the reference curve for every year of age, and it makes the charts easier to use, because the x-axis is in years rather than in age categories. Drawbacks, however, are that this approach lacks an explicit formula to convert measurements into quantiles and z-scores, and that the produced curves may be irregular near the extremes.[24]

These reference curves can serve as a useful benchmark in hand OA in both research and clinical practice settings. By plotting the AUSCAN score of an individual on the chart, their measurement can be expressed as a centile. These charts can be used to compare AUSCAN scores across different populations (see figure 2), to compare scores of the same population on different occasions or to detect aberrant individual scores.[25] It is also possible to plot a sequence of measurements over time for an individual in the same chart. A person whose individual curve tracks along the same centile over time develops hand complaints expected according to their increase in age. Yet if their individual curve crosses centiles up or down, that person may develop complaints faster or slower than average. One has to be cautious with the latter interpretation, however, because our analyses were performed cross-sectionally and therefore do not contain information on the variability between individuals in the increase in AUSCAN over time.[25] Cross-sectional curves that are interpreted in a longitudinal manner (i.e. following an individual over time) can be especially misleading when the rate of change is high, for example growth during

infancy or puberty, because a mean cross-sectional curve partly smooths out this peak growth.[26] However, the increase of AUSCAN over time is only moderate, and it is unlikely that variations between individuals in slope of AUSCAN over time are pronounced. Therefore, we believe that these reference curves can also be applied in the follow-up of individuals over time, as long as results are interpreted with caution.

The strong associations of AUSCAN with many other factors besides primary hand OA underline the fact that this instrument does not measure hand OA-specific complaints. This should be kept in mind when using the AUSCAN. AUSCAN pain scores of individuals with self-reported FM were even higher than those of participants with primary hand OA. As we also know that FM-like symptoms are prevalent in hand OA patients, this finding stresses the difficulties and complexity in recognizing the origin of complaints in hand OA patients.[27] Furthermore, our study provides more evidence that the burden of disease in patients with hand OA is at least similar to that of RA patients, because both subgroups had equally high AUSCAN scores.[28]

REFERENCES

1. Picavet HSJ, Schouten JSAG. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC3-study. *Pain* 2003;102:167-78.
2. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
3. Kloppenburg M. Hand osteoarthritis--nonpharmacological and pharmacological treatments. *Nat Rev Rheumatol* 2014;10:242-51.
4. Bellamy N, Campbell J, Haraoui B, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthritis Cartilage* 2002;10:863-69.
5. Kloppenburg M, Bøyesen P, Visser W, et al. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies. *J Rheumatol* 2015;42:2190-7.
6. Kloppenburg M, Maheu E, Kraus VB, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015;23:772-86.
7. Bellamy N, Hochberg M, Tubach F, et al. Development of multinational definitions of minimal clinically important improvement and patient acceptable symptomatic state in osteoarthritis. *Arthritis Care Res* 2015;67:972-80.
8. Bellamy N, Wilson C, Hendrikz J. Population-based normative values for the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index: part 2. *Semin Arthritis Rheum* 2011;41:149-56.
9. de Mutsert R, den Heijer M, Rabelink TJ, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol* 2013;28:513-23.
10. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
11. Korn EL, Graubard BL. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health* 1991;33:1166-73.
12. Lumley T. Analysis of complex survey samples. 2004. http://www.jstatsoft.org/v09/i08/paper. (14 March 2016, date last accessed).
13. Ministerie van VWS. Hoeveel mensen hebben overgewicht? 2013. www.rivm.nl/nldemaat.
14. Royston P, Wright EM. A method for estimating age-specific reference intervals ('normal ranges') based on fractional polynomials and exponential transformation. *J R Stat Soc Ser A-G* 1998;161:79-101.
15. Koenker R. Quantile regression. Cambridge: Cambridge University Press, 2005.
16. Lassere M, Houssein D, Scott D, et al. Reference curves of radiographic damage in patients with rheumatoid arthritis: Application of quantile regression and fractional polynomials. *J Rheumatol* 1997;24:1288-94.
17. Paller CJ, Campbell CM, Edwards RR, et al. Sex-based differences in pain perception and treatment. *Pain Med* 2009;10:289-99.
18. Putrik P, Ramiro S, Hifinger M, et al. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. *Ann Rheum Dis* 2016;75:715-20.
19. Wright EM, Royston P. Calculating reference intervals for laboratory measurements. *Stat Methods Med Res* 1999;8:93-112.
20. WHO Multicentre Growth Reference Study Group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization, 2006.
21. van Saase JL, van Romunde LK, Cats A, et al. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-80.
22. Peeters GM, Alshurafa M, Schaap L, et al. Diagnostic accuracy of self-reported arthritis in the general adult population is acceptable. *J Clin Epidemiol* 2015;68:452-59.
23. Visser AW, Bøyesen P, Haugen IK, et al. Instruments measuring pain, physical function, or patient's global assessment in hand osteoarthritis: a systematic literature search. *J Rheumatol* 2015;42:2118-34.
24. van Buuren S. Worm plot to diagnose fit in quantille regression. *Stat Med* 2007;7:363-76
25. van Buuren S. Growth references. In: Klenar C, Savage M, Cowell C, eds. Growth Disorders 2nd Ed. London: Hodder Arnold, 2007:165-81.
26. Cole TJ. The development of growth references and growth charts. *Ann Hum Biol* 2012;39:382-94.
27. Slatkowsky-Christensen B, Mowinckel P, Kvien TK. Health status and perception of pain: a comparative study between female patients with

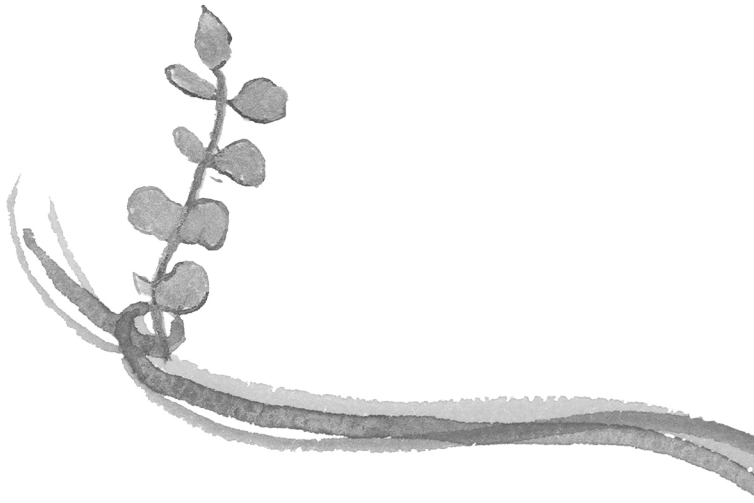
hand osteoarthritis and rheumatoid arthritis. *Scand J Rheumatol* 2009;38:342-48.

28. Slatkowsky-Christensen B, Mowinckel P, Loge JH, et al. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. *Arthritis Rheum* 2007;57:1404-9.



CHAPTER 11

Performance of the Michigan Hand Outcomes Questionnaire in hand osteoarthritis



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ABSTRACT

Objective. To investigate the performance of the Michigan Hand Outcomes Questionnaire (MHQ) in hand osteoarthritis (OA) by evaluating truth, discrimination and feasibility.

Design. Symptomatic hand OA patients from the Hand Osteoarthritis in Secondary Care (HOSTAS) cohort completed questionnaires (demographics, MHQ, Australian/Canadian Hand Osteoarthritis Index [AUSCAN], Functional Index for Hand Osteoarthritis [FIHOA] and visual analogue scale [VAS] pain) at baseline (n=383), 1- and 2-year follow-up (n=312, n=293). Anchor questions at follow-up assessed whether pain/function levels were (un)acceptable and had changed compared to baseline. Correlations between MHQ and other pain/function questionnaires were calculated. Validity of unique MHQ domains (work performance, aesthetics, satisfaction), discrimination across disease stages, and responsiveness were assessed by categorizing patients by external anchors (employment, joint deformities, erosions, and anchor questions). Between-group differences were assessed with linear regression, probability plots and comparison of medians.

Results. MHQ pain and function subscales correlated moderately-to-good with other instruments (r_s 0.63-0.81). Work performance scores were worse in patients with reduced working capacity than in employed patients. Aesthetics scores were worse in patients with more deformities. Patients with unacceptable complaints had worse satisfaction scores. All pain/function instruments discriminated between patients with acceptable vs unacceptable pain/function, while only MHQ activities of daily living (ADL), FIHOA, and MHQ aesthetics could discriminate between erosive and non-erosive disease. MHQ and AUSCAN were most responsive.

Conclusions. MHQ has several unique aspects and advantages justifying its use in hand OA, including the unique assessment of work performance, aesthetics, and satisfaction. However, MHQ, AUSCAN and FIHOA appear to measure different aspects of pain and function.

INTRODUCTION

Hand osteoarthritis (OA) is a common disease with steeply increasing prevalence after the age of 50.[1] Patients experience various symptoms, including hand pain, functional limitations, and decreased quality of life.[2] Besides, many patients report dissatisfaction with their hands' appearance.[3-5] Since hand function is essential in many occupational activities, work productivity is likely also affected, though research in that area is scarce for hand OA.[6]

To measure burden of disease and effectiveness of therapeutic interventions, good outcome measures are essential. A recent systematic review showed that the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) and Functional Index for Hand Osteoarthritis (FIHOA) are among the most frequently used instruments to measure pain and function in hand OA.[7] However, these questionnaires have some disadvantages: the AUSCAN is not freely available in the public domain, and the FIHOA includes some outdated and culturally challenging questions (e.g., handwriting more than 10 min, men use a screw driver while women sew, accepting a handshake).[8,9] The domain pain is often measured on a visual analogue scale (VAS), yet a single-item tool may not cover all relevant aspects, while a multi-item questionnaire like the AUSCAN pain scale may provide a more in-depth comprehension of pain.

The Michigan Hand Outcomes Questionnaire (MHQ) was specifically developed to measure outcomes of patients with hand disorders by a panel of patients with various hand conditions, hand therapists, and hand surgeons.[10] It consists of six subscales, measuring overall hand function, activities of daily living (ADL), pain, work performance, aesthetics, and satisfaction. Most subscales assess right and left hand separately. Its validity and reliability have been shown in patients undergoing hand surgery,[10] and in rheumatoid arthritis patients.[11,12] The MHQ has only partly been validated in hand OA.[13,14] This study aimed to examine the performance of the MHQ in hand OA by evaluating truth, discrimination and feasibility, guided by the Outcome Measures in Rheumatology (OMERACT) filter.[15,16] The MHQ was also compared to other widely used pain and function questionnaires in hand OA.

METHODS

Study design and population

Analyses were performed in the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort including patients diagnosed with primary hand OA by their treating rheumatologist at the Leiden University Medical Center (LUMC) outpatient clinic (for details on recruitment and selection[17]). All participants who completed the MHQ at baseline were included in the present study (n=383). Participants who completed the MHQ at the 1- and 2-year follow-up visit were included in longitudinal analyses (n=312 and n=293). The study was approved by the LUMC medical ethics committee. All participants gave written informed consent.

Data collection

Participants completed standardized questionnaires at baseline, 1- and 2-year follow-up visits. Employment status was assessed in eight categories, which were combined into: employed (fulltime/part-time job), reduced working capacity (sick leave, partial/complete disability to work), currently unemployed, and retired. Answers of participants using the option 'different' were reassigned to one of the other categories. Descriptions recorded most frequently were 'volunteering' (categorized as part-time job) and 'housewife' (categorized as currently unemployed). Participants with reduced working capacity could indicate whether this was due to hand OA or other causes.

The MHQ has six subscales: overall hand function (10 items), ADL (17 items), pain (5 items), work performance (5 items), aesthetics (8 items), and satisfaction (12 items). Items were rated on a 5-point Likert scale. Where applicable, right and left hand scores were averaged. Scores of each subscale were summated and subsequently normalised to 0-100, according to the published manual.[10] For each subscale higher scores are better, except for pain (higher scores indicate more pain).

The AUSCAN was completed on a 5-point Likert scale. Scores from the three subscales pain (5 items), stiffness (1 item) and function (9 items) range from 0 to 20, 4 and 36, respectively (higher is worse).[8] The FIHOA was completed on a 4-point Likert scale (10 items, range 0-30, higher is worse).[9] Self-reported hand pain was recorded on a 100 mm VAS.

Additionally, anchor questionnaires for pain and function were collected after 1- and 2-year follow-up in a random patient subgroup. Patients indicated whether their complaints of hand OA were acceptable or unacceptable at this moment (1-year follow-up n=95 [pain] and n=94 [function], 2-year follow-up n=142 [pain] and n=142 [function]), and whether their complaints were worse, unchanged, or improved compared to baseline (1-year follow-up n=114 [pain] and n=115 [function], 2-year follow-up n=164 [pain] and n=165 [function]).

Participants underwent standardized physical examination by trained research nurses at baseline and after 2-year follow-up. The number of hand joints with deformities was assessed in distal and proximal interphalangeal (DIP/PIP), IP-1, first metacarpal, and first carpometacarpal joints (range 0-22). Deformity was defined as >15° lateral deviation from the midline or squaring of the first carpometacarpal joint. Grip strength was measured with a hydraulic hand dynamometer (Saehan Corporation, Masan, South-Korea), and the average of two hands was calculated.

Hand radiographs were obtained at baseline and after 2-year follow-up. Osteophytes were assessed according to the Osteoarthritis Research Society International atlas, and summed to obtain a total score (range 0-58).[18] Presence of erosive disease was scored using the Verbruggen-Veys scoring system, defined as at least one joint in the erosive or remodelling (E/R) phase.[19] Radiographs were scored paired, in known time-order, by a well-trained reader (WD).[20]

Statistical analyses

Assessment of the MHQ was guided by the OMERACT filter, evaluating truth ('Does the MHQ measure what it intends to measure?'), discrimination ('Can the MHQ discriminate across disease stages?' and 'Can the MHQ identify change over time?' [further referred to as responsiveness]), and feasibility.[15,16]

Presence of floor/ceiling effects was explored by calculating the percentage of participants with the lowest/highest possible score at baseline for each questionnaire. A floor/ceiling effect was deemed present when ≥15% of participants scored the lowest/highest value.[21]

Truth

Correlation of the MHQ pain and function subscales with other questionnaires hypothesized to measure the same construct was assessed by calculating Spearman rank correlation coefficients (r_s). At least moderate correlation ($r_s \geq 0.50$) was expected between MHQ-pain and AUSCAN-pain and VAS pain, and between MHQ function subscales and AUSCAN-function and FIHOA. To further explore underlying differences, individual items of the questionnaires were compared. Items of function questionnaires were also grouped into those primarily assessing grip strength (e.g., hold heavy object) vs fine motor skills tasks (e.g., button shirt). Correlations between the four function scales, and grip strength and radiographic damage were tested, and hypothesized to be weak (r_s=0.30-0.50).

Validity of domains not captured in other questionnaires was assessed using external anchors to categorize patients. The work performance subscale was evaluated by comparing scores of participants with a different employment status (employed vs reduced working capacity), and between participants indicating hand OA or other circumstances as the cause of reduced working capacity. MHQ-aesthetics scores were compared between patients with <3, 3-5 and >5 joints with deformities (cut-offs based on tertiles). Scores on the satisfaction subscale at the 1- and 2-year visit were compared cross-sectionally between patients who indicated their complaints to be 'acceptable' vs 'unacceptable' at the same visit. Between-group differences were visualised on cumulative probability plots, in which individual MHQ scores of each patient are plotted in a cumulative order, presenting the cumulative probability per subgroup.[22] Mean between-group differences were calculated with linear regression (independent variable: patient category, dependent variable: MHQ subscale). Patients who were employed, with less deformities, and indicating to have 'acceptable' complaints were hypothesized to have higher scores on the corresponding MHQ subscale compared to the other categories.

Discrimination across disease stages

MHQ scores were compared across subgroups of participants in different disease stages. First, patients with erosive vs non-erosive disease. Since erosive OA is generally viewed as a more severe form of hand OA, scores on all outcome measures were expected to be worse in this group. Second, patients with 'acceptable' vs 'unacceptable' complaints at the 1- and 2-year follow-up visit. MHQ, AUSCAN, FIHOA, and VAS scores at the same follow-up visit were compared cross-sectionally between the groups in cumulative probability plots, and by comparing median scores (Mann-Whitney test).

Responsiveness
Data after 1-year and 2-year follow-up were used to assess responsiveness. Participants were divided into subgroups reporting worse vs stable/improved complaints after 1- and 2-year follow-up compared to baseline. Between-group differences in the change scores (follow-up minus baseline) of MHQ-pain and function subscales, AUSCAN-pain and -function, FIHOA, and VAS pain were compared as before (cumulative probability plots and medians).

Feasibility
To investigate feasibility, the MHQ was compared to other instruments with regard to costs, length of the questionnaire, number of missing items, and interpretability of the scores. Lower costs, lower number of (missing) items, and easily interpretable scores were viewed as advantages of a questionnaire.

Data were analysed using Stata V14, StataCorp LP, Texas.

RESULTS

Of 383 participants, 84% were women, with a median age of 60.3 years, and 90% fulfilled American College of Rheumatology (ACR) hand OA criteria (table 1).[23] At baseline, participants had moderate pain and functional impairment as measured on the different questionnaires. The majority was employed (table 1).

Of the six MHQ subscales, scores on the scales of satisfaction, overall hand function and pain were the worst, while scales of work performance, ADL, and aesthetics were less affected. MHQ scores were evidently worse compared to a healthy population.[24] At baseline, the interquartile range (IQR) of the scores on the MHQ function subscales represented only 17.5% (overall hand function) and 21.4% (ADL) of the maximum possible score, while the IQR of the FIHOA and AUSCAN-function represented 9 (30%) and 12 points (33%) of the maximum possible score, respectively. In contrast, the spread of the IQR of the scores on the different pain questionnaires was comparable. A ceiling effect was present for MHQ subscales work performance and aesthetics, but not for the other questionnaires. There were no floor effects (supplementary table 1).

Assessment of truth of MHQ pain and function domains

Correlations between MHQ-pain and other pain instruments were moderate (table 2). MHQ function subscales overall hand function and ADL both correlated moderately with AUSCAN-function and FIHOA, though correlations with MHQ-ADL were consistently better than with the overall hand function subscale (table 2). Correlations of MHQ function subscales with grip strength and radiographic damage were weak as expected (table 2). AUSCAN-function and FIHOA correlated similarly to these domains (r_s=-0.43/0.28 [grip strength/radiographic damage], and r_s=-0.39/r_s=0.27, respectively).

Table 1. Characteristics of study population at baseline (n=383), 1-year follow-up (n=312), and 2-year follow-up (n=293).

	Baseline		
Women, n (%)	321 (84)		
Age, years	60.3 (55.1-66.6)		
BMI, kg/m^2	26.6 (24.1-30.3)		
Employment status, n (%)			
Contributing to workforce	228 (60)		
Fulltime/part-time employed	179 (79)		
Reduced working capacity	49 (21)		
Due to hand OA	21 (43)		
Due to other causes	22 (45)		
Cause unknown	6 (12)		
Not contributing to workforce	155 (40)		
No job	40 (26)		
Retired	115 (74)		
Fulfilling ACR criteria, n (%)	343 (90)		
Erosive OA*, n (%)	112 (29)		
OARSI osteophyte score, 0-58	5 (12-19)		
Joints with deformity, 0-22	3 (1-6)		
Grip strength, kg	17.5 (22.3-28)		
	Baseline	**1 year**	**2 years**
AUSCAN			
Pain, 0-20	10 (7-12)	9 (6-12)	9 (5-11)
Stiffness, 0-4	2 (1-2)	2 (1-2)	2 (1-2)
Function, 0-36	16 (10-22)	16 (9-22)	16 (9-22)
FIHOA, 0-30	9 (4-13)	9 (4.5-13.5)	10 (5-14)
VAS pain, 0-100	35.5 (19.5-50)	*n/a*	32.5 (16.5-53.5)
MHQ, 0-100			
Overall hand function	57.5 (50-67.5)	57.5 (50-65)	57.5 (47.5-65)
ADL	80.5 (68.2-89.6)	79.9 (66.1-89.1)	77.5 (64.1-87.3)
Work performance	75 (50-95)	75 (55-95)	75 (55-95)
Pain	45 (31.3-60)	42.5 (30-55)	45 (30-55)
Aesthetics	81.3 (68.8-93.8)	84.4 (68.8-93.8)	81.3 (68.8-93.8)
Satisfaction	50 (35.4-66.7)	52.1 (35.4-70.8)	50 (31.3-70.8)

Median (interquartile range) unless otherwise specified. ACR, American College of Rheumatology; ADL, activities of daily living; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; BMI, body mass index; FIHOA, Functional Index of Hand Osteoarthritis; MHQ, Michigan Hand Outcomes Questionnaire; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; VAS, visual analogue scale. *Erosive OA defined as at least one joint in E/R-phase according to Verbruggen-Veys scoring method.

In the FIHOA 4/10 questions assessed fine motor skills, and one assessed grip strength. Yet in the AUSCAN function more items evaluating grip strength (4/9) and less evaluating fine motor skills were present (2/9). The MHQ-ADL had 4/12 questions on grip strength and 3/12 on fine motor skills (supplementary table 2). The item "opening a jar", assessed in AUSCAN-function and MHQ-ADL, was the most often affected. MHQ overall hand function was unlike the other function questionnaires, with more general questions of hand function, movement, strength and sensation.

Table 2. Spearman correlation coefficients between MHQ and other pain/function instruments.

	MHQ pain	MHQ overall hand function	MHQ ADL
AUSCAN pain	-0.70		
VAS pain	-0.66		
AUSCAN function		-0.65	-0.81
FIHOA		-0.63	-0.81
Grip strength		0.39	0.42
Radiographic damage*		-0.25	-0.26

ADL, activities of daily living; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; CMC-1, first carpometacarpal; DIP, distal interphalangeal; FIHOA, Functional Index of Hand Osteoarthritis; IP-1, first interphalangeal; MHQ, Michigan Hand Outcomes Questionnaire; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal; STT, scaphotrapeziotrapezoid; VAS, visual analogue scale. *OARSI osteophyte sum score of DIP 2-5, PIP 2-5, IP-1, CMC-1, and STT joints.

Assessment of truth of unique MHQ domains

Participants with reduced working capacity had worse scores on the MHQ work performance subscale compared to employed participants as shown in figure 1A, with a mean between-group difference of -25.7 (95% confidence interval [CI] -32.8; -18.6). Moreover, participants who indicated that hand OA was the cause of having a reduced working capacity had worse scores on the MHQ work performance scale than those who indicated there to be another cause (figure 1B, mean between-group difference -21.4 [-37.1; -5.8]).

To evaluate the aesthetics subscale, participants were divided into groups with increasing number of hand joints with OA deformities. Although the between-group difference was not large, participants with more deformities scored worse on the aesthetics subscale (figure 1C). Per additional deformity, the aesthetics score decreased with a mean of -1.03 (-1.60; -0.45) points.

The satisfaction subscale was tested using the anchor question of acceptability of the complaints of pain and function to categorize participants. Those who rated their pain at the 2-year follow-up visit as being unacceptable (n=19) had significantly worse scores on the satisfaction subscale at that visit than those who thought their level of pain was acceptable (n=123) (figure 1D), with a mean between-group difference of -27.2 (-37.1; -17.3). A similar result was found for participants rating their function at the 2-year follow-up visit as unacceptable (n=16) vs acceptable (n=126) (mean difference -28.5 [-39.1; -17.8]). Results at 1 year were comparable (data not shown).

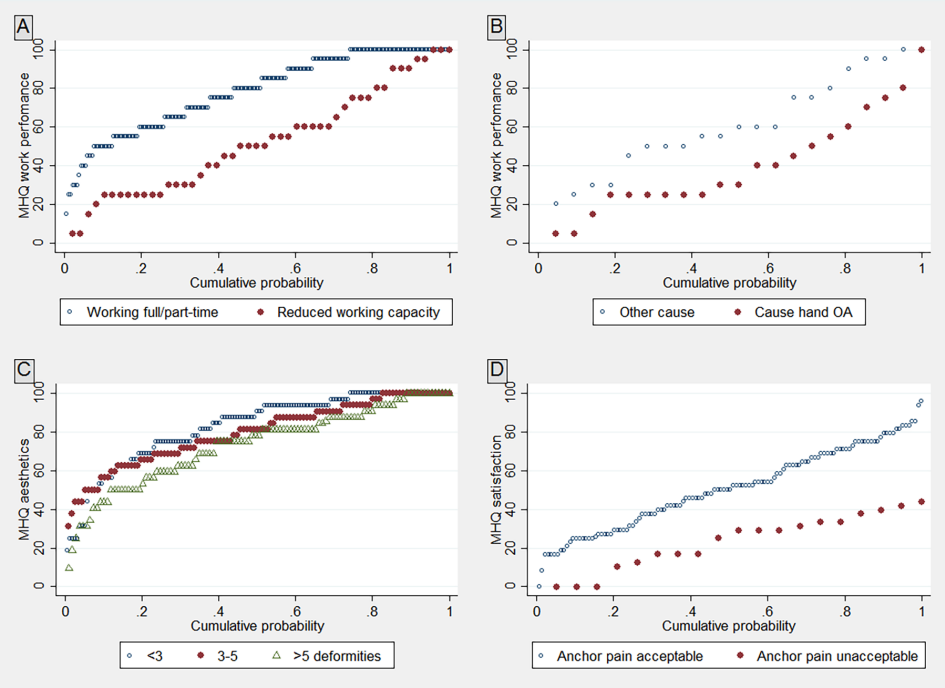


Figure 1. Cumulative probability plots comparing scores of MHQ work performance (A, B), aesthetics (C), and satisfaction (D) subscales across applicable external anchors.

Discrimination across disease stages

The scores of participants with erosive OA were compared to those with non-erosive OA (table 3). Although statistically significant between-group differences were found for MHQ-ADL and FIHOA, differences were small. None of the other function (MHQ overall function, AUSCAN-function) or pain scales (MHQ, AUSCAN or VAS pain) was able to clearly distinguish between the groups. Further exploration of the function questionnaires revealed that scores on the grip strength tasks were not different between patients with erosive and non-erosive OA, while a significant difference was apparent in the fine motor skills tasks. This difference was largest for fine motor skills tasks from MHQ-ADL (median [IQR] 20 [15; 30] vs. 15 [5; 25] for erosive vs. non-erosive OA, p=0.003), though tasks from AUSCAN-function and FIHOA showed the same trend (both $p<0.05$).

MHQ work performance and satisfaction subscales did not differ between those with erosive and non-erosive OA, while the scores on the MHQ aesthetics subscale of participants with erosive OA were evidently lower compared to the reference group (table 3).

Using the questions on acceptability of pain or function levels as the anchor to distinguish groups with more or less severe disease, all instruments that measure pain and function were similarly able to discriminate between those with acceptable vs unacceptable pain or function (table 3). None of the instruments performed better than another.

Responsiveness

To assess responsiveness, the anchor question assessing change in complaints of pain and function was used to divide participants into groups who experienced worse complaints compared to baseline, and those who indicated they remained stable or had improved (table 3). At the 2-year follow-up assessment, n=110 out of 164 who completed the anchor question reported worse pain, while n=54 reported stability (n=41) or improvement (n=9). For function, n=115 out of 165 had worsened, while n=50 stayed stable (n=36) or improved (n=18). Cumulative probability plots provide additional information to better assess differences in responsiveness between the questionnaires, including an assessment of the amount of change, minimum/maximum change scores, proportions of patients with a certain change score, and whether a questionnaire can discriminate over the whole spectrum of change or only in a certain range. The plots showed that both MHQ function subscales and AUSCAN-function could discriminate between these groups, while FIHOA could not (figure 2A, table 3). All pain scales discriminated between the two groups, though MHQ performed best, based on the largest between-group difference (figure 2B, table 3). Change scores in those reporting worse complaints were small for all questionnaires, while change scores in those reporting improvement were generally larger (not shown). Analyses were repeated using one-year follow-up data, achieving similar results (not shown).

Feasibility

Use of the MHQ requires online application for a license, though is free for academic/non-profit use. FIHOA and VAS are also freely available, while the AUSCAN is copyrighted, requiring a paid license to use. The MHQ has the most questions (n=58) and subscales. It is the only questionnaire with separately assessing right and left hand. The MHQ-ADL subscale is the longest function scale (17 items); the length of the others is comparable (MHQ overall hand function 10, FIHOA 10 and AUSCAN-function 9 items). The MHQ- and AUSCAN-pain subscales both contain 5 items, whereas the VAS is a single question. While the MHQ, FIHOA and AUSCAN are standardized questionnaires, wording of the VAS may differ among studies. Number of missing items was low (<1%) and not different for the questionnaires (supplementary table 3). Scores on the MHQ-pain subscale have to be interpreted in the opposite direction as compared to the questionnaire's other subscales, which may negatively impact interpretability.

Table 3. Discrimination across disease stages (baseline scores) and responsiveness (change scores over 2 years) of MHQ and other questionnaires.

I. Discrimination across disease stages			
Domain	**Non-erosive OA (n=268)**	**Erosive OA (n=112)**	**p-value**
Function			
MHQ overall hand function, 0-100	60 (50; 67.5)	56.3 (50; 65)	0.37
MHQ ADL, 0-100	81.3 (69.8; 90.2)	76.8 (64.5; 87.9)	0.04
AUSCAN function, 0-36	15 (10; 21)	17 (10; 22)	0.22
FIHOA, 0-30	8 (4; 12)	10 (5; 14)	0.01
Pain			
MHQ pain, 0-100	45 (30; 60)	47.5 (35; 60)	0.23
AUSCAN pain, 0-20	9 (6; 12)	10 (7; 12.5)	0.11
VAS pain, 0-100	34 (19.5; 49)	38.3 (20.3; 54)	0.05
Additional domains			
MHQ work performance, 0-100*	75 (55; 95)	80 (60; 100)	0.09
MHQ aesthetics, 0-100	87.5 (71.9; 96.9)	75 (59.4; 87.5)	<0.001
MHQ satisfaction, 0-100	52.1 (37.5; 68.8)	50 (33.3; 65.6)	0.21
Function	**Function acceptable (n=126)†**	**Function unacceptable (n=16)†**	
MHQ overall hand function, 0-100	56.3 (47.5-62.5)	42.5 (32.5-47.5)	<0.001
MHQ ADL, 0-100	76.4 (65.3-84.5)	51.1 (45.2-71.0)	<0.001
AUSCAN function, 0-36	16 (10-21)	22.5 (17-25)	0.01
FIHOA, 0-30	10 (6-14)	14.5 (11.5-17)	0.02
Pain	**Pain acceptable (n=123)†**	**Pain unacceptable (n=19)†**	
MHQ pain, 0-100	45 (30-55)	65 (50-75)	<0.001
AUSCAN pain, 0-20	9 (5-11)	14 (11-15)	<0.001
VAS pain, 0-100	33 (16-53)	63 (53.5-72)	<0.001
II. Responsiveness			
Function	**Function worse (n=115)†**	**Function stable/improved (n=50)†**	
MHQ overall hand function, 0-100‡	-5 (-12.5; 5)	1.3 (-2.5; 7.5)	0.001
MHQ ADL, 0-100‡	-4.4 (-11.4; 3.2)	0 (-5.9; 7.3)	0.01
AUSCAN function, 0-36§	1 (-3; 4)	-1 (-5; 2)	0.01
FIHOA, 0-30§	1 (-2; 3)	0 (-2; 2)	0.16
Pain	**Pain worse (n=110)†**	**Pain stable/improved (n=54)†**	
MHQ pain, 0-100§	0 (-10; 15)	-10 (-20; 5)	<0.001
AUSCAN pain, 0-20§	0 (-2; 2)	-1 (-5; 0.5)	0.004
VAS pain, 0-100§	2.5 (-10.5; 14)	-2 (-14; 4)	0.04

Median (interquartile range). P-value for between-group difference, derived from Mann-Whitney test. ADL, activities of daily living; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; FIHOA, Functional Index of Hand Osteoarthritis; MHQ, Michigan Hand Outcomes Questionnaire; OA, osteoarthritis; VAS, visual analogue scale. *Calculated for participants in the workforce at baseline (n=174 with non-erosive OA and n=53 with erosive OA). †Two-year follow-up data. ‡Positive values indicate improvement compared to baseline. §Negative values indicate improvement compared to baseline.

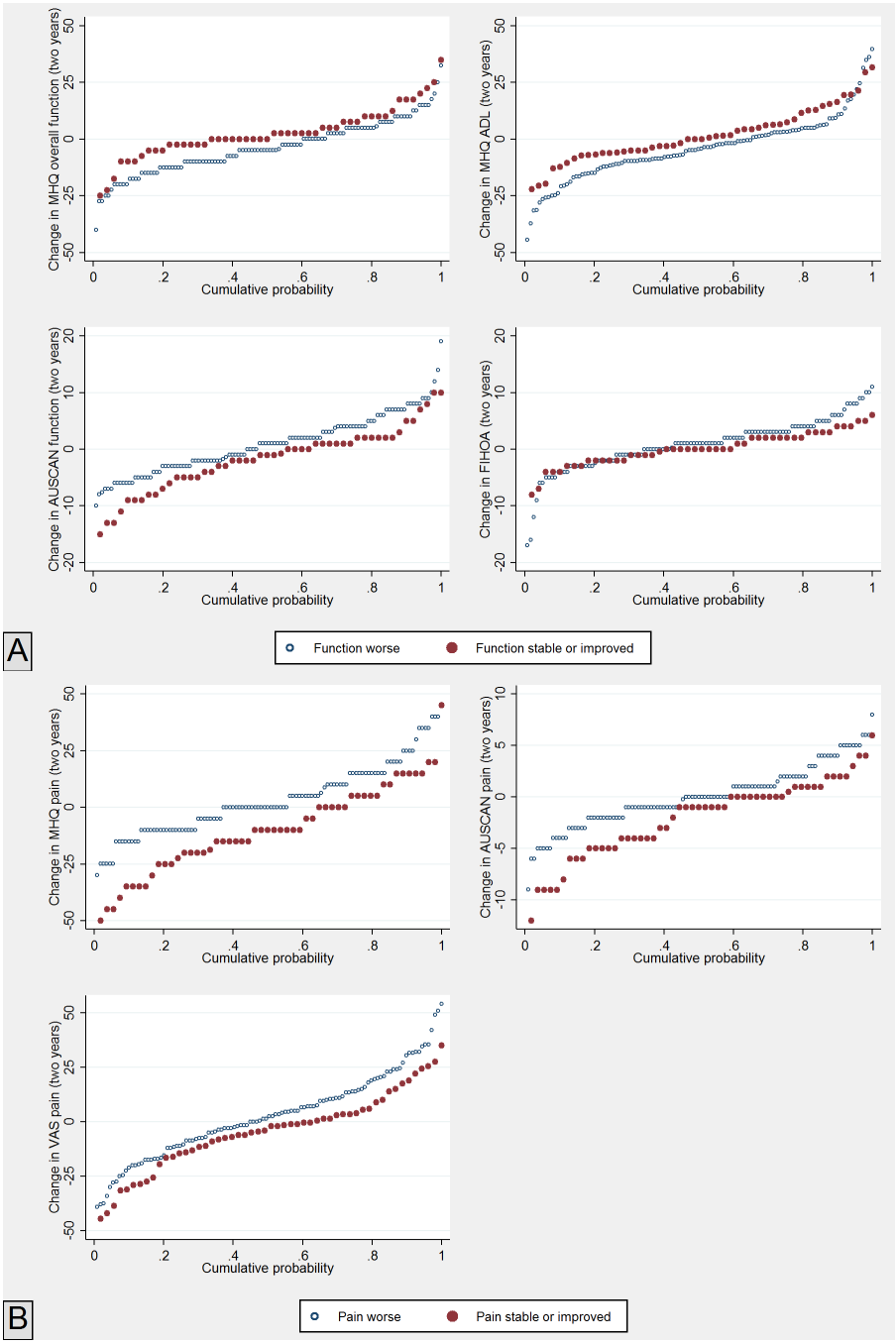


Figure 2. Cumulative probability plots comparing change scores of questionnaires assessing function (A) and pain (B) of patients who stated after 2 years that their complaints had worsened vs stayed stable or improved.

DISCUSSION

We studied performance of the MHQ in hand OA patients regarding the aspects truth, discrimination, and feasibility according to the OMERACT filter.[15,16] The three domains unique for the MHQ (work, aesthetics and satisfaction) were demonstrated to be valid, compared to relevant external anchors. These subscales can provide useful insights in domains that are likely of importance for hand OA patients but currently understudied in absence of valid measurement instruments. Furthermore, MHQ-pain and function subscales measured partly the same, but partly also different aspects of pain and function as other widely used pain and function questionnaires in hand OA (AUSCAN, FIHOA, VAS). Discrimination across disease stages and responsiveness of MHQ was similar to the reference instruments and on some aspects even better. Regarding feasibility, MHQ has the advantage of being freely available and possibility to assess left and right hand separately, though it was the most lengthy (also reflected in previously published longer time to complete[25]) and different direction of effect of different subscales may negatively impact its interpretability.

A core set of domains to be measured in hand OA studies, as well as a preliminary set of instruments to be used, was developed by OMERACT.[26] Before endorsing the MHQ as a core instrument to measure outcomes in hand OA, investigation of its metric properties should be performed.[26] Two previous studies assessed measurement properties of the MHQ in hand OA patients.[13,14] Both concluded it to be valid and reliable, yet neither included specific hand pain questionnaires or the often used AUSCAN as a reference. A small study by Poole *et al* compared several hand function tests, including the Cochin hand function scale, FIHOA, MHQ, and three performance-based instruments, in a sample of 40 volunteers with self-reported hand OA.[13] They found a correlation of -0.86 between the MHQ total score (including all subscales) and the FIHOA, which is higher than the correlation we found between the MHQ function subscales and FIHOA. However, the results are not directly comparable since their study did not look at the MHQ function subscales specifically. A study by Marks *et al* investigated the MHQ in 177 thumb base OA patients receiving conservative or surgical treatment.[14] They assessed correlations between MHQ subscales and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and Short-Form 12, and found lower correlations than we did. Our use of specific hand pain and function (subscales of) questionnaires as a comparator, while Marks *et al* used the more generic (total) DASH, which reflects functioning of the total arm, may explain the difference.

The MHQ was compared to the most often used hand pain and function instruments, but a golden standard is not available. Although the moderate correlations indicate less than perfect concordance between the different questionnaires, one cannot conclude from this which is more truthful.

In-depth comparison of the individual items of the questionnaires revealed that each assessed rather different aspects of pain and function. While the AUSCAN-pain asks about pain severity during rest and several tasks (lifting, squeezing, turning, gripping), the MHQ-pain focusses on the frequency of experiencing pain in several situations (in general, while sleeping, during ADL) and whether it affects the respondent's happiness. The questionnaires

may therefore answer different research questions, and reflect different dimensions of disease impact. Although the MHQ-ADL, AUSCAN-function and FIHOA appeared to be more alike at first glance, all assessing the ability to perform certain tasks with one's hands, the type of tasks that were assessed differed. In accordance with a previous study, we found that fine motor skills tasks were only affected in more severe disease stages.[27] Furthermore, in agreement with previous studies, we found that "opening a jar" (assessed in AUSCAN and MHQ, but not FIHOA) was the most often affected item.[27,28] Since the different function questionnaires place more or less emphasis on certain types of tasks (e.g., grip strength or fine motor skills) by including relatively more or less items assessing it, the selection of a function questionnaire should also depend on the targeted population.

Another difference between the studied questionnaires, was the use of different recall periods, ranging from none specified (FIHOA) to 48 h (AUSCAN) or a week (MHQ). This may also explain the moderate correlations. While it is undoubtedly better to define a time period, shorter and longer time periods both have their advantages. A shorter time period reduces the amount of recall bias, yet may be more subject to fluctuations in symptom severity due to short term circumstances like daily activities or work.

In this study, correlations between self-reported pain and function on the one side, and hand strength or radiographic damage on the other, were only weak. The limited association between clinical symptoms and radiographic damage is known from many previous studies.[29] In this respect, the MHQ was comparable to other pain and function questionnaires for hand OA.

While discrimination between patients who indicated their complaints to be acceptable or non-acceptable was clear for all questionnaires, discrimination between erosive and non-erosive disease was not. Only MHQ-ADL, FIHOA, and MHQ-aesthetics were able to detect a difference between these two groups, though differences on the MHQ-ADL and FIHOA were small. It is possible that inclusion of relatively more fine motor skills tasks increased the ability of these questionnaires to discriminate between these hand OA subtypes. A previous study comparing clinical signs and symptoms of erosive and non-erosive hand OA patients, generally found larger between-group differences than the current study. This may be due to differences in patient population, as that study assessed patients with polyarticular OA whose hands may not have been primarily affected.[30]

Despite a 2-year follow-up, not much change occurred in this cohort. Since inclusion occurred often after their first visit at our outpatient clinic, patients were likely included at the height of their complaints, resulting in the phenomenon 'regression to the mean'. Nevertheless, in absence of disease-modifying interventions, disease progression will have occurred in a number of patients. These two trends may have balanced each other out, resulting in average little change over time. It also reflects the previously described heterogeneous character of the disease course, for about half of the patients deteriorates, while a quarter improves.[31] Moreover, assessment of pain and function at patient level using questionnaires may not capture changes on joint level. Complaints in one joint may improve, while complaints in another joint may arise or worsen, so on patient level we measure no change over time. Nevertheless, participants who self-reported worse or stable/improved complaints over time were compared to assess responsiveness. In this respect, the MHQ and AUSCAN performed best. However, for all

questionnaires change scores of patients reporting worse complaints were small. This may indicate that these instruments are not so sensitive with regard to worsening. In trial settings though, assessment of improvement is more important. Change scores of those reporting improvement were indeed relatively larger. The instruments may thus be more sensitive to measure improvement, or it could be indicative of a threshold phenomenon (i.e., improvement has to be above a certain threshold before a patient reports to be improved).

Strengths of this study are its large sample size, the inclusion of the most often used hand pain and function instruments in hand OA for comparison, as well as external anchor questions. The most important limitation is the lack of an (effective) treatment group to be able to assess sensitivity-to-change.

In conclusion, this study shows that the MHQ has several advantages that justify its use in future hand OA studies. Most important benefits are the three unique domains, that the questionnaire is free to use, and on some aspects better discriminative abilities than other questionnaires. However, MHQ, AUSCAN and FIHOA do appear to measure different aspects of pain and function, and it cannot be concluded from this study which questionnaire is more valid in the setting of hand OA, which may further depend on the specific study question. Assessment of the MHQ's sensitivity-to-change is warranted, preferably in future (positive) clinical trials.

REFERENCES

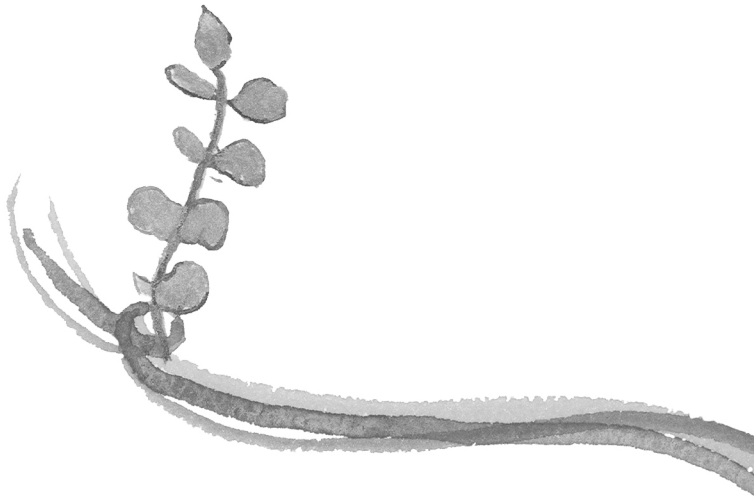
1. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2012;8:22-31.
2. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
3. Hodkinson B, Maheu E, Michon M, et al. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. *Ann Rheum Dis* 2012;71:45-9.
4. Liu R, Damman W, Beaart-van de Voorde L, et al. Aesthetic dissatisfaction in patients with hand osteoarthritis and its impact on daily life. *Scand J Rheumatol* 2016;45:219-23.
5. Neuprez A, Bruyère O, Maheu E, et al. Aesthetic discomfort in hand osteoarthritis: results from the LIège Hand Osteoarthritis Cohort (LIHOC). *Arthritis Res Ther* 2015;17:346.
6. Marks M, Vliet Vlieland T, Audigé L, et al. Healthcare costs and loss of productivity in patients with trapeziometacarpal osteoarthritis. *J Hand Surg Eur Vol* 2015;40:927-34.
7. Visser AW, Bøyesen P, Haugen IK, et al. Instruments measuring pain, physical function, or patient's global assessment in hand osteoarthritis: a systematic literature search. *J Rheumatol* 2015;42:2118-34.
8. Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthritis Cartilage* 2002;10:855-62.
9. Dreiser R, Maheu E, Guillou G, et al. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995;62:43S-53S.
10. Chung K, Pillsbury M, Walters M, et al. Reliability and valdity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg* 1998;23A:575-87.
11. Massy-Westrop N, Krishnan J, Ahern M. Comparing the AUSCAN Osteoarthritis Hand Index, Michigan Hand Outcomes Questionnaire, and Sequential Occupational Dexterity Assessment for patients with rheumatoid arthritis. *J Rheumatol* 2004;31:1996-2001.
12. Waljee J, Chung K, Kim H, et al. Validity and responsiveness of the Michigan Hand Questionnaire in patients with rheumatoid arthritis: a multicenter, international study. *Arthritis Care Res* 2010;62:1569-77.
13. Poole JL, Lucero SL, Mynatt R. Self-reports and performance-based tests of hand function in persons with osteoarthritis. *Phys Occup Ther Geriatr* 2010;28:249-58.
14. Marks M, Audigé L, Herren D, et al. Measurement properties of the German Michigan Hand Outcomes Questionnaire in patients with trapeziometacarpal osteoarthritis. *Arthritis Care Res* 2014;66:245-52.
15. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol* 1998;25:198-9.
16. Boers M, Kirwan JR, Wells G, Beaton D, et al. Developing Core Outcome Measurement Sets for Clinical Trials: OMERACT Filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
17. Damman W, Liu R, Kroon F, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand OSTeoArthritis in Secondary care cohort. *J Rheumatol* 2017;44:1659-66.
18. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15:A1-56.
19. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308-20.
20. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-7.
21. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007;60:34-42.
22. Landewé R, van der Heijde D. Radiographic progression depicted by probability plots: presenting data with optimal use of individual values. *Arthritis Rheum* 2004;50:699-706.
23. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
24. Nolte MT, Shauver MJ, Chung KC. Normative values of the Michigan Hand Outcomes Questionnaire for patients with and without hand conditions. *Plast Reconstr Surg* 2017;140:425e-33e.
25. Poole JL. Measures of Hand Function. Arthritis Hand Function Test (AHFT), Australian Canadian Osteoarthritis Hand Index (AUSCAN), Cochin Hand Function Scale, Functional Index for Hand Osteoarthritis (FIHOA), Grip Ability Test (GAT), Jebsen Hand Function Test (JHFT), and Michigan Hand Outcomes Questionnaire (MHQ). *Arthritis Care Res* 2011;63:S189-99.
26. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of

instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190-7.
27. Haugen IK, Moe RH, Slatkowsky-Christensen B, et al. The AUSCAN subscales, AIMS-2 hand/finger subscale, and FIHOA were not unidimensional scales. *J Clin Epidemiol* 2011;64:1039-46.
28. Kroon F, Ramiro S, Royston P, et al. Reference curves for the Australian/Canadian Hand Osteoarthritis Index in the middle-aged Dutch population. *Rheumatology (Oxford)* 2017;56:745-52.
29. Visser AW, Bøyesen P, Haugen IK, et al. Radiographic scoring methods in hand osteoarthritis - a systematic literature search and descriptive review. *Osteoarthritis Cartilage* 2014;22:1710-23.
30. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. *Ann Rheum Dis* 2010;69:1784-88.
31. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.



CHAPTER 12

Validity, reliability, responsiveness and feasibility of four hand mobility measures in hand osteoarthritis



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ABSTRACT

Objectives. To investigate metric properties of four hand mobility tests in hand OA patients, using the OMERACT filter.

Methods. Trained assessors examined the Hand Mobility in Scleroderma test (HAMIS), fingertip-to-palm distance (FPD), modified Kapandji index (MKI) and number of hand joints with limited mobility in participants from two cohorts [Genetics Arthrosis and Progression (n=207), Hand OSTeoArthritis in Secondary care (n=174)]. Validity was appraised by assessment of correlations with other outcome measures, and ability to measure thumb vs finger mobility specifically, using cumulative probability plots. Proportion of participants changing in hand mobility based on the smallest detectable difference was calculated for responsiveness. Intraclass correlation coefficients (ICCs) for intra- and interobserver reliability, and feasibility (time to perform tests) were studied in a random sample (n=20).

Results. Participants displayed large variation in mobility scores. Strongest correlations were observed with structural damage (r_s=0.43-0.52) and bony swelling (r_s=0.46-0.58); correlation patterns were similar among tests. HAMIS, FPD and MKI could all measure finger mobility specifically, but only HAMIS measured thumb mobility particularly. Interobserver reliability was best for HAMIS, ICC 0.90 (95% CI: 0.76, 0.96); intraobserver reliability was excellent for all (ICCs 0.94-0.97). In 2 years, little change was observed; HAMIS was the most sensitive-to-change (smallest detectable difference 3.7% of maximum score). The mean performance time ranged from 0.7 (SD 0.5, for FPD) to 5.7 (SD 1.3, for HAMIS) min.

Conclusions. HAMIS, FPD, MKI and number of joints with limited mobility are all valid, reliable and feasible measures to assess hand mobility in hand OA, although HAMIS had slightly more favourable properties. Studies assessing sensitivity-to-change in clinical trial setting are warranted.

INTRODUCTION

Hand OA leads to pain, restrictions in daily activity and decreased quality of life.[1] Many patients suffer from decreased range of motion of the fingers and difficulty in making a fist.[2] It was acknowledged by hand OA experts that so-called 'hand mobility' is important for patients, and therefore it was proposed by the OMERACT hand OA working group as a core domain to be assessed in observational studies and trials.[3,4] However, hand mobility is seldom investigated in hand OA studies due to a lack of disease-specific instruments, and it may be perceived as a lengthy examination. Development of a disease-specific instrument for assessing hand mobility was therefore listed on the OMERACT research agenda.[3]

Several instruments for measuring hand mobility were encountered in the literature, including the Hand Mobility in Scleroderma test (HAMIS),[5,6] fingertip-to-palm distance during maximal finger flexion (FPD),[7] and modified Kapandji index (MKI).[8,9] These performance-based tests were all developed and validated in other disease areas, i.e. to assess hand mobility in SSc patients (HAMIS, FPD) or as a tool for assessing the effect of surgical interventions of the hand and wrist (MKI). Previous studies have shown that the HAMIS and FPD are valid and reliable in SSc,[5-7] and the latter has been recommended as an outcome measure in SSc clinical trials.[10] Good reliability and validity of the MKI and HAMIS were demonstrated in RA patients.[8,9,11,12] Poor-to-moderate reliability of the thumb opposition subscore of the MKI was reported in a population with self-reported hand problems.[13]

With respect to hand OA, only one study compared several self-reported and performance-based tests of function, including the HAMIS as a performance-based test.[14] However, the validity and reliability of the FPD and MKI has not been investigated in hand OA before, nor were the tests compared with one another. It is also unclear whether these tests perform differently in patients with predominantly IP compared with CMC OA, although it is not unlikely that IP OA patients experience most limitations in movements of the fingers, whereas the CMC OA patients suffer limited thumb mobility.

Our aim was to investigate the metric properties of these three hand mobility tests, also in comparison with the assessment of hand mobility by a trained research nurse, in patients with symptomatic hand OA, using the OMERACT filter: truth, discrimination and feasibility.[15]

METHODS

Study design and patient population

Analyses were performed in two cohorts. Cross-sectional analyses investigating truth were performed in the Genetics ARthrosis and Progression (GARP) study, consisting of 192 siblings with symptomatic OA at multiple sites in the hands or in two or more of the following sites: hand, knee, hip or spine. Participants with hand OA according to ACR criteria, who completed the 6-year follow-up visit were included in this study (n=207).[16] Discrimination and feasibility were investigated in the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort including consecutive patients from Leiden University Medical Center

outpatient clinic with primary hand OA diagnosed by their treating rheumatologist. Participants fulfilling hand OA ACR criteria who underwent hand mobility evaluation at two visits (baseline, 2-year follow-up) were included in the analysis (n=174). Both studies were approved by the medical ethics committee of the Leiden University Medical Center (Protocol numbers P76/98-16 and P09.004). All participants gave written informed consent. Details on recruitment and selection of both cohorts have been published elsewhere.[17,18]

Hand mobility measures

Hand mobility tests were performed during standardized physical examination by a trained researcher. The HAMIS consists of nine tasks, assessing finger, thumb and wrist mobility [each scored 0 (no impairment) to 3 (cannot perform), maximum score 27 per hand].[5,6] The FPD was obtained by measuring the distance (millimetres) of the second to fifth finger between fingertip and distal palmar crease while making a full fist, and summing the distances (higher scores indicate more limitation).[7] For the MKI, opposition of the thumb and flexion and extension of the fingers was assessed using anatomic landmarks of the hand as references, obtaining a total score by summing the scores of three items (range 0-50 per hand, lower scores indicating more limitation).[8,9] Total scores for each test were calculated as the mean of two hands. Additionally, the HAMIS and MKI were split in separate components assessing finger [HAMIS: finger flexion, extension and abduction (range 0-9); MKI: flexion and extension of second to fifth finger (range 0-40)] and thumb mobility [HAMIS: thumb abduction and pincer grip (range 0-6); MKI: thumb opposition (range 0-10)] specifically. Component scores were calculated by summing relevant subscores. The FPD was not split, since it solely assesses finger flexion. Finally, hand mobility was also assessed during physical examination by trained research nurses, who evaluated the presence of limited mobility while making a fist in the distal and proximal IP joints, IP-1, first MCP joint and CMC-1. The number of joints with limited mobility was summed to reach a total score (range 0-22). A detailed description of the hand mobility measures can be found in the supplementary data.

Furthermore, the number of hand joints with bony swellings (0-30) and deformities (0-22) were measured. Grip strength (kilogram) was measured using a hydraulic hand dynamometer (Saehan Corporation, Masan, South-Korea) and the average of two hands was calculated.

Questionnaires

Patients indicated location of painful or stiff joints on a hand diagram (range 0-30). Subsequently, patients were assigned to one of three groups for pre-specified subgroup analyses: (i) CMC symptoms only; (ii) IP symptoms only; or (iii) symptoms at both sites. Self-reported hand pain and function were assessed with the Australian/Canadian Osteoarthritis Hand Index on a five-point Likert scale (higher scores being worse).[19]

Imaging

On hand radiographs, osteophytes and joint space narrowing were graded 0-3 in DIP, PIP and CMC-1 joints, and 0-1 in IP-1 and scaphotrapezotrapezoidal joints, using the Osteoarthritis Research Society International atlas, and summed to obtain a total OP or joint space narrowing

score (range 0-58).[20] Presence of erosive joints was assessed in DIPs and PIPs according to the Verbruggen-Veys scoring method, defined as a joint in the erosive (E) or remodelling (R) phase.[21] Intra-reader reliability for radiographic scoring was published previously and was good in both studies.[22,23]

MRI of the right DIP and PIP joints was performed in HOSTAS at baseline. Coronal and axial T1-weighted post-contrast images were acquired on an ONI-MSK-Extreme 1.5T extremity MRI unit (GE, WI, USA). Synovitis was graded 0-3 using a modified version of the Oslo hand OA MRI scoring system.[24] Published intra-reader reliability was good.[23] Only MRIs that were performed within 3 weeks of physical examination were used for analyses.

Use of the OMERACT filter to evaluate hand mobility tests

Truth

Correlations of each hand mobility test with other outcome measures were assessed using Spearman correlation coefficients (r_s), as data were not normally distributed. Correlation coefficients of ≤0.30, 0.31-0.50, 0.51-0.70 and >0.71 were considered very weak, weak, moderate and strong, respectively. It was hypothesized that the tests measure at large the same concept, and that the mutual correlation would therefore be at least moderate. A convergent correlation was hypothesized between the tests and structural damage, self-reported hand function and joint activity (measured as synovitis on MRI). Weaker correlations were expected with grip strength and self-reported pain.

Multivariable linear regression analysis was performed to investigate whether hand mobility tests are capable of measuring a unique domain that is not measured by (a combination of) other outcome measures. The assessed domains were structural damage, physical function, grip strength, pain and joint activity.[3] Explained variance was assessed using the coefficient of determination (R^2), which shows how much variation in the dependent variable (hand mobility) is explained by the model. A lower R^2 was interpreted as a lower explained variance, indicating that hand mobility was for a larger part a unique domain. The final model, with the highest R^2, was selected using a manual forward selection approach. Improvement of subsequent models was assessed using the *F*-statistic with $p<0.05$ and a ≥10% change in R^2 defined *a priori* as a meaningful improvement in model fit.

To investigate whether the finger and thumb components of the HAMIS, FPD and MKI measure mobility specifically at those sites, we compared total scores as well as finger- and thumb-subscores amongst patients with CMC or IP symptoms only, and those with symptoms at both sites using cumulative probability plots. In these plots, individual hand mobility (sub)scores of each participant in each subgroup are plotted in a cumulative order (from the lowest value starting at zero, to the highest value ending at 1060%), calculating the cumulative probability per subgroup.

Discrimination

To evaluate intra- and interobserver reliability, a random sample of 20 patients undergoing pre-planned visits for the HOSTAS study were rescored with each method by the same observer (at a later time the same day) and by a different observer, both blinded to the scores of the first assessment. Intraclass correlation coefficients were calculated (average measure, mixed-effect models, absolute agreement), and additionally Bland-Altman plots were drawn.[25]

Responsiveness was assessed using baseline and 2-year follow-up data from HOSTAS. The smallest detectable difference (SDD) of each test was calculated using interobserver reliability data as $\pm 1.96^{*}(SD_{\text{delta status score}} /\sqrt{k})$, with k=2.[25] The proportion of participants whose hand mobility improved, remained stable or worsened was calculated using the SDD as the cut-off.

Feasibility
To investigate feasibility, information was collected in the same sample of 20 on the time it took to complete the tests, and the appliances needed.

Data were analysed using SPSS V23 (Armonk, NY, USA).

RESULTS

Population description

Characteristics of the participants of both cohorts are presented in table 1. Participants displayed large variation in scores, although hand mobility appeared not greatly affected in most patients. Scores were slightly worse in HOSTAS compared to GARP.

Truth

Correlation with other outcome measures
As shown in table 2, analyses in GARP showed that the hand mobility tests correlated well among one another (r_s=0.53-0.73). Correlation coefficients of hand mobility tests with other outcomes were, however, moderate at best. Correlations did not increase when adopting the hand as the unit of analysis (supplementary table 3). The strength of correlations with other outcomes was similar for all tests (see table 2). Structural damage, measured with the Osteoarthritis Research Society International osteophyte score and number of joints with bony swellings, demonstrated the best correlation with the hand mobility tests (r_s= 0.43-0.52 and r_s= 0.46-0.58). Self-reported hand function was weakly correlated with hand mobility (r_s=0.25-0.43), as were grip strength (r_s=0.08-0.33) and pain (r_s=0.25-0.34). Replication of these correlations in HOSTAS produced similar results (see supplementary table 4). Synovitis on MRI, as a measure of joint activity, was only available in HOSTAS, and showed weak to moderate correlations with hand mobility (r_s=0.33-0.55).

Hand mobility as a unique domain
In GARP, the multivariable regression model explained 38-46% of the variance, depending on the mobility test investigated (see supplementary table 5). This means, that the tests measure in part something that is also assessed by (a combination of) other domains, but partly also a unique domain. The domain partially explaining hand mobility scores was structural damage, and a trend for self-reported function was seen, although the latter did not contribute to number of joints with limited mobility. We repeated the regression analysis in participants of the HOSTAS cohort in whom synovitis on MRI (as a measure of joint activity) was available for analysis (n=67). These

analyses resulted in an explained variability of 29-52% with structural damage, grip strength and to a lesser extent self-reported function (HAMIS and MKI) or joint activity (FPD and number of joints with limited mobility) as the contributing domains.

Table 1. Characteristics of included participants of the GARP and HOSTAS study.

	GARP cohort (N=207)	HOSTAS study (N=174)
Female, n(%)	178 (86.0)	144 (82.8)
Age, years	64.2 (59.5-69.1)	60.1 (54.6-65.9)
BMI, kg/m^2	27.0 (24.2-31.3)	26.9 (24.7-29.9)
Dominant hand right, n(%)	157 (75.8)	131 (75.3)
Number of self-reported painful joints, 0-30	8 (3-14)	10 (6-14)
AUSCAN		
Pain subscale, 0-20	8 (5-11)	10 (6.8-12)
Stiffness subscale, 0-4	2 (1-2)	2 (1-2)
Function subscale, 0-36	16 (9-22)	15 (9-21)
Number of joints with bony swelling, 0-30	14 (10-18)	12 (8-15)
Number of joints with deformity, 0-22	1 (0-3)	4 (2-6)
Grip strength, kg	19.5 (14.3-25.3)	23.3 (18.2-28.4)
HAMIS, 0-54	3.5 (2-5.5)	4.5 (3-7)
Finger-palm distance, mm	7 (0-43)	34.5 (7.5-83.8)
Modified Kapandji Index, 0-50	48 (45-49.5)	43 (39-45.6)
Number of joints with limited mobility, 0-22	2 (0-6)	5 (2-10)
OARSI osteophyte score, 0-58	10 (6-16)	11 (5-20)
OARSI JSN score, 0-58	18 (13-24)	8 (3-18.3)
Number of erosive joints, 0-30	0 (0-1)	0 (0-2)
Synovitis score MRI, 0-24[a]	-	5 (2-7)

Median (IQR) unless indicated otherwise. [a]MRI data of the DIPs and PIPs of the right hand performed within 3 weeks of physical examination were available for 67 participants from the HOSTAS study. AUSCAN, Australian/Canadian osteoarthritis hand index; GARP, Genetics ARthrosis and Progression; HAMIS, hand mobility in scleroderma; HOSTAS, Hand OSTeoArthritis in Secondary care; JSN, joint space narrowing; OARSI, Osteoarthritis Research Society International.

Finger and thumb mobility

In GARP, differences in hand mobility scores among the HAMIS, FPD and MKI were investigated across subgroups of participants with CMC symptoms only (n=7), IP symptoms only (n=74) and symptoms at both sites (n=126). Cumulative probability plots show that all (subscores of) tests measuring finger mobility specifically, could discriminate between participants with finger and combined OA vs CMC OA (figure 1A). However, although the HAMIS thumb subscore appeared to be able to discriminate between thumb vs finger complaints, the MKI thumb subscore was not (figure 1B). The suggestion that the thumb subscores of HAMIS and MKI do not measure the same concept, was confirmed by a low correlation between these scores (r_s=-0.27), whereas correlations among the finger tests were moderate to good (r_s=0.68-0.82).

Table 2. Correlations of hand mobility tests with other outcome measures in the GARP study.

	HAMIS	Finger-palm distance	MKI	Number of joints with limited mobility
HAMIS		0.53*	-0.63*	0.66*
Finger-palm distance	0.53*		-0.73*	0.53*
MKI	-0.63*	-0.73*		-0.65*
Number of joints with limited mobility	0.66*	0.53*	-0.65*	
Structural damage				
Total OARSI osteophyte score	0.47*	0.43*	-0.43*	0.52*
Number of bony swellings	0.46*	0.47*	-0.47*	0.58*
Hand function				
AUSCAN function	0.43*	0.25*	-0.32*	0.28*
Hand strength				
Grip strength	-0.33*	-0.16*	0.22*	-0.08
Hand pain				
AUSCAN pain	0.34*	0.25*	-0.28*	0.25*
Joint activity				
Synovitis on MRI[a]	0.47*	0.52*	-0.33*	0.55*

[a]Data from HOSTAS, correlations between MRI of the DIP and PIP joints of the right hand and hand mobility scores of that hand are shown. *Statistically significant ($p<0.05$). AUSCAN, Australian/Canadian osteoarthritis hand index; GARP, Genetics ARthrosis and Progression; HAMIS, hand mobility in scleroderma; HOSTAS, Hand OSTeoArthritis in Secondary care; MKI, modified Kapandji index; OARSI, Osteoarthritis Research Society International.

Discrimination

Reliability

As shown in table 3 the intraobserver reliability was >0.94 for all tests , and interobserver reliability >0.78. Bland-Altman plots (supplementary figures S1 and S2) showed that differences between observers could be quite large for FPD and number of joints with limited mobility. However, no clear systematic bias could be detected, other than a possible trend towards a slightly improved HAMIS and MKI score during the second observation by the same rater, which may indicate a learning curve for patients and/or observers.

The SDD of HAMIS was the lowest [2.0 (3.7% of maximum possible score)], followed by MKI [6.1 (12.1%)], number of joints with limited mobility [7.1 (23.7%)] and FPD [42.5 mm (22.3% of maximum observed score)].

Responsiveness

Change scores after 2 years of follow-up of 174 participants of HOSTAS are presented in table 4. A small increase in radiographic damage was observed, as well as an increase in number of joints with bony swelling. However, most other clinical parameters did not change over time. On average, the four mobility tests also remained stable over time. Using the SDDs as a cut-off, the number of participants with a 'true' change over time was determined, revealing a similar percentage of participants worsening over time according to HAMIS, MKI and FPD (7.5, 8.1 and 8.2%, respectively) and a slightly higher percentage worsening according to the number of joints with limited mobility (14.0%). Using the SDD as a cut-off, 69.0% (HAMIS) to 81.5% (MKI) of participants remained stable over time, and 10.4% (MKI) to 23.5% (HAMIS) improved.

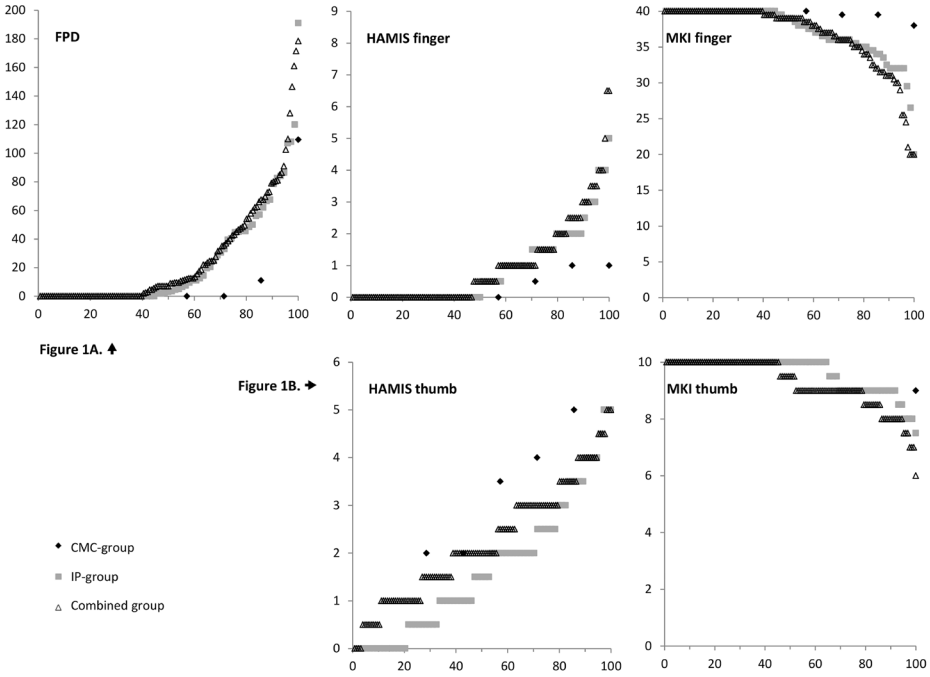


Figure 1. Cumulative probability plots of hand mobility tests in subgroups of hand OA patients.

A. Tests assessing finger mobility. **B**. Tests assessing thumb mobility. Cumulative probability plots, on which scores of each individual are plotted in a cumulative order, comparing hand mobility scores between subgroups with complaints at CMC or IP joints only, and those with complaints at both sites.

Table 3. Reliability and time to perform the hand mobility test in 20 patients of the HOSTAS study.

	Intraobserver reliability[a] ICC (95% CI)	**Interobserver reliability**[b] ICC (95% CI)	**Time in minutes** mean (SD)
HAMIS	0.94 (0.84-0.97)	0.90 (0.76-0.96)	5.7 (1.3)
Finger-palm distance	0.95 (0.87-0.98)	0.79 (0.54-0.91)	0.7 (0.5)
Modified Kapandji Index	0.97 (0.93-0.99)	0.78 (0.52-0.91)	3.1 (0.9)
Number of joints with limited mobility	0.97 (0.93-0.99)	0.81 (0.52-0.93)	1.1 (0.8)

[a]Average of n=2 observers for number of joints with limited mobility, and n=1 observer for the other tests. [b]Calculated for n=2 observers for number of joints with limited mobility, and n=5 observers for the other tests. HAMIS, hand mobility in scleroderma; HOSTAS, Hand OSTeoArthritis in Secondary care; ICC, intraclass correlation coefficient; OARSI, Osteoarthritis Research Society International.

Table 4. Change scores of participants in the HOSTAS study (n=174) after 2 years of follow-up.

	Change score mean difference, 95% CI
Number of self-reported painful joints, 0-30	0.44 (-0.57 to 1.45)
AUSCAN	
Pain subscale, 0-20	-0.60 (-1.14 to -0.06)
Stiffness subscale, 0-4	-0.01 (-0.14 to 0.13)
Function subscale, 0-36	-0.06 (-0.88 to 0.76)
Number of joints with bony swelling, 0-30	1.06 (0.42 to 1.69)
Number of joints with deformity, 0-22	-0.87 (-1.32 to -0.42)
Grip strength, kg	0.37 (-0.57 to 1.30)
HAMIS, 0-54	-0.79 (1.11 to -0.47)
Finger-palm distance, mm	-2.61 (-8.57 to 3.34)
Modified Kapandji index, 0-50	0.79 (-0.03 to 1.62)
Number of joints with limited mobility, 0-22	0.13 (-0.79 to 1.05)
OARSI osteophyte score, 0-58[a]	1.71 (1.28 to 2.13)
OARSI JSN score, 0-58[a]	1.27 (0.74 to 1.79)
Number of erosive joints, 0-30[a]	0.33 (0.18 to 0.47)

[a]Radiographs at two time points available from 79 participants. AUSCAN, Australian/Canadian osteoarthritis hand index; HAMIS, hand mobility in scleroderma; HOSTAS, Hand OSTeoArthritis in Secondary care; JSN, joint space narrowing; OARSI, Osteoarthritis Research Society International.

Feasibility

The time to perform each hand mobility test is shown in table 3. The FPD and number of joints with limited mobility were performed the fastest, that is, in 0.7 and 1.1 min, respectively, with minimal appliances needed (a ruler for the first, and none for the latter). Performance of the MKI and HAMIS, consisting of five and nine items per hand, respectively, took longer, although the time per task was similar for these two tests (both mean 0.6 min). The appliances needed to perform HAMIS was the most extensive (n=6, including five custom-made cylinders of different diameters to ensure consistency).

DISCUSSION

In this study, we examined the metric properties of four hand mobility tests, using the OMERACT filter. All tests showed good reliability and feasibility, similar convergent correlations with other outcome measures and appeared to measure in part a unique domain not explained by (a combination of) other outcome domains. The latter endorses the usefulness of measuring hand mobility as a separate outcome, as proposed by the OMERACT hand OA working group.[3] In general, the tests all seem to measure approximately the same concept. However, although HAMIS, FPD and MKI were all able to specifically measure finger mobility, only HAMIS could distinguish between patients with and without reduced thumb

mobility. Since thumb involvement is prevalent in hand OA, this is an important strength of the HAMIS.[26] While the MKI also includes a subscore for the thumb, it did not distinguish CMC from IP OA patients. Notably, MKI and HAMIS assess different thumb movements: HAMIS measures thumb abduction and pincer grip, whereas MKI measures thumb opposition. It could be hypothesized that the first two movements are more impaired in thumb base OA than the latter, explaining the observed difference between the tests, although data supporting this hypothesis is scarce.

We observed only a small proportion of patients with a deterioration in hand mobility over 2 years, despite, for example, radiographic progression, and some even showed improved mobility. Based on the calculated SDD, HAMIS appeared the most responsive. The low observed rate of progression in hand mobility could mean that the tests are not sensitive enough to measure change over time, which would make the tests less useful for longitudinal studies. Another possibility is that changes in hand mobility do not occur within a 2-year timeframe, which would suggest that this outcome is not useful to assess in (usually short-term) clinical trials. It may also reflect that hand OA is a heterogeneous disease, with some progressing, but others experiencing a more stable disease course. The lack of a gold standard for measuring hand mobility makes it difficult to distinguish these possible explanations. Moreover, our analyses were performed in a prospective cohort study, in which no intervention was administered to the patients besides usual care. Therefore, regression to the mean may explain why some patients showed an improvement in hand mobility, since patients' inclusion usually occurred at time of diagnosis at the rheumatologist, causing patients to be included often at the peak of their complaints. Other explanations for the relatively high number of patients showing improved hand mobility may be the disease course under usual care (e.g. less joint activity over time, or adjustment of ligaments and other joint structures to structural changes). Unlike radiographic damage, hand mobility may not only deteriorate over time. Future studies assessing responsiveness of these tests, including an assessment of sensitivity-to-change, are warranted and should ideally be performed in clinical trial settings.[27]

The assessment of hand joint mobility by a trained research nurse, as investigated in this study, is not a previously published test, but is based on routine clinical physical examination. Our data suggest, that this assessment is not superior to the other three methods regarding any of the assessed metric properties, although it did also not perform substantially worse. Our data do not provide a reason to advocate the use of this assessment of hand mobility over one of the other three tests in research settings. However, as this test is less easy to standardise, we prefer the other three published tests.

To our knowledge, this is the first study comparing different hand mobility tests in hand OA patients. One previous study compared several self-reported and performance-based hand function tests in hand OA patients, including the finger extension, and thumb and finger abduction items of the HAMIS as one of the performance-based tests.[14] That study reported mild joint limitations, as in our study, but found a slightly higher correlation with self-reported function ($r \approx 0.50$), although this discrepancy may be explained by the restriction of their analyses to thumb and finger movements. Bijsterbosch *et al* compared the FPD and HAMIS in patients with and without erosive hand OA, reporting more limitations in patients with erosive disease.[28]

Strengths of this study are the performance of multiple hand mobility tests in two relatively large cohorts, in which many other clinical and radiological data were available, allowing an extensive comparison of metric properties among these tests, using OMERACT methodology. Although the cohorts included two clinically distinct hand OA populations, which is reflected by the differences in baseline characteristics, we observed similar results, adding to the validity of these findings. However, some limitations have to be acknowledged. Measurement of range of motion using a goniometer is also regularly performed to estimate joint mobility, but we did not assess this. It is, however, time-consuming, and reported reproducibility is variable.[29] The hand functional index (HFI) is another test of joint mobility, consisting of nine items from the more widely known Keitel Function Test, which we did not assess.[30] The HFI was developed for RA, although one study looked in hand OA patients and reported a moderate correlation with self-reported function.[14] Since the HFI was used as a template to develop the HAMIS, items from these tests largely overlap, and metric properties in hand OA patients will likely be similar.[6] Another limitation is that the number of participants in the CMC OA subgroup was rather small, and conclusions based on those results should therefore be drawn with caution. Moreover, most participants did not exhibit major limitations in hand mobility, which may very well reflect the average hand OA patient, although ideally to assess metric properties of a test one would like to include patients in all ranges of the scale. Also, the percentage of women in both cohorts was high, and although this reflects a typical cohort of hand OA patients, it precluded a detailed assessment whether our results are generalizable to both sexes. Finally, as outlined above, we were not able to assess sensitivity-to-change after an intervention in our data, and this needs to be done in further studies.

In conclusion, our data suggest that FPD, MKI, HAMIS and the number of joints assessed for the presence of limited mobility are all valid, reliable and feasible measures to assess hand mobility in hand OA patients, although HAMIS had slightly more favourable properties. Future hand OA studies should incorporate hand mobility as an outcome measure, to enhance the knowledge on this outcome in hand OA.

REFERENCES

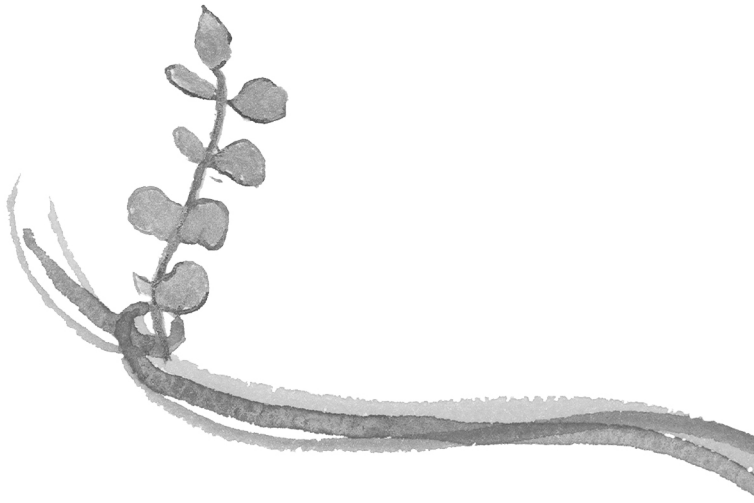
1. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
2. Kjeken I, Dagfinrud H, Slatkowsky-Christensen B, et al. Activity limitations and participation restrictions in women with hand osteoarthritis: patients' descriptions and associations between dimensions of functioning. *Ann Rheum Dis* 2005;64:1633-38.
3. Kloppenburg M, Bøyesen P, Visser W, et al. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190-97.
4. Kloppenburg M, Maheu E, Kraus V, et al. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the OsteoArthritis Research Society International. *Osteoarthritis Cartilage* 2015;23:772-86.
5. Sandqvist G, Eklund M. Validity of HAMIS: a test of hand mobility in scleroderma. *Arthritis Care Res.* 2000;13:382-7.
6. Sandqvist G, Eklund M. Hand Mobility in Scleroderma (HAMIS) test: the reliability of a novel hand function test. *Arthritis Care Res.* 2000;13:369-74.
7. Torok KS, Baker NA, Lucas M, et al. Reliability and validity of the delta finger-to-palm (FTP), a new measure of finger range of motion in systemic sclerosis. *Clin Exp Rheumatol* 2010;28:S28-36.
8. Kapandji A. (Clinical test of apposition and counter-apposition of the thumb). (French). *Ann Chir Main.* 1986;5:67-73.
9. Kapandji A. (Proposal for a clinical score for flexion-extension of the long fingers). (French). *Ann Chir Main.* 1987;6:288-94.
10. Merkel PA, Clements PJ, Reveille JD, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. *J Rheumatol.* 2003;30:1630-47.
11. Lefevre-Colau MM, Poiraudeau S, Oberlin C, et al. Reliability, validity, and responsiveness of the modified Kapandji index for assessment of functional mobility of the rheumatoid hand. *Arch Phys Med Rehabil.* 2003;84:1032-8.
12. Poole JL, Cordova KJ. Can hand assessments designed for persons with scleroderma be valid for persons with rheumatoid arthritis? *J Rheumatol.* 2005;32:2278-80.
13. Myers H, Thomas E, Hay E, et al. Hand assessment in older adults with musculoskeletal hand problems: a reliability study. *BMC Musculoskelet Disord* 2011;12:3.
14. Poole JL, Lucero SL, Mynatt R. Self-reports and performance-based tests of hand function in persons with osteoarthritis. *Phys Occup Ther Geriatr* 2010;28:249-58.
15. Boers M, Kirwan J, Gossec L, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;41:1025-30.
16. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
17. Riyazi N, Meulenbelt I, Kroon HM, et al. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. *Ann Rheum Dis* 2005;64:438-43.
18. Damman W, Liu R, Kroon F, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand OSTeoArthritis in Secondary care cohort. *J Rheumatol* 2017;44:1659-66.
19. Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthritis Cartilage* 2002;10:855-62.
20. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15:A1-56.
21. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39:308-20.
22. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.
23. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-7.
24. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. *Ann Rheum Dis* 2011;70:1033-8.
25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.
26. Dahaghin S, Bierma-Zeinstra S, Ginai A, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:628-7.

27. Boers M, Kirwan JR, Tugwell P, et al. *The OMERACT Handbook*: OMERACT, 2016. https://omeract.org/resources (22 March 2017, date last accessed).
28. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. *Ann Rheum Dis* 2010;69:1784-8.
29. Kooij YE, Fink A, Nijhuis-van der Sanden PT, et al. The reliability and measurement error of protractor-based goniometry of the fingers: A systematic review. *J Hand Ther* 2017;30:457-67.
30. Eberl DR, Fasching V, Rahlfs V, et al. Repeatability and objectivity of various measurements in rheumatoid arthritis: a comparative study. *Arthritis Rheum* 1976;19:1276-86.



CHAPTER 13

Report from the Hand Osteoarthritis Working Group at OMERACT 2018: update on core instrument set development



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ABSTRACT

Objective. To evaluate hand osteoarthritis tools for core instrument set development.

Methods. For OMERACT2018, a systematic literature review and advances in instrument validation were presented.

Results. Visual analog and numerical rating scales were considered valuable for pain and patient's global assessment, despite heterogeneous phrasing and missing psychometric evidence for some aspects. The Modified Intermittent and Constant Osteoarthritis Pain scale was lacking evidence. The Michigan Hand Outcomes Questionnaire had advantages above other pain/function questionnaires. The Hand Mobility in Scleroderma scale was valid, although responsiveness was questioned. Potential joint activity instruments were evaluated.

Conclusion. The development of the core instrument set is progressing, and a research agenda was also developed.

INTRODUCTION

Hand osteoarthritis (OA) is a highly prevalent disorder, causing a considerable burden of disease.[1] Simultaneous involvement of multiple hand joints and presence of different subsets (e.g., nodal, thumb base, and erosive OA) make it difficult to study. To advance our understanding, high-quality studies with optimal outcome measurement are essential.

The Outcome Measures in Rheumatology (OMERACT) Hand OA Working Group (WG), assembled in 2010, endorsed a core domain set for clinical trials of symptom and structure modification and observational studies at OMERACT 2014,[2] which was included in the Osteoarthritis Research Society International recommendations for design and conduct of clinical trials in hand OA.[3] The core domain set includes 6 domains for all settings [pain, physical function, patient's global assessment (PtGA), health-related quality of life (HRQOL), joint activity, and hand strength], and 2 additional domains for trials of structure modification and observational studies (hand mobility and structural damage). HRQOL and hand mobility are not mandatory domains.

A preliminary core instrument set was also proposed including visual analog (VAS) or numerical rating scales (NRS) for pain, Functional Index for Hand OA (FIHOA), tender joint count, and pinch/grip strength.[2] Subsequent goals of the WG were to (1) evaluate relevant instruments according to The OMERACT Handbook,[4] and (2) update the research agenda on the final core instrument set selection.[5] Progress was discussed at OMERACT 2018.

METHODS

Instrument and domain selection

The selection of instruments and domains presented and discussed at OMERACT 2018 were based on the needs addressed in the previous research agenda. Several discussions among members of the hand OA WG were held during the annual meetings of European League Against Rheumatism (2016, 2017) and the American College of Rheumatology (2017) and during a telephone conference organized by the steering committee (April 2017) prior to OMERACT 2018 to guide the program of the special interest group meeting (SIG).

Review of instruments measuring pain and PtGA

A systematic literature review (SLR) was performed (RW, BK, AA) including studies reporting on hand pain and PtGA measured on VAS or NRS in patients with hand OA. A previous SLR on measurement properties of pain and function instruments in hand OA until January 2014 was used as a basis.[6] Relevant manuscripts from that SLR were extracted. Additionally, medical literature databases (Pubmed, Embase, Web of Science, COCHRANE, CINAHL, Academic Search Premier, ScienceDirect) were searched from January 2014 to January 2018 applying similar methodology as the 2014 SLR (see supplementary file). Psychometric features of the scales, such as reliability, responsiveness, construct validity, and clinical trial discrimination, were extracted and evaluated according to The OMERACT

Handbook.[4] These features were discussed at OMERACT 2018 during the SIG meeting that was attended by 24 participants representing clinicians, researchers, patients, and regulatory authorities.

Special attention was given to the phrasing and other details of the VAS/NRS question.

Construct validity of the modified Intermittent and Constant OA Pain (ICOAP; IKH)[7-9] was studied in the Nor-Hand study to investigate whether constant and intermittent pain were separate constructs in hand OA.

Investigation of other potential core instruments

Work was conducted by WG members on the relevant validity and psychometric properties of other tools: (1) properties of the Michigan Hand Outcomes Questionnaire (MHQ; FK)[10,11] were compared to more commonly used hand OA questionnaires, specifically the Australian/Canadian Hand OA Index (AUSCAN) and FIHOA[12,13]; (2) performance of Hand Mobility in Scleroderma (HAMIS) and its responsiveness was compared to other mobility instruments (FK)[14]; (3) assessment of tender joint count to measure joint activity (FK).[15,16]

Research agenda

Guided by discussions prior to and at OMERACT 2018, a research agenda was developed.

RESULTS

Domain pain and PtGA: progress in instrument validation

From the previous SLR, 32 relevant manuscript were selected, providing data on VAS/NRS pain and/or PtGA.[6] Since January 2014, 18 relevant manuscripts were published and could be added (S1-S50, see reference list in supplementary file). Details of all included manuscripts can be found in supplementary table 1. Summary results of the search (supplementary figure 1) and psychometric features of both scales within these domains were discussed by the WG (table 1). VAS range 0-100 mm was the most studied scale (in 26/46 studies for pain and 10/15 studies for PtGA). No study reported test-retest reliability data on the use of either scale in these domains. For pain, good construct validity of VAS was shown (S3,S24,S50), while only limited data were available for NRS (S41). Twenty-two (S1,S2,S4,S6-S13,S15-S18,S21,S22,S26,S37,S38,S42 ,S46) and 8 studies (S15,S25,S28,S33,S34,S41,S45,S47) showed evidence for responsiveness of VAS and NRS, respectively, and 13 (S7-S12,S17,S21,S22,S26,S37,S38,S46) and 6 studies (S14,S28,S33,S34,S41,S47) for clinical trial discrimination for VAS and NRS, respectively.

For PtGA, construct validity was not studied. Evidence to support responsiveness for VAS was available in 10 studies (S3,S6,S12,S13,S15,S18,S22,S29,S38,S40), and 3 studies for NRS (S14,S28,S45) . The capacity to discriminate in clinical trials was shown for VAS PtGA in agreement with the primary outcome in 5 studies (S12,S22,S29,S38,S40), while only 1 study supported this for NRS (S28).

Strikingly, phrasing of the question accompanying VAS/NRS in both domains was very heterogeneous, and details were often not reported. For pain, substantial variety existed in which aspect(s) of pain were assessed (e.g., pain at rest or upon exertion, average or worst pain), location and joint(s) referred to (e.g., target joints, dominant hand, both hands) and time of recall (undefined or ranging from current to 2 weeks; supplementary table 2). Similarly, for PtGA, time of recall was undefined in most studies (3/15 studies did specify; all 48 h; supplementary table 3). After presentation of these findings at OMERACT 2018, the WG proposed that clear standardized phrasing accompanying these instruments should be defined for pain and PtGA. It was proposed that PtGA should assess the effect of the disease on the patient's general well-being. Review of results of previously held focus groups was suggested to analyze what is most relevant to patients.[17]

Results of the validation study of the modified ICOAP were discussed at OMERACT 2018. Detailed results are presented elsewhere.[9] In short, in patients with hand OA, constant and intermittent pain largely overlapped and were not separate constructs, in contrast to the situation in knee and hip OA.[7,8] The existence of separate constructs in hand OA seemed clinically plausible but might be influenced by hand OA location (finger vs thumb base) and involvement of multiple hand joints at different disease stages. It was suggested to seek more patient input, since the development of ICOAP was based on focus group discussions with patients with knee and hip OA, but not hand OA. However, previous focus groups of patients with hand OA have already identified a range of pain concepts, such as fluctuating pain and psychological consequences of pain, which are not represented in the commonly used instruments to assess hand OA.[17]

Based on the available evidence, it was concluded that VAS and NRS are most likely the best instruments to measure pain and PtGA. However, evidence about some essential psychometric properties is missing, in particular regarding reliability, construct validity for NRS pain/PtGA, and clinical trial discrimination for NRS PtGA.

Evaluation of other potential core instruments and research agenda

The results of comparison of MHQ with AUSCAN and FIHOA for measuring domains pain and function were discussed in light of OMERACT Filter 2.1 (table 2).[4,10-13] While displaying similar measurement properties, important advantages of MHQ above other instruments were that it can overcome issues of copyright (AUSCAN) and outdated questions (FIHOA). The possibility to propose more than 1 instrument for a core domain, with the accompanying risk of jeopardizing standardization, was discussed.

Assessment of HAMIS performance in comparison to other mobility instruments was published previously.[14] Though HAMIS appeared the most useful to measure hand mobility compared to other instruments, the WG debated that responsiveness data are weak. Over a 2-year period, limited change over time was observed,[14] either indicating that the domain itself does not change, or that the instrument cannot detect this change.

Table 1. Metric properties of VAS and NRS measuring pain and patient global assessment (PGA): construct validity, reliability, longitudinal construct validity (responsiveness) and clinical trial discrimination.

Domain	Scale	Construct validity	Reliability	Longitudinal construct validity (responsiveness)	
		Studies showing significant correlation with:	No. studies	No. studies showing change	No. studies showing no change, in disagreement with other outcomes
Pain	VAS	AUSCAN pain: r = 0.77-0.81 (S3, S24, S50)	0	22 (S1,S2,S4,S6-S13,S15-S18,S21, S22,S26,S37,S38, S42,S46)*	3 (S31,S39,S44)
	NRS	AUSCAN pain: R^2 = 0.606 (S41) AUSCAN function: R^2 = 0.471 (S41)	0	8 (S15,S25,S28, S33,S34,S41,S45, S47)	0
PGA	VAS	0	0	10 (S3,S6,S12, S13,S15,S18,S22, S29,S38,S40)*	0
	NRS	0	0	3 (S14,S28,S45)	0

*Saviola et al., 2017 (S38): no hard data shown, only described in full text. S(number): refers to the reference in the Supplementary reference list. VAS, visual analog scale; NRS, numeric rating scale; AUSCAN, Australian/Canadian Hand OA Index; r, coefficient of correlation; R^2, correlation.

	Clinical trial discrimination			
Percentage of studies that detected change	No. studies showing discrimination between arms in agreement with primary outcome	No. studies not showing discrimination between arms in agreement with primary outcome	No. studies showing discrimination between arms in disagreement with primary outcome	No. studies not showing discrimination between arms in disagreement with primary outcome
88	13 (S7-S12,S17, S21,S22,S26, S37,S38,S46)	6 (S1,S5,S6, S23,S32,S44)	2 (S13,S42)	7 (S15,S19,S30, S39,S43,S48, S49)
100	6 (S14,S28,S33, S34,S41,S47)	0	1 (S16)	1 (S25)
100	5 (S12,S22,S29, S38,S40)	2 (S6,S40)	1 (S15)	0
100	1 (S28)	0	0	1 (S14)

Table 2. Comparison of properties of Michigan Hand Outcomes Questionnaire (MHQ), Australian/Canadian Hand Osteoarthritis Index (AUSCAN), and Functional Index for Hand Osteoarthritis (FIHOA).

Variables	MHQ[10]
Domain: Pain	
No. items	5
Floor and ceiling effects*	No (1.8% with lowest score, 0% with highest score)
Aspect of pain assessed	Frequency of experiencing pain in several situations (in general, during sleep or ADL) and whether it affects the respondent's happiness.
Specific other comments	No
Domain: Function	
No. items	Overall hand function scale: 10; ADL scale: 17
Floor and ceiling effects*	No (subscales overall hand function/ADL: 0%/0% with lowest score, 1.3%/3.1% with highest score)
Aspect of function assessed	Overall hand function scale: general questions of hand function, movement, strength and sensation. ADL scale: ability to perform certain tasks (turning doorknob, picking up coin, holding glass of water, turning key in lock, holding heavy object with one hand, opening jar, buttoning shirt, using cutlery, carrying large and heavy objects, washing dishes, washing hair, tying shoelaces or knots); 4/12 grip strength tasks, 3/12 fine motor skills tasks.
Specific other comments	Separate assessment of left and right hand.
General aspects	
Recall period	1 week
Other available subscales (domain)	Work performance (N/A); aesthetics (structural damage); satisfaction (N/A)
Total no. items	58
Method of scoring	Includes normalizing to 0-100 scale, presented in user manual
Costs	Freely available for academic or non-profit institutions, permission needed before use (online application form)
Available in multiple languages	Yes
Interpretability comments	Pain scale has to be interpreted in opposite direction compared to other subscales

*Data reviewed in HOSTAS cohort (n = 383), Leiden University Medical Center, Leiden, the Netherlands. ADL, activities of daily living; N/A, not available; VAS, visual analog scale.

	AUSCAN[12]	FIHOA[13]
	5	-
	No (1.8% with lowest score, 1.3% with highest score)	-
	Pain severity during rest and several tasks (lifting, squeezing, turning, gripping)	-
	No	-
	9	10
	No (1.8% with lowest score, 0.3% with highest score)	No (4.2% with lowest score, 0% with highest score)
	Ability to perform certain tasks (turning doorknobs, holding heavy object with one hand, buttoning shirt, using cutlery, carrying large and heavy objects, turning taps, fastening jewelry, wringing cloth); 4/9 grip strength tasks, 2/9 fine motor skills tasks.	Ability to perform certain tasks (turning key in lock, holding heavy objects, buttoning shirt, using cutlery, tying shoelaces or knots, cutting with scissors, clenching fist, sewing (women) / using screwdriver (men), writing for a long time, accepting a handshake); 1/10 grip strength tasks, 4/10 fine motor skills tasks.
	No	Some items may be culturally challenging (accepting a handshake), or outdated (writing for more than 10 minutes; women sew and men use a screwdriver)
	48 h	Not specified
	Stiffness (N/A)	N/A
	15	10
	Dependent on version used (Likert scale, VAS), presented in user manual	Simple addition of scores, user guide available online
	Copyrighted, payment of fee and permission needed before use	No
	Yes	Yes
	No	No

Table 3. Future research agenda to promote core instrument set selection for hand OA.

- Definition of standardized phrasing for VAS and NRS pain and PGA
- Assessment of test-retest reliability of VAS and NRS pain and PGA
- Investigation of construct validity for NRS pain and PGA, and discriminative capacity in clinical trials for NRS PGA
- Investigation of validity of combinations of instruments to assess joint activity, including e.g., tender joints, self-reported painful joints, swollen joints, pain while gripping, and inflammatory signs on imaging
- Assessment of reliability of soft tissue joint swelling in hand OA
- Investigation of psychometric properties of grip and pinch strength to measure core domain hand strength
- Review of available instruments to assess health-related quality of life in hand OA, and development of a disease-specific instrument
- Investigation of the metric properties of ultrasound and magnetic resonance imaging
- Investigation of the value of computer tomography

OA, osteoarthritis; VAS, visual analog scale; NRS, numerical rating scale; PtGA, patient's global assessment.

Progress in instrument development for joint activity is published in conference abstracts.[15,16] Lack of a well-accepted definition hampers instrument development for this domain. Potential instruments include ultrasound and magnetic resonance imaging to detect inflammation, palpation to reveal pain, self-reported painful joint count, soft tissue swelling, and pain while gripping. In the WG discussion, it was suggested that some instruments complement each other, and a combination may be useful. Prediction of radiological progression was proposed as an anchor to assess suitable instruments.

Following discussion of these results, an agenda was developed to guide future research (table 3).

DISCUSSION

Progress results were presented and discussed regarding the development of a core instrument set for hand OA. The core instrument set was developed through investigation of the psychometric properties of candidate instruments according to The OMERACT Handbook,[4] assessing construct validity, reliability, responsiveness, and clinical trial discrimination. The results serve as the basis of an updated research agenda.

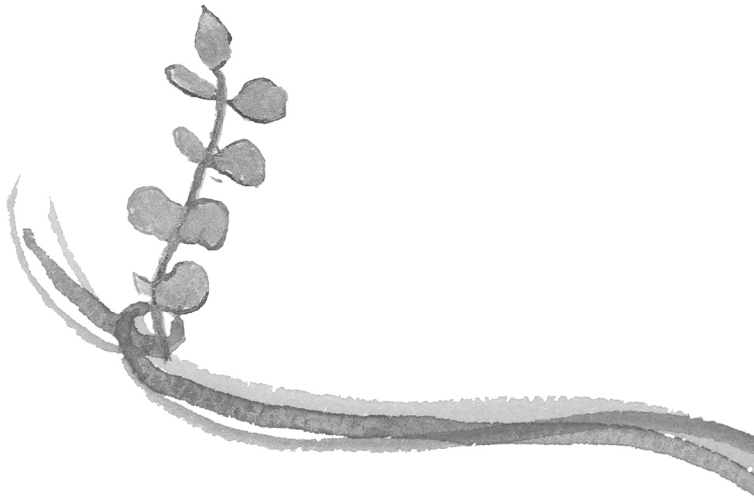
REFERENCES

1. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
2. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190-7.
3. Kloppenburg M, Maheu E, Kraus VB, et al. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015;23:772-86.
4. Boers M, Kirwan JR, Tugwell P, et al. The OMERACT Handbook. [Internet. Accessed May 17, 2017]. Available from: https://omeract.org/resources.
5. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
6. Visser AW, Bøyesen P, Haugen IK, et al. Instruments measuring pain, physical function, or patient's global assessment in hand osteoarthritis: a systematic literature search. *J Rheumatol* 2015;42:2118-34.
7. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure – an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409-14.
8. Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis - an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:415-22.
9. Gløersen M, Steen Pettersen P, Kvien TK, et al. Validation of the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire in patients with hand osteoarthritis. Results from the Nor-Hand study. *J Rheumatol* 2018 [submitted].
10. Chung KC, Pillsbury MS, Walters MR, et al. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg Am* 1998;23:575-87.
11. Kroon FPB, Boersma A, Boonen A, et al. Performance of the Michigan Hand Outcomes Questionnaire in hand osteoarthritis. *Osteoarthritis Cartilage* 2018;26:1627-35.
12. Bellamy N, Campbell J, Haraoui B, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthritis Cartilage* 2002;10:855-62.
13. Dreiser RL, Maheu E, Guillou GB, et al. Validation of an algofunctional index for osteoarthritis of the hand. *Rev Rhum Engl Ed* 1995;62:43S-53S.
14. Kroon FPB, Damman W, Liu R, et al. Validity, reliability, responsiveness and feasibility of four hand mobility measures in hand osteoarthritis. *Rheumatology* 2018;57:525-32.
15. Damman W, Liu R, Kortekaas M, et al. Construct validity of the Doyle Index in the outcome domain of joint activity in hand osteoarthritis patients. *Osteoarthritis Cartilage* 2016;24:S434.
16. Kroon FP, van der Plas JL, van Beest S, et al. Investigation of self-reported painful joint count as an outcome measure in hand osteoarthritis. *Osteoarthritis Cartilage* 2018;26:S213-S4.
17. Stamm T, van der Giesen F, Thorstensson C, et al. Patient perspective of hand osteoarthritis in relation to concepts covered by instruments measuring functioning: a qualitative European multicentre study. *Ann Rheum Dis* 2009;68:1453-60.



CHAPTER 14

Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system.



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ABSTRACT

Objective. To develop the Outcome Measures in Rheumatology (OMERACT) thumb base osteoarthritis (OA) magnetic resonance imaging (MRI) scoring system (TOMS) for assessment of inflammatory and structural abnormalities in this hand OA subset, and test its cross-sectional reliability.

Methods. Included features and their scaling were agreed upon by members of the OMERACT MRI Task Force, using the Hand OA MRI scoring system as a template. A reliability exercise was performed in which 3 readers participated, using a preliminary atlas with examples to facilitate reading. Each reader independently scored a set of 20 MRI (coronal and axial T1- and T2-weighted fat-suppressed images, of which 5 included T1-weighted fat-suppressed post-Gadolinium images). Intra- and interreader reliability were assessed using ICC, percentage exact agreement (PEA), and percentage close agreement (PCA).

Results. The TOMS assessed the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints for synovitis, subchondral bone defects (including erosions, cysts, and bone attrition), osteophytes, cartilage, and bone marrow lesions on a 0-3 scale (normal to severe). Subluxation was evaluated only in the CMC-1 joint (absent/present). Reliability of scoring for both joints was comparable. Inter-reader ICC were good for all features (0.77-0.99 and 0.74-0.96 for CMC-1 and STT joints, respectively). Intrareader reliability analyses gave similar results. PCA was ≥ 65% for all features. PEA was low to moderate, with better performance for subchondral bone defects, subluxation and bone marrow lesions.

Conclusions. A thumb base OA MRI scoring system has been developed. The OMERACT TOMS demonstrated good intrareader and interreader reliability. Longitudinal studies are warranted to investigate reliability of change scores and responsiveness.

INTRODUCTION

Hand osteoarthritis (OA) affects the interphalangeal (IP) joints and the thumb base, including the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints.[1] Thumb base OA may consist of a separate hand OA subset, with distinct risk factors.[1] However, much is unknown about the pathophysiology and disease course of hand OA subsets. New imaging modalities including magnetic resonance imaging (MRI) with visualization of all affected joint compartments may lead to increased insights into this disease.

Previously, the Hand OA MRI scoring system (HOAMRIS) for IP OA was developed with good cross-sectional and moderate longitudinal reliability.[2,3] However, although the thumb base is commonly affected in patients with hand OA,[4] no MRI scoring systems assessing these joints exist to date. MRI studies of the thumb base of patients with hand OA can contribute to the understanding of this disease subset, including its differences from and similarities with IP OA.

The aim was to develop the Outcome Measures in Rheumatology (OMERACT) thumb base OA MRI scoring system (TOMS) for the assessment of inflammatory and structural abnormalities in thumb base OA, and to test its cross-sectional reliability using OMERACT methodology.[5,6]

METHODS

Development of the OMERACT TOMS

Using HOAMRIS as a template, members of the OMERACT MRI Task Force iteratively discussed in several Web-based meetings the joints and features (including definitions and scaling) to be included, as well as a list of preferred sequences and planes, and agreed by consensus.

Table 1 provides an overview of the proposed MRI features. Each feature was evaluated on 0-3 scales in the CMC-1 and STT-joints, except subluxation, which was scored absent/present in the CMC-1 joint only. The proximal and distal joint parts were scored separately for subchondral bone defects, osteophytes, and bone marrow lesions (BML). For CMC-1, the proximal part of the first metacarpal bone (from the articular surface to a 1-cm depth) and distal half of the trapezium were evaluated (range 0-6). For STT, the proximal half of the trapezium and trapezoid and the distal half of the scaphoid were scored (range 0-9). Increments of 0.5 were introduced for synovitis, subchondral bone defects, and BML to increase potential responsiveness of the score.

Reliability exercise

A reliability exercise was conducted by 2 rheumatologists (VF, FG) and 1 radiologist (CP) with extensive experience in assessing hand/wrist MRI. Two readers (VF, FG) repeated the exercise after 1 month, after recoding and rearranging the MRI in a different order. A preliminary atlas with examples of most grades of each feature was developed prior to the exercise, approved by the members of the task force and distributed among readers to facilitate scoring. Each reader scored 20 MRI: 15 MRI were acquired on a 1.5T extremity MRI unit (ONI, GE) in patients

with hand OA from the Hand Osteoarthritis in Secondary Care (HOSTAS) study at Leiden University Medical Center (Leiden, the Netherlands), and 5 MRI were acquired on a 3.0T MRI unit (Philips Ingenia) in patients with hand OA from Sheba Medical Center (Tel Aviv, Israel). MRI were selected by a nonreader to include a wide range of severity of pathology in the thumb base (based on Kellgren-Lawrence arthritis grading scale scores). MRI from HOSTAS included coronal and axial T1-weighted (T1w) fast spin echo (FSE), and T2w FSE images with fat-saturation (fs; Supplementary file 1). MRI from the Sheba Medical Center additionally included coronal and axial T1w-fs post-Gadolinium (Gd) images. A general wrist acquisition was used. Data collection in both centers was approved by the local ethics committee. All HOSTAS participants signed informed consent; written consent was waived for use of MRI from the Sheba Medical Center.

Statistical analysis

Each MRI feature was analyzed separately for the CMC-1 and STT joints. Separate scores for the distal and proximal joint parts were combined into a single sum score per joint where appropriate. Median and interquartile range were calculated for each feature based on the mean value of the 3 readers. Reliability was assessed by calculating ICC, percentage exact agreement (PEA), and percentage close agreement (PCA). Single and average measure ICC (mixed-effect models, absolute agreement) were calculated to assess intrareader and interreader reliability, respectively. ICC values ≤ 0.20 were considered poor, > 0.20 to < 0.40 fair, ≤ 0.40 to < 0.60 moderate, ≤ 0.60 to < 0.80 good, and ≥ 0.80 very good reliability.[7] PEA was defined as a difference of 0 between minimum and maximum scores across readers, and PCA as a difference of ≤ 1 between minimum and maximum scores.

Table 1. Definitions and scaling of features in proposed OMERACT thumb base osteoarthritis MRI scoring system.

MRI feature	Definition	Scaling	Advised plane and MRI sequence
Synovitis*	Thickened synovium with enhancement after Gd injection.	0= normal, 1= mild (1%-33%), 2= moderate (34%-66%), 3= severe (67%-100%). Based on thirds of the presumed maximum thickness of enhancing tissue in the synovial compartment.	Coronal and axial. T1w pre- and post-Gd with fs. In absence of post-Gd images, T2w-fs/STIR/PD-fs can be used.
Subchondral bone defects*†	Subchondral bone loss, including erosions (sharply marginated bone lesions with cortical break), cysts (sharply marginated bone lesions without cortical break), and bone attrition (diffuse loss of bone contour).	0= no bone defects; 1= mild (≤ 25% of bone volume or joint surface affected), 2= moderate (26%-50% of bone volume or joint surface affected), 3= severe (> 50% of bone volume or joint surface affected).	Coronal and axial. T1w and T2w-fs/ STIR/PD-fs.
Osteophytes†	Abnormal bone protuberance at joint margins or surfaces.	0= no osteophytes, 1= mild (1-2 small osteophytes), 2= moderate [≥ 3 small osteophytes and/or ≥ 1 moderate osteophyte(s)], 3= severe [≥ 1 large osteophyte(s)].	Coronal (and sagittal if available). T1w.

Table 1. Continued

MRI feature	Definition	Scaling	Advised plane and MRI sequence
Cartilage assessment	Loss of cartilage, or loss of cartilage space based on the inter-bone distance. (If assessment of cartilage and cartilage space are in conflict, direct visualization of the cartilage should be prioritized)	0= no loss of cartilage or cartilage space, 1= mild (cartilage loss without complete denuding, or cartilage space loss without bone-to-bone contact), 2= moderate (cartilage loss with denuding ≤ 50% of joint surface or focal complete cartilage space loss with bone-to-bone contact ≤ 50% of the articulating area), 3= severe (cartilage loss with denuding > 50% of joint surface or complete cartilage space loss over > 50% of the articulating area).	Coronal. T1w-fs-3D-GE, otherwise use T1w-fs, T2w-fs or PD-fs.
Subluxation‡	Subluxation of the CMC-1 joint in the frontal plane.	0= MC-1 subluxed 0%-25% of the MC width, 1= MC-1 subluxed ≥ 26% of the MC width.	Coronal. T1w.
Bone marrow lesions*†	Lesions within the trabecular bone with signal characteristic consistent with increased water content§ and with ill-defined margins.	0= no bone marrow lesions, 1= mild (1%-33%), 2= moderate (34%-66%), 3= severe (67%-100%). Based on thirds of assessed bone volume.	Coronal and axial. T2w-fs/STIR/PD-fs.

*In longitudinal studies, 0.5 increments may be used for synovitis, subchondral bone defects, and bone marrow lesions. †Proximal and distal parts of a joint are scored separately for subchondral bone defects, osteophytes, and bone marrow lesions. ‡Only the CMC-1 joint is evaluated for this feature. §High signal intensity on STIR/T2w-fs images. CMC-1, first carpometacarpal joint; fs, fat saturated; Gd, gadolinium; GE, gradient echo; MC-1, first metacarpal; PD, proton density; STIR, short-tau inversion recovery; w, weighted.

RESULTS

Supplementary table 1 shows characteristics of the 15 HOSTAS patients. Most MRI features were present in the majority of patients (table 2). STT joint scores were overall lower compared with CMC-1, despite higher possible score range for certain features. Time required to perform TOMS was comparable to that required to score 2 joints with HOAMRIS.

All features demonstrated good to very good interreader ICC values (table 3). PCA was ≥ 65% for all features. PEA was low to moderate, with better performance for subchondral bone defects, subluxation, and BML. Similar results were found for intrareader reliability (supplementary table 2). Reliability of the CMC-1 and STT joints were generally comparable.

When analyzing the reliability of subchondral bone defects, osteophytes, and BML for the distal and proximal joint parts separately, we generally saw ICC comparable to the aggregated scores. However, for subchondral bone defects in the trapezoid and osteophytes in the trapezoid and the proximal side of the trapezium, ICC were moderate (data not shown).

Readers gave slightly higher scores when assessing synovitis on post-Gd images as compared with the T2w-fs images (data not shown), whereas reliability was comparable (CMC-1: ICC 0.75, 95% CI 0.05-0.97 vs ICC 0.83, 95% CI 0.59-0.94; and STT: ICC 0.68, 95% CI -0.37 to 0.96 vs ICC 0.78, 95% CI 0.47-0.92 for images with vs without Gd).

Table 2. Median (IQR) scores of each MRI feature and n (%) with each feature present for the CMC-1 and STT joints (n=20).

MRI feature [range for CMC-1/STT]	**CMC-1 joint**		**STT joint**	
	median (IQR)	n (%)	median (IQR)	n (%)
Synovitis [0-3/0-3]	1.4 (1.0-2.3)	20 (100)	1.0 (0.4-1.7)	18 (90)
Subchondral bone defects [0-6/0-9]	1.4 (1.0-2.8)	18 (90)	1.0 (0.3-2.0)	17 (85)
Osteophytes [0-6/0-9]	2.2 (1.2-4.0)	19 (95)	0.3 (0.0-0.9)	13 (65)
Cartilage assessment [0-3/0-3]	1.5 (0.4-2.3)	16 (80)	1.0 (0.4-1.3)	16 (80)
Subluxation [absent or present]		12 (60)		
Bone marrow lesions [0-6/0-9]	1.7 (0.0-3.8)	13 (65)	1.4 (0.1-2.9)	15 (75)

Separate scores for the distal and proximal part of the joint were combined into a single sum score per joint. The n (%) is of patients with each feature present in at least 1 of 3 readers. CMC-1, first carpometacarpal; IQR, interquartile range; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid.

Table 3. Interreader reliability of MRI features for the CMC-1 and STT joints (3 readers).

	CMC-1 joint			**STT joint**		
	AvmICC (95% CI)	PEA n/N (%)	PCA n/N (%)	AvmICC (95% CI)	PEA n/N (%)	PCA n/N (%)
Synovitis	0.81 (0.60-0.92)	3/20 (15)	15/20 (75)	0.75 (0.48-0.90)	7/20 (35)	18/20 (90)
Subchondral bone defects	0.88 (0.73-0.95)	23/40 (58)	36/40 (90)	0.81 (0.60-0.92)	42/60 (70)	58/60 (97)
Osteophytes	0.83 (0.56-0.93)	10/40 (25)	31/40 (78)	0.74 (0.44-0.89)	41/60 (68)	56/60 (93)
Cartilage assessment	0.79 (0.48-0.92)	6/20 (30)	13/20 (65)	0.83 (0.64-0.93)	8/20 (40)	16/20 (80)
Subluxation	0.77 (0.52-0.91)	13/20 (65)				
Bone marrow lesions	0.99 (0.98-1.00)	32/40 (80)	40/40 (100)	0.96 (0.91-0.98)	43/60 (72)	57/60 (95)

Separate scores for the distal and proximal part of the joint were combined into a single sum score per joint to calculate ICCs. AvmICC, average measure ICC; CMC-1, first carpometacarpal; MRI, magnetic resonance imaging; PCA, percent close agreement; PEA, percent exact agreement; STT, scaphotrapeziotrapezoid.

DISCUSSION

In this study the OMERACT MRI Task Force proposed the first thumb base MRI scoring system, TOMS, and evaluated its cross-sectional reliability. The score was feasible and had good to very good reliability for the assessment of structural and inflammatory features in the CMC-1 and STT joints.

The previously published OMERACT HOAMRIS for the IP joints was used as a prototype in the development of the TOMS.[3] Two major differences between the scoring systems can be noted. First, erosive damage and cysts were combined into 1 score (subchondral bone defects) because it was judged that the distinction could not be made reliably in the thumb base joints. Second, because of larger joint size, it was reasoned that direct cartilage assessment is feasible in the thumb base when using appropriate MRI sequences, and should be prioritized over indirect cartilage assessment. Further, it was decided to score distal and proximal joint parts separately for some features, similar to the first Oslo MRI scoring system for IP OA.[8] Because only 2 joints are evaluated, this addition provides more detailed information without decreasing feasibility. In future studies of pharmacological and nonpharmacological interventions, HOAMRIS and TOMS can be used as complimentary scoring systems, since both assess similar features. Combined assessment with MRI of the fingers and thumb base of patients with hand OA in future trials can provide information about hypothesized differences in the pathophysiology of these OA subtypes.[1]

Assessment of the scaphotrapezoid articulation was also included in the scoring system. Previous cadaver studies have shown frequent degenerative changes of the scaphotrapezoid joint, although its relative contribution to STT joint OA complaints is unclear, partly because of poor visualization with traditional radiography.[9,10]

All included MRI were performed using a standard wrist acquisition technique. Although dedicated thumb base acquisitions do exist, these are not widely used in clinical practice. It is unclear whether the use of a dedicated thumb base acquisition would yield different results, and this should be evaluated in future studies.

Only 5 MRI included post-Gd imaging. No previous studies have compared the reliability and validity of MRI-defined synovitis with and without contrast in patients with hand OA. In knee OA, synovitis is commonly assessed without contrast, although contrast-enhanced MRI appears to be a more reliable and valid measure of synovial inflammation, with the ability to differentiate inflamed synovium from effusion.[11,12] Østergaard *et al* found that omitting contrast from MRI examination of synovitis in the metacarpophalangeal and wrist joints in patients with rheumatoid arthritis decreased reliability.[13] In our sample, reliability was good using both contrast and noncontrast images. This warrants more detailed analysis, preferably comparing synovitis scores between different sequences within the same patient in a larger sample.

Before TOMS can be recommended as a core instrument according to the OMERACT filter,[6] assessment of the reliability of change scores and its responsiveness in longitudinal studies is needed. Future studies will reveal whether reliability of TOMS is similar when used by other trained readers compared with expert readers who developed the scoring system,

which for the HOAMRIS was shown to be either better or worse.[14,15] Further, readers used a preliminary atlas during the exercises, which has likely increased agreement across readers, as was previously shown for HOAMRIS.[3] A comprehensive atlas including all grades of all features in both joints would facilitate scoring and increase reliability of the TOMS. Validity of the scoring system should be investigated in future studies by assessing correlations with signs and symptoms, and other imaging modalities including traditional radiography and ultrasound.

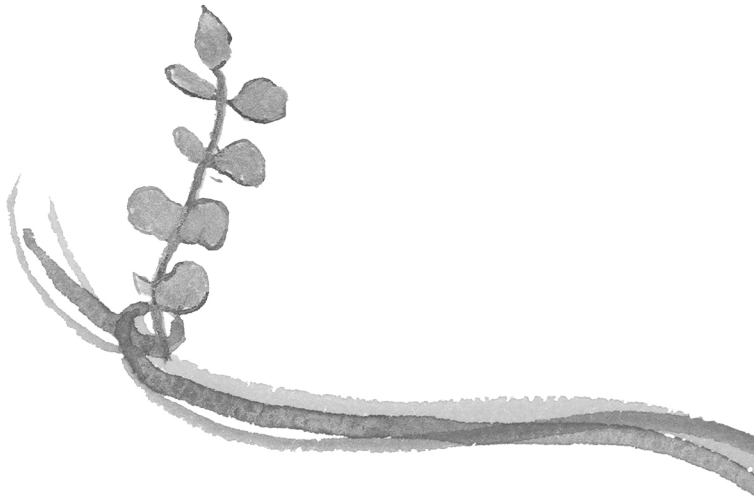
REFERENCES

1. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
2. Haugen IK, Eshed I, Gandjbakhch F, et al. The longitudinal reliability and responsiveness of the OMERACT hand osteoarthritis magnetic resonance imaging scoring system (HOAMRIS). *J Rheumatol* 2015;42:2486-91.
3. Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386-91.
4. Dahaghin S, Bierma-Zeinstra S, Ginai A, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
5. Boers M, Kirwan J, Gossec L, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;41:1025-30.
6. Boers M, Tugwell P, Beaton D, et al. *The OMERACT handbook*: OMERACT, 2016. https://omeract.org/resources (18 January 2017, date last accessed).
7. Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. *Stat Med* 1994;13:2465-76.
8. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. *Ann Rheum Dis* 2011;70:1033-38.
9. Bhatia A, Pisoh T, Touam C, et al. Incidence and distribution of scaphotrapezotrapezoidal arthritis in 73 fresh cadaveric wrists. *Ann Chir Main Memb Super* 1996;15:220-5.
10. Moritomo H, Viegas S, Nakamura K, et al. The scaphotrapezio-trapezoidal joint. Part 1: An anatomic and radiographic study. *J Hand Surg* 2000;25A:899-910.
11. Guermazi A, Roemer FW, Crema MD, et al. Imaging of non-osteochondral tissues in osteoarthritis. *Osteoarthritis Cartilage* 2014;22:1590-605.
12. Hayashi D, Roemer FW, Katur A, et al. Imaging of synovitis in osteoarthritis: current status and outlook. *Semin Arthritis Rheum* 2011;41:116-30.
13. Østergaard M, Conaghan PG, O'Connor P, et al. Reducing invasiveness, duration, and cost of magnetic resonance imaging in rheumatoid arthritis by omitting intravenous contrast injection -- Does it change the assessment of inflammatory and destructive joint changes by the OMERACT RAMRIS? *J Rheumatol* 2009;36:1806-10.
14. Ramonda R, Favero M, Vio S, et al. A recently developed MRI scoring system for hand osteoarthritis: its application in a clinical setting. *Clin Rheumatol* 2016;35:2079-86.
15. Kortekaas MC, Kwok WY, Reijnierse M, et al. Magnetic resonance imaging in hand osteoarthritis: intraobserver reliability and criterion validity for clinical and structural characteristics. *J Rheumatol* 2015;42:1224-30.



CHAPTER 15

Atlas for the OMERACT thumb base osteoarthritis MRI scoring system (TOMS)



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ABSTRACT

This paper presents an atlas for the Outcome Mearsures in Rheumatology Clinical Trials (OMERACT) thumb base osteoarthritis MRI scoring system (TOMS). The atlas includes reference images of each grade of each feature that is assessed in TOMS (synovitis grade 0-3, subchondral bone defects grade 0-3, osteophytes grade 0-3, cartilage assessment grade 0-3, subluxation and bone marrow lesions grade 0-3) in the first carpometacarpal and scapho-trapezio-trapezoid joint. The presented reference images can be used to guide scoring of thumb base MRIs in patients with hand osteoarthritis according to the OMERACT TOMS.

ATLAS

Hand OA affects the interphalangeal and thumb base joints, including the CMC-1 and STT joints. Much is still unknown about the pathophysiology of thumb base OA. Although MRI studies have led to more insights in interphalangeal OA, thumb base MRI studies are still lacking. To facilitate this, recently the first MRI scoring system for thumb base OA was developed by the OMERACT MRI Working Group, the TOMS.[1]

Representative examples of each grade of the different features that are assessed in the TOMS are presented (see table 1 for definitions and scaling of each feature). Images from patients with hand OA were obtained from the Hand Osteoarthritis in Secondary Care (HOSTAS) study at Leiden University Medical Center (Leiden, The Netherlands). Images were acquired on a 1.5 T extremity MRI unit (ONI, GE, Wisconsin, USA). Examples of synovitis evaluated on contrast-enhanced images were obtained from patients with hand OA from the Nor-Hand study at Diakonhjemmet Hospital (Oslo, Norway), and were acquired on a 1.5 T MRI unit (Siemens Aera, Germany) after administration of gadolinium contrast. Example images were selected by a single reader with experience in using the TOMS and subsequently approved by three experienced radiologists (of which one is also experienced in using the score).

Table 1. Definitions and scaling of features in proposed OMERACT TOMS.

MRI feature	Definition	Scaling	Advised plane and MRI sequence
Synovitis*	Thickened synovium with enhancement after Gd injection.	0= normal, 1= mild (1%-33%), 2= moderate (34%-66%), 3= severe (67%-100%). Based on thirds of the presumed maximum thickness of enhancing tissue in the synovial compartment.	Coronal and axial. T1w pre- and post-Gd with fs. In absence of post-Gd images, T2w-fs/STIR/PD-fs can be used.
Subchondral bone defects*†	Subchondral bone loss, including erosions (sharply marginated bone lesions with cortical break), cysts (sharply marginated bone lesions without cortical break), and bone attrition (diffuse loss of bone contour).	0= no bone defects; 1= mild (≤25% of bone volume or joint surface affected), 2= moderate (26%-50% of bone volume or joint surface affected), 3= severe (>50% of bone volume or joint surface affected).	Coronal and axial. T1w and T2w-fs/ STIR/PD-fs.
Osteophytes†	Abnormal bone protuberance at joint margins or surfaces.	0= no osteophytes, 1= mild (1-2 small osteophytes), 2= moderate (≥3 small osteophytes and/or ≥ 1 moderate osteophyte(s)), 3= severe (≥1 large osteophyte(s)).	Coronal (and sagittal if available). T1w.

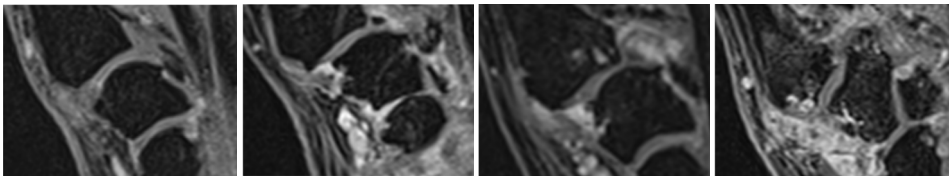
Table 1. Continued.

MRI feature	Definition	Scaling	Advised plane and MRI sequence
Cartilage assessment	Loss of cartilage, or loss of cartilage space based on the inter-bone distance.‡	0= no loss of cartilage or cartilage space, 1= mild (cartilage loss without complete denuding, or cartilage space loss without bone-to-bone contact), 2= moderate (cartilage loss with denuding ≤50% of joint surface or focal complete cartilage space loss with bone-to-bone contact ≤50% of the articulating area), 3= severe (cartilage loss with denuding >50% of joint surface or complete cartilage space loss over >50% of the articulating area).	Coronal. T1w-fs-3D-GE, otherwise use T1w-fs, T2w-fs or PD-fs.
Subluxation§	Subluxation of the CMC-1 joint in the frontal plane.	0= MC-1 subluxed 0%-25% of the MC width, 1= MC-1 subluxed ≥26% of the MC width.	Coronal. T1w.
Bone marrow lesions*†	Lesions within the trabecular bone with signal characteristic consistent with increased water content¶ and with ill-defined margins.	0= no bone marrow lesions, 1= mild (1%-33%), 2= moderate (34%-66%), 3= severe (67%-100%). Based on thirds of assessed bone volume.	Coronal and axial. T2w-fs/STIR/PD-fs.

Table was reprinted with permission from Kroon *et al*.[1] All rights reserved. *In longitudinal studies, 0.5 increments may be used for synovitis, subchondral bone defects, and bone marrow lesions. †Proximal and distal parts of a joint are scored separately for subchondral bone defects, osteophytes, and bone marrow lesions. ‡If assessment of cartilage and cartilage space are in conflict, direct visualization of the cartilage should be prioritized. §Only the CMC-1 joint is evaluated for this feature. ¶High signal intensity on STIR/T2w-fs images. CMC-1, first carpometacarpal joint; fs, fat saturated; Gd, gadolinium; GE, gradient echo; MC-1, first metacarpal; PD, proton density; OA, osteoarthritis; OMERACT, Outcome Measures in Rheumatology Clinical Trials; STIR, short-tau inversion recovery; STT, scapho-trapezio-trapezoid; TOMS, thumb base OA MRI scoring system; w, weighted.

Synovitis CMC-1

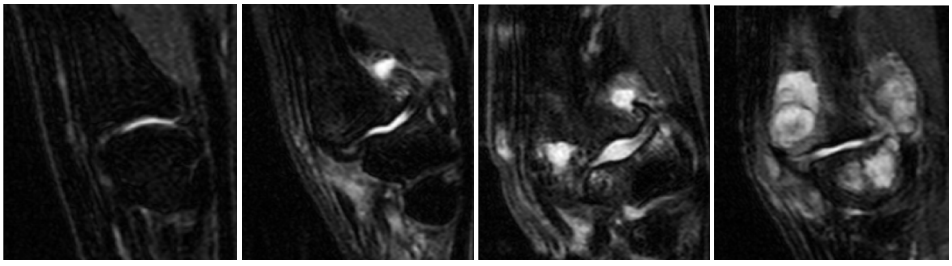
T1 weighted fat-saturated postcontrast images



Normal Grade 1 Grade 2 Grade 3

Synovitis CMC-1

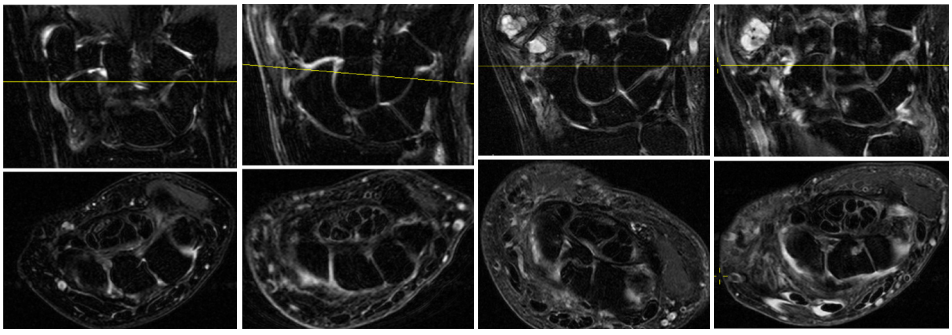
T2 weighted fat-saturated images



Normal Grade 1 Grade 2 Grade 3

Synovitis STT

T2 weighted fat-saturated images



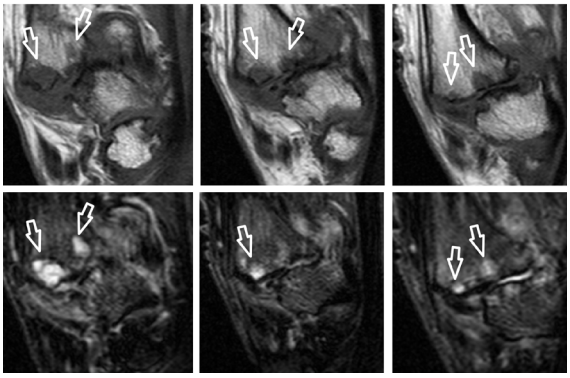
Normal Grade 1 Grade 2 Grade 3

Subchondral bone defects CMC-1: proximal first metacarpal

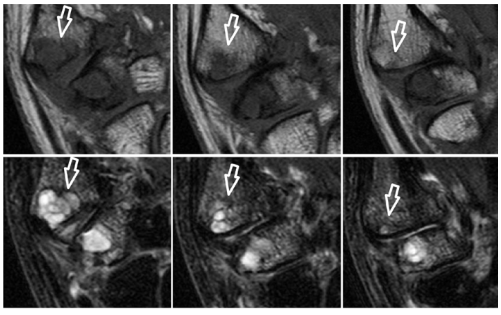
T1 weighted and T2 weighted fat-saturated images



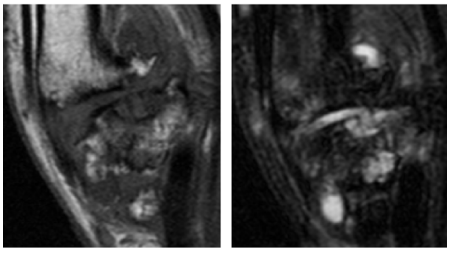
Grade 1



Grade 2



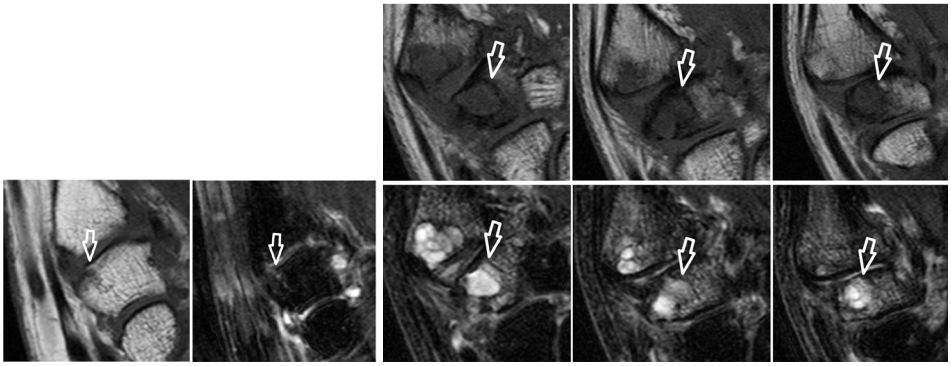
Grade 3



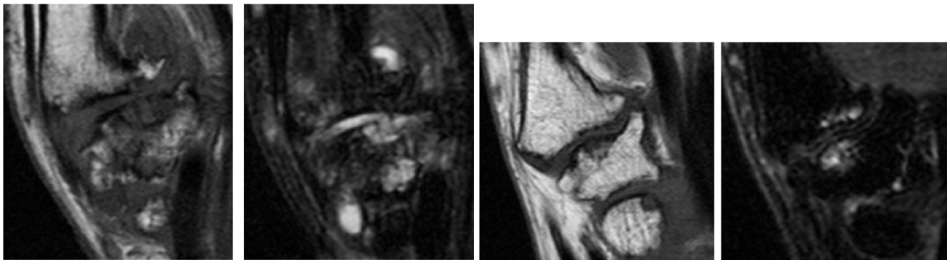
Grade 3 (attrition)

Subchondral bone defects CMC-1: distal trapezium

T1 weighted and T2 weighted fat-saturated images



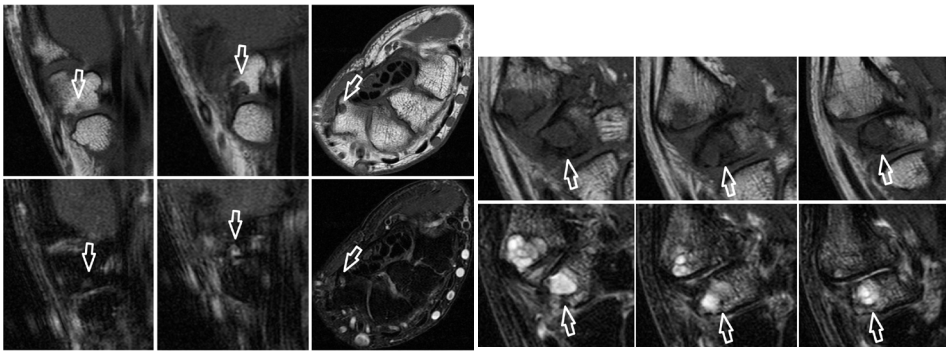
Grade 1 Grade 2



Grade 3 Grade 3 (attrition)

Subchondral bone defects STT: proximal trapezium

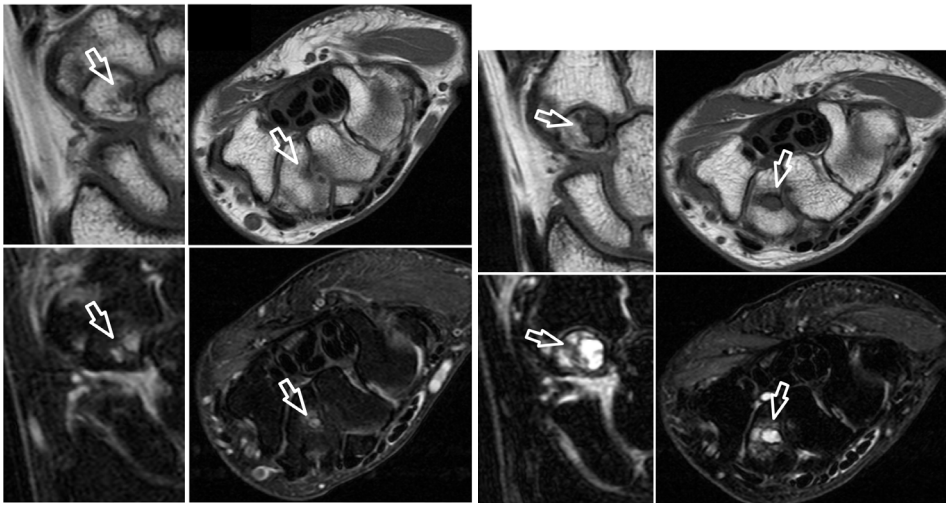
T1 weighted and T2 weighted fat-saturated images



Grade 1 Grade 2

Subchondral bone defects STT: proximal trapezoid

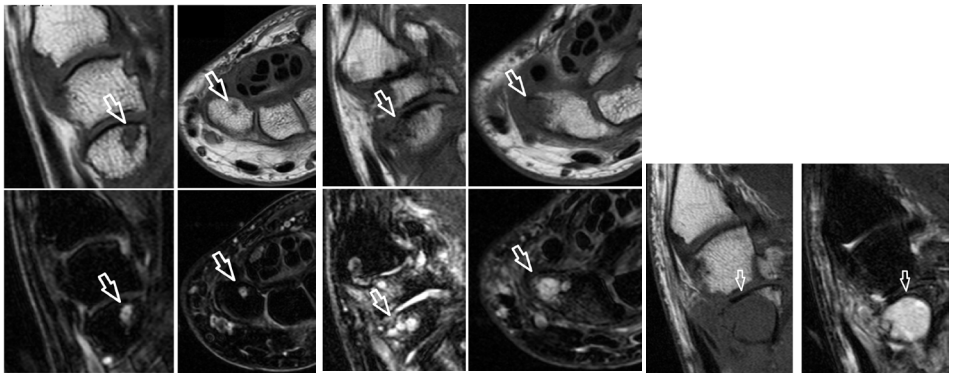
T1 weighted and T2 weighted fat-saturated images



Grade 1 Grade 2

Subchondral bone defects STT: distal scaphoid

T1 weighted and T2 weighted fat-saturated images



Grade 1 Grade 2 Grade 3

Osteophytes CMC-1: proximal first metacarpal

T1 weighted images



Grade 1



Grade 2





Grade 3

Osteophytes CMC-1: distal trapezium

T1 weighted images





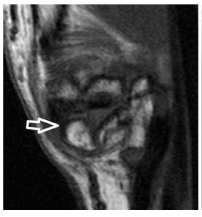
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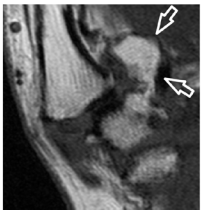




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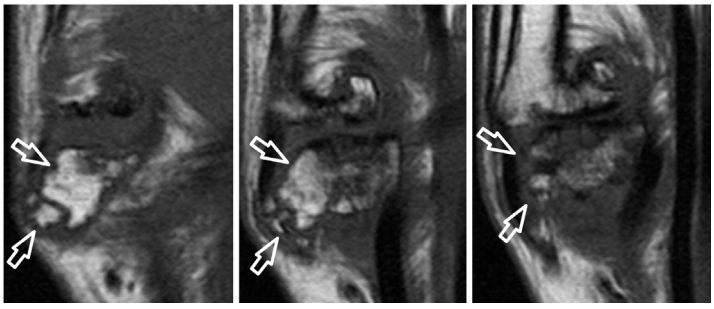
Grade 3

Osteophytes STT: proximal trapezium

T1 weighted images



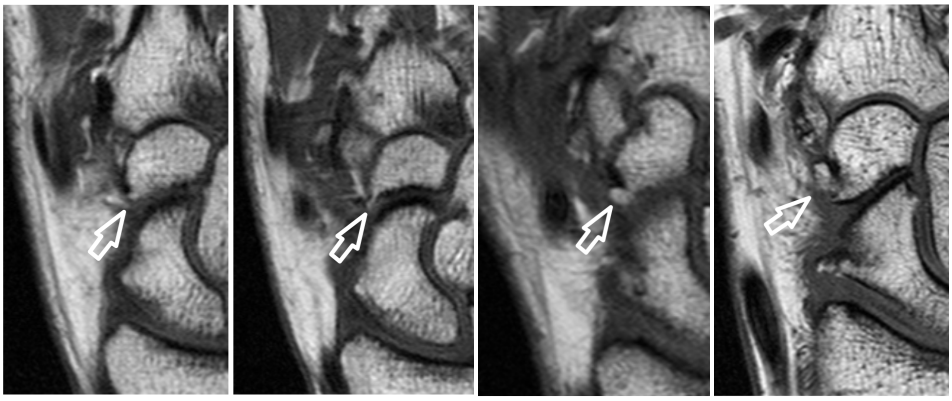
Grade 1 Grade 2



Grade 3

Osteophytes STT: proximal trapezoid

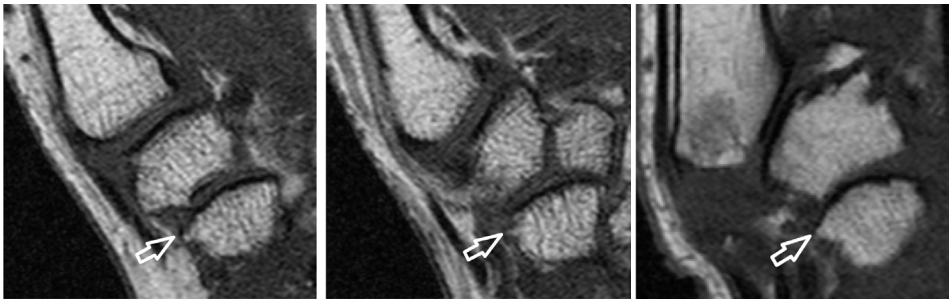
T1 weighted images



Grade 1 Grade 2 Grade 3

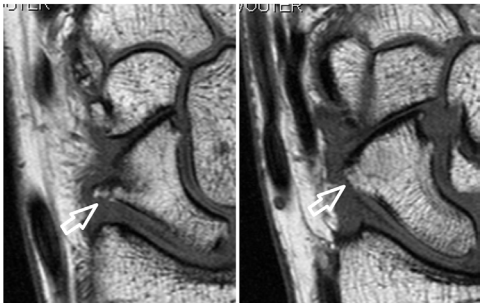
Osteophytes STT: distal scaphoid

T1 weighted images



Grade 1

Grade 2



Grade 3

Cartilage assessment CMC-1

T1 weighted images



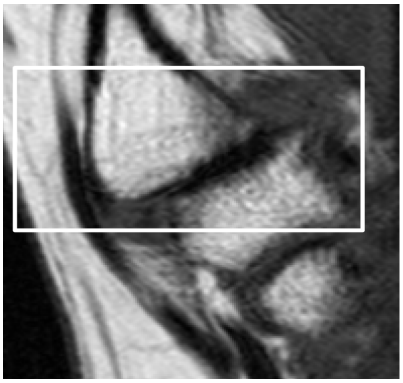
Normal



Grade 1



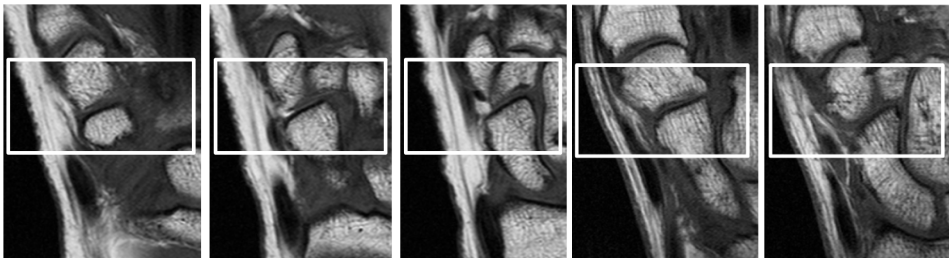
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Grade 3

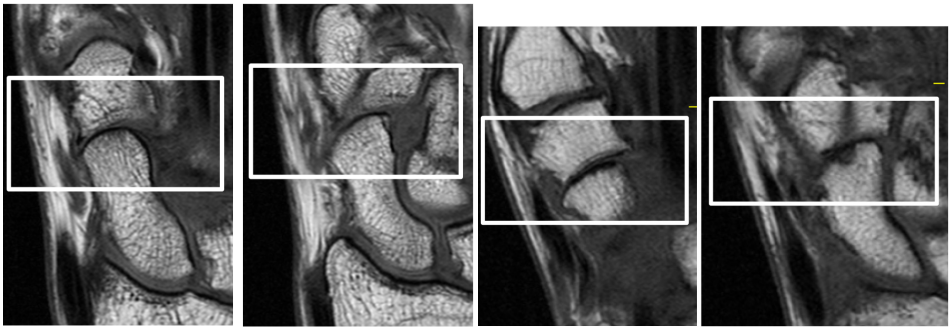
Cartilage assessment STT

T1 weighted images



Normal

Grade 1

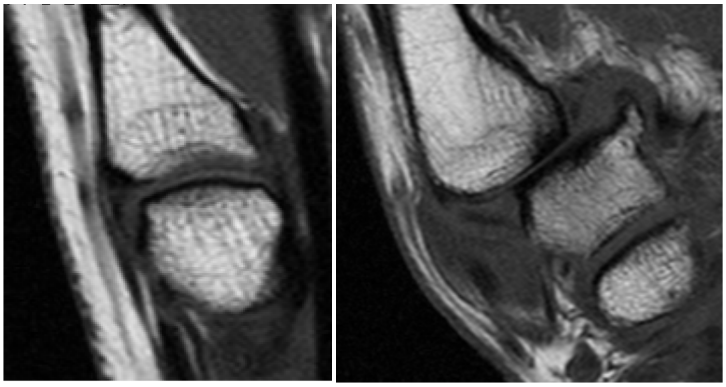


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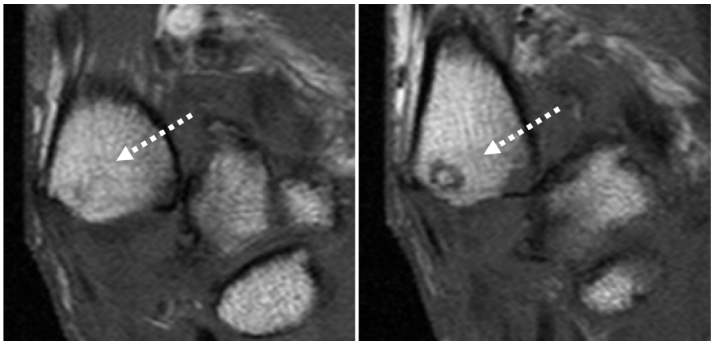
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Subluxation CMC-1

T1 weighted images



Normal Subluxation present

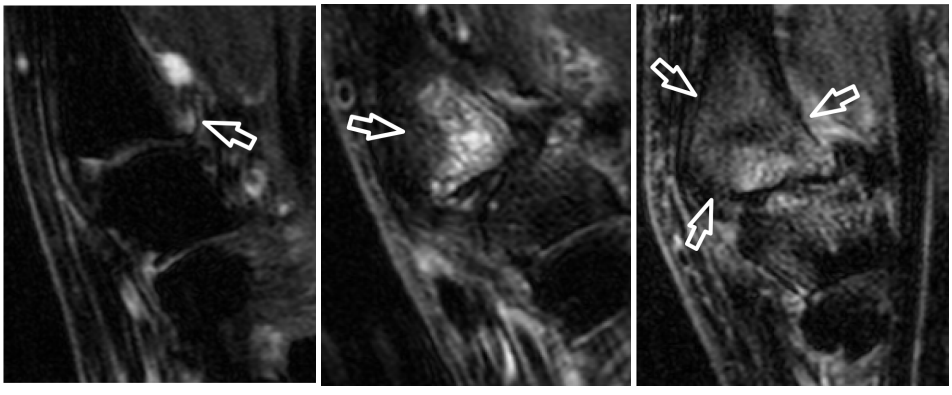


Subluxation present (severe)

[arrow points into direction of subluxation]

Bone marrow lesions CMC-1: proximal first metacarpal

T2 weighted fat-saturated images



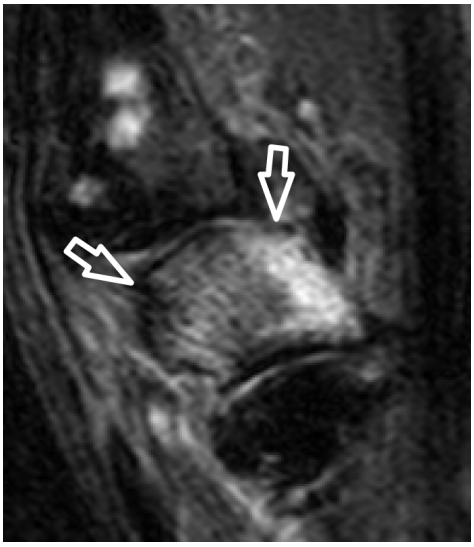
Grade 1 Grade 2 Grade 3

Bone marrow lesions CMC-1: distal trapezium

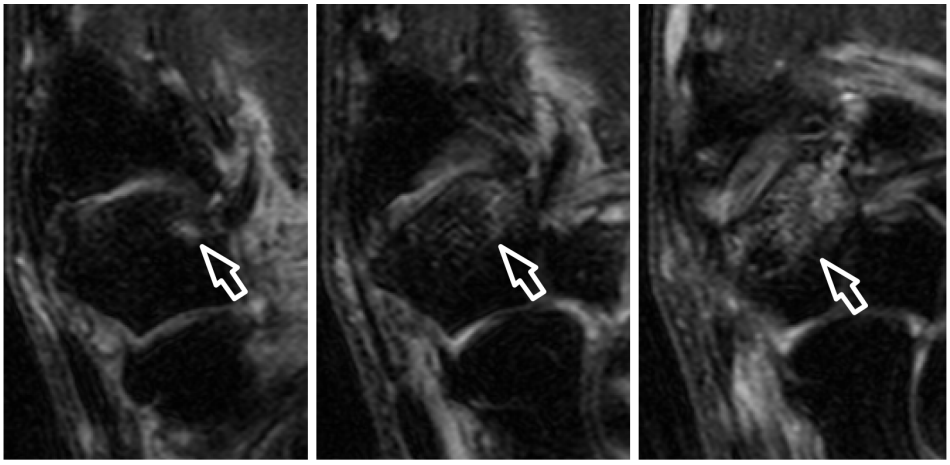
T2 weighted fat-saturated images



Grade 1



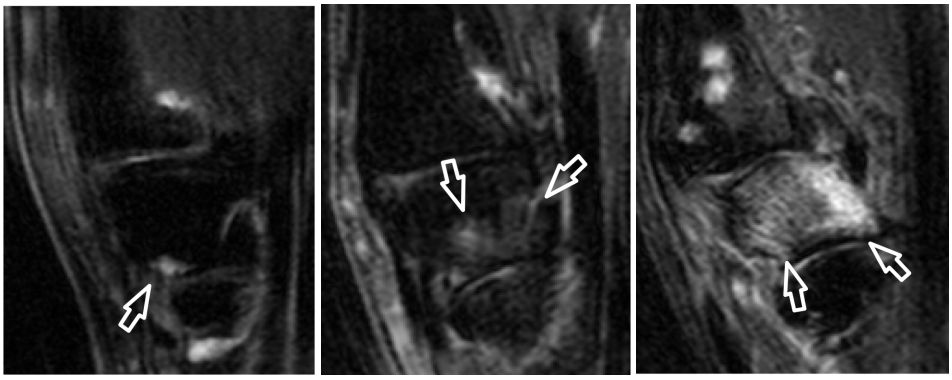
Grade 3



Grade 2

Bone marrow lesions STT: proximal trapezium

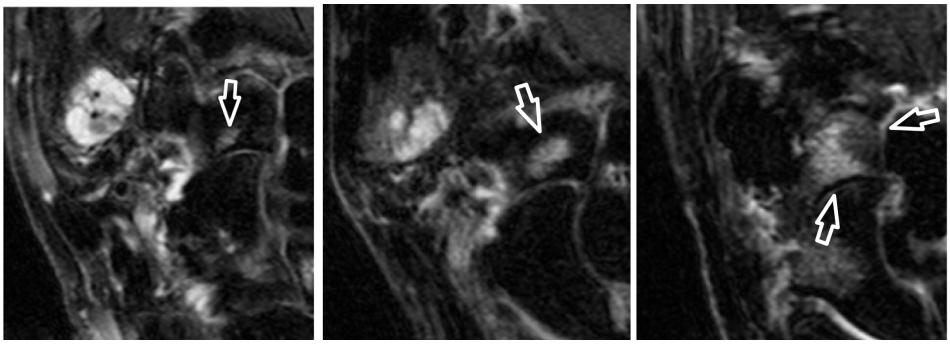
T2 weighted fat-saturated images



Grade 1 Grade 2 Grade 3

Bone marrow lesions STT: proximal trapezoid

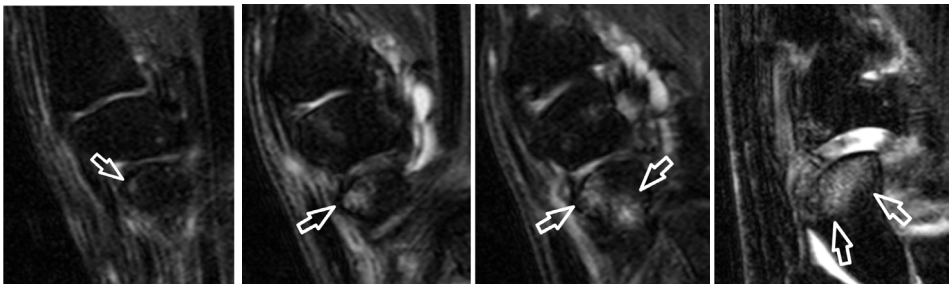
T2 weighted fat-saturated images



Grade 1 Grade 2 Grade 3

Bone marrow lesions STT: distal scaphoid

T2 weighted fat-saturated images



Grade 1 Grade 2 Grade 3

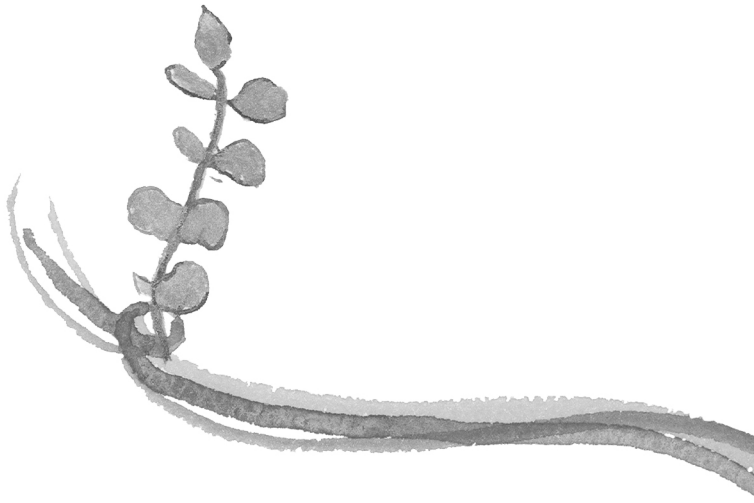
REFERENCES

1. Kroon FPB, Conaghan PG, Foltz V, et al. Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system. *J Rheumatol* 2017;44:1694-8.



CHAPTER 16

Longitudinal reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS)



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ABSTRACT

Objective. To assess the longitudinal reliability of the Outcome Measures in Rheumatology (OMERACT) Thumb base Osteoarthritis Magnetic resonance imaging (MRI) Scoring system (TOMS).

Methods. Paired MRI of patients with hand osteoarthritis were scored in 2 exercises (6-mo and 2-yr follow-up) for synovitis, subchondral bone defects (SBD), osteophytes, cartilage assessment, bone marrow lesions (BML), and subluxation. Interreader reliability of delta scores was assessed.

Results. Little change occurred. Average-measure intraclass correlation coefficients were good-excellent (³ 0.71), except synovitis (0.55-0.83) and carpometacarpal-1 osteophytes/cartilage assessment (0.47/0.39). Percentage exact/close agreement was 52-92%/68-100%, except BML in 2-years (28%/64-76%). Smallest detectable change was below the scoring increment, except in SBD and BML.

Conclusion. TOMS longitudinal reliability was moderate-good. Limited change hampered assessment.

INTRODUCTION

The thumb base, including the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints, is often involved in hand osteoarthritis (OA). Thumb base OA is associated with particular risk factors and requires distinct therapeutic interventions compared to interphalangeal finger OA.[1] Therefore, outcome measures specifically assessing thumb base OA are needed.

In response, the Outrcome Measures in Rheumatology (OMERACT) magnetic resonance imaging (MRI) working group developed a scoring system of MRI findings in the thumb base: Thumb base OA MRI Scoring system (TOMS).[2] This tool has been shown to exhibit good cross-sectional reliability, but data concerning longitudinal reliability are lacking.[2] With the term *longitudinal reliability*, we mean the ability to reliably score sequential images, taking into account interreader variability. Understanding the reliability of TOMS for measuring change is needed for effectively implementing this tool.

This study investigated the longitudinal reliability of TOMS in 2 settings: a prospective observational study with long-term follow-up and a clinical trial with short-term follow-up.[3,4]

METHODS

Reliability exercises

Two reliability exercises were performed. An atlas was available to facilitate scoring.[5] Features assessed were synovitis, subchondral bone defects (SBD), osteophytes, cartilage assessment, bone marrow lesions (BML), and subluxation.[2] All features but subluxation were evaluated on 0-3 scales in the CMC-1 and STT joints, with 0.5 increments for synovitis, SBD, and BML. Proximal and distal joint parts were scored separately for SBD, osteophytes, and BML. Subluxation was scored absent/present in the CMC-1 joint. In both exercises, MRI were selected to represent a large range of pathology.

In the first exercise, paired MRI (baseline, 2-yr follow-up) of 25 patients from the Hand Osteoarthritis in Secondary Care (HOSTAS) prospective cohort study (Leiden University Medical Center[6]) were scored in known time-order by 3 independent readers [1 rheumatologist (FG) and 2 rheumatology fellows (SvB, FK), all experienced in using TOMS]. Coronal and axial T1-weighted (T1w) fast spin echo (FSE), and T2w FSE images with fat-suppression (fs) were obtained on a 1.5T extremity MRI unit (ONI, GE; supplementary file). No contrast agent was used. Therefore, synovitis was scored on T2w-fs images, as per the original scoring system.[2]

The second exercise was conducted by an experienced radiologist (CP) and a rheumatology fellow (FK). Paired MRI (baseline, 6-mos follow-up) of 24 patients with hand OA from a multicenter randomized double-blind trial comparing lutikizumab to placebo[7] were scored for synovitis and BML. One reader (CP) scored in unknown and the other in known time-order (FK) for logistical reasons. Coronal and axial T1w-fs images with/without gadolinium-based contrast-enhancement, and short-tau inversion recovery or T2w-fs images were obtained according to standardized protocol. Because of incomplete coverage, the STT could only be assessed in 16 patients, and the trapezoid bone was not evaluated.

Data collection for both studies was approved by local ethics committees (P09.004, NCT02384538). All participants provided written informed consent.

Statistical analyses

Separate scores of distal and proximal joint compartments were combined into 1 sum score per joint where applicable. Median and interquartile range (baseline status scores) or range (delta scores) was calculated for each feature, based on the average of the readers. Interreader reliability of delta scores was assessed by calculating intraclass correlation coefficients (ICC; average measure, mixed-effect models, absolute agreement), and percentage exact and close agreement (PEA/PCA). ICC ≤ 0.20 were considered poor, > 0.20 to < 0.40 fair, ≥ 0.40 to < 0.60 moderate, ≥ 0.60 to < 0.80 good, and ≥ 0.80 excellent reliability.[8] PEA/PCA were defined as a difference of 0/≤ 1 between minimum and maximum scores across readers. For each feature the smallest detectable change (SDC) was calculated.[9] We determined how many patients changed beyond measurement error (i.e., change score > SDC), and whether the smallest scoring increment for each feature could be scored reliably (i.e., smallest increment > SDC).

RESULTS

Table 1 presents baseline characteristics of patients from both reliability exercises. Thirteen trial participants received placebo and 11 lutikizumab. Baseline scores of MRI features were generally low (table 2). Highest scores were given for CMC-1 osteophytes. Overall, more MRI abnormalities were seen in the CMC-1 compared to the STT joint.

Baseline scores of synovitis and BML were comparable in the 2 studies. On average, little change was observed after 6 months and 2 years (table 2). However, individual patients showed change in synovitis and BML, both increasing and decreasing (supplementary figure 1). Cartilage and bone features generally showed less improvement and more deterioration over time.

Table 3 presents the longitudinal reliability in both studies. ICC for most features in both thumb base joints were good to excellent. Fair to moderate ICC were found for cartilage assessment and osteophytes in the CMC-1 joint. ICC for synovitis in the different studies and joints varied from moderate to excellent. ICC could not be estimated for some features (STT synovitis in the clinical trial, STT osteophytes, and subluxation).

Since calculation of ICC was influenced by the small amount of change that occurred over time in both studies, PEA and PCA values were also calculated. PEA/PCA of all features in both joints ranged from 52-92% and 68-100%, except for BML in the CMC-1 in the 3-reader exercise (PEA 28%/PCA 64%). PEA values in that exercise were all lower than for the clinical trial.

Table 1. Baseline characteristics of patients with hand osteoarthritis in 2 reliability exercises.

Clinical characteristic	HOSTAS cohort n=25	Clinical trial n=24
Women	23 (92)	20 (83)
Age, yrs, mean (SD)	60.0 (7.5)	65.9 (6.8)
Fulfilling ACR hand OA criteria	24 (96)	24 (100)
Pain on palpation thumb base	16 (64)	14 (58)
KL grade CMC-1		
Grade 0	10 (40)	7 (29)
Grade 1	5 (20)	0 (0)
Grade 2	5 (20)	8 (33)
Grade 3	3 (12)	5 (21)
Grade 4	2 (8)	4 (17)
Osteophyte STT†	2 (8)	7 (44)*
Joint space narrowing STT†	6 (24)	6 (38)*

Values are n (%) unless otherwise specified. *STT data from 16 patients. †According to Osteoarthritis Research Society International atlas[10]. ACR, American College of Rheumatology; CMC-1, first carpometacarpal; HOSTAS, Hand Osteoarthritis in Secondary Care; KL, Kellgren-Lawrence; OA, osteoarthritis; STT, scaphotrapeziotrapezoid.

The SDC was calculated for all features and should be considered in light of the range and smallest increment of that feature's score (table 3). Most SDC were lower than that feature's smallest scoring increment, although the SDC of SBD and BML in particular were higher than the increment of 0.5. In the cohort study, the SDC for BML in the CMC-1 was even higher than 1 (SDC = 1.27), although in the clinical trial the SDC was better (SDC = 0.87). Most participants did not change more than the SDC (supplementary table 1). The largest number of participants with a delta score larger than the SDC, either increasing or decreasing, occurred for synovitis and BML. Features related to cartilage and bone generally deteriorated. Of these, SBD showed the most participants with change.

Table 2. Baseline status (median, interquartile range) and change scores (median, range) of each MRI feature for the CMC-1 and STT joint in 2 reliability exercises.

MRI feature, range CMC-1/STT	**HOSTAS cohort, n=25**		
	CMC-1		**STT**
	Baseline	Change, 2 yrs	Baseline
Synovitis, 0-3/0-3	1.3 (0.7;1.7)	0 (-1.7;1)	0.7 (0.3;1.3)
Subchondral bone defects, 0-6/0-9	1.7 (0.7;2.3)	0.2 (-0.7;2.2)	0.7 (0;1.7)
Osteophytes, 0-6/0-9	2.3 (1.7;4)	0 (0;0.7)	0.7 (0.3;1)
Cartilage assessment, 0-3/0-3	1 (0.7;1.7)	0 (-0.3;0.7)	0.7 (0;1.3)
Subluxation, absent or present	8 (32%)†	0 (0;0.3)	
Bone marrow lesions, 0-6/0-9	1.7 (0.7;4.3)	0 (-3.2;4.7)	1 (0.3;2.3)

Based on average score of all readers, except subluxation†. Separate scores for the distal and proximal part of the joint combined into sum score per joint. *STT scored in 16 patients, trapezoid not included. †n (%) with subluxation scored by at least 2 readers. CMC-1, first carpometacarpal; HOSTAS, Hand Osteoarthritis in Secondary Care; MRI, magnetic resonance imaging; STT, scaphotrapeziotrapezoid.

Table 3. Interreader reliability of change scores of MRI features for the CMC-1 and STT joint in 2 reliability exercises.

MRI feature [smallest increment]	**CMC-1**		
	AvmICC (95% CI)	PEA, n (%)	PCA, n (%)
HOSTAS cohort, n=25			
Synovitis [0.5]	0.83 (0.68;0.92)	14 (56)	25 (100)
Subchondral bone defects [0.5]	0.72 (0.47;0.87)	13 (52)	17 (68)
Osteophytes [1]	0.47 (-0.02;0.75)	22 (88)	25 (100)
Cartilage assessment [1]	0.39 (-0.18;0.71)	16 (64)	25 (100)
Subluxation [1]	†	23 (92)	
Bone marrow lesions [0.5]	0.84 (0.69;0.93)	7 (28)	16 (64)
Clinical trial, n=24*			
Synovitis [0.5]	0.55 (-0.07;0.80)	17 (71)	23 (100)
Bone marrow lesions [0.5]	0.89 (0.75;0.95)	17 (71)	22 (92)

*STT scored in 16 patients, trapezoid not included. †Reliable estimation of ICC not possible owing to low variability. AvmICC, average measure intraclass correlation coefficient; CMC-1, first carpometacarpal; HOSTAS, Hand Osteoarthritis in Secondary Care; MRI, magnetic resonance imaging; PCA, percent close agreement; PEA, percent exact agreement; SDC, smallest detectable change; STT, scaphotrapeziotrapezoid.

		Clinical trial, n=24			
		CMC-1		STT*	
	Change, 2 yrs	Baseline	Change, 6 mos	Baseline	Change, 6 mos
	0 (-0.7;1)	1.5 (1;2)	0 (-1;1)	0.5 (0;1)	0 (0;0.5)
	0 (-0.2;2.3)				
	0 (0;0.3)				
	0 (-1.7;1)				
	0 (-2.7;3)	1.3 (0.5;2.5)	0 (-5;4)	0 (0;1.3)	0 (-2.5;3)

		STT			
	SDC	AvmICC (95% CI)	PEA, n (%)	PCA, n (%)	SDC
	0.45	0.56 (0.12;0.79)	15 (60)	24 (96)	0.48
	0.73	0.71 (0.44;0.86)	16 (64)	22 (88)	0.63
	0.22	†	23 (92)	25 (100)	0.18
	0.39	0.72 (0.47;0.87)	20 (80)	24 (96)	0.43
	0.18				
	1.27	0.92 (0.83;0.96)	7 (28)	19 (76)	0.67
	0.65	†	14 (88)	16 (100)	0.37
	0.87	0.90 (0.68;0.97)	13 (87)	14 (93)	0.77

DISCUSSION

In our report, we show the longitudinal reliability of a recently developed OMERACT MRI scoring system to assess inflammatory and structural features in thumb base osteoarthritis (TOMS). Based on ICC, PEA, and PCA values, our investigation showed that reliability of assessment of delta scores using the TOMS was good.

The longitudinal reliability of the similar Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (HOAMRIS) to evaluate interphalangeal joints was previously published.[11] Because the HOAMRIS and TOMS assess similar features, similar reliability is expected. Reliability of change scores in the HOAMRIS exercise (20 patients, 3 readers) for erosive damage and cysts were similar to those for SBD in TOMS. BML were also reliably assessed in both studies. However, our results for synovitis, osteophytes, and cartilage assessment were better compared to HOAMRIS. Observed differences between the studies may partly be explained by a higher number of assessed joints for HOAMRIS, leading to lower PEA/PCA values. Interphalangeal joints are also smaller, and the field strength of the magnetic resonance scanner was lower, which made reliable assessment more difficult.

ICC of the previous cross-sectional reliability exercise of the TOMS were generally higher, while PEA/PCA values were lower.[2] These differences were found because assessment of ICC of delta scores in a cohort with little change over time generally results in lower values, because ICC values are not only dependent on measurement error, but also on between-subject variability. Between-subject variability is part of the calculation used to produce ICC values, and low between-subject variability can cause unreasonably low ICC values.[12]

Results of the 2 exercises performed in our study were generally comparable, although the difference in blinding for time-order among readers of the clinical trial may have resulted in lower results for agreement between these readers. PEA values in the 3-reader exercise were all lower than for the 2-reader exercise, which can at least partially be attributed to the higher number of readers who have to reach exact agreement in the first case.

Assessment of longitudinal reliability was hampered by the small magnitude of change. Continuous change scores and the number of patients changing more than the SDC were low. Both cohorts reflect the characteristic disease course. In the cohort study no intervention was given, and inflammatory features were not expected to change. However, over a 2-year period, cartilage and bone damage were expected to increase, which they did, though only mildly. Generally, radiographic progression in the CMC-1 over 2 years is slow.[13] Moreover, we selected participants with and without thumb base OA for this methodological exercise, which may have attributed to the low amount of change that was observed over time.

Most SDC were low and below the feature's smallest scoring increment, showing that a change of 1 increment reflects a measurable change in that feature. Only SBD and BML had an SDC above their defined smallest increment of 0.5, and it could be argued that 0.5 increments are too small to be reliably assessed for these features.

Results from our study provide evidence that the OMERACT TOMS can be used to evaluate thumb base MRI in studies of different settings. Future studies are warranted, in particular positive clinical trials, to evaluate sensitivity to change, as well as validation studies.

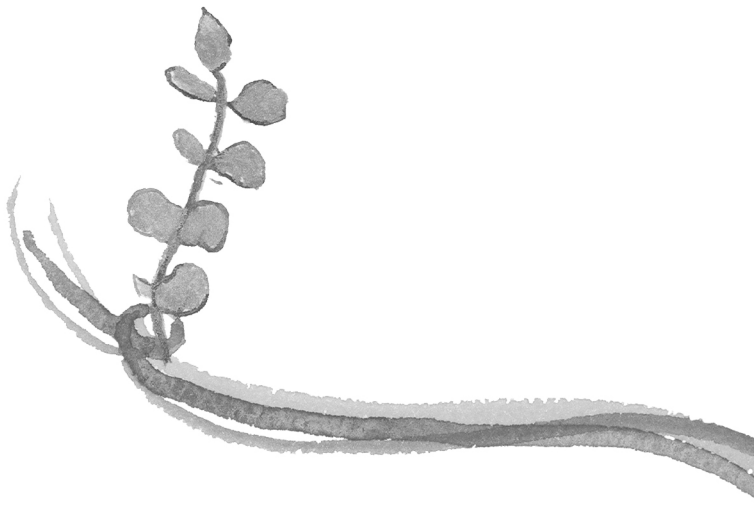
REFERENCES

1. Kloppenburg M, Kwok W-Y. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2012;8:22-31.
2. Kroon FP, Conaghan PG, Foltz V, et al. Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system. *J Rheumatol* 2017;44:1694-8.
3. Boers M, Kirwan JR, Tugwell P, et al. The OMERACT Handbook. [Internet. Accessed November 12, 2018.] Available from: https://omeract.org/resources
4. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
5. Kroon FP, Peterfy CG, Conaghan PG, et al. Atlas for the OMERACT thumb base osteoarthritis MRI scoring system (TOMS). *RMD Open* 2018;4:e000583.
6. Damman W, Liu R, Kroon FP, et al. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand OSTeoArthritis in Secondary care cohort. *J Rheumatol* 2017;44:1659-66.
7. Kloppenburg M, Peterfy C, Haugen I, et al. A phase 2a, placebo-controlled, randomized study of ABT-981, an anti-interleukin-1alpha and -1beta dual variable domain immunoglobulin, to treat erosive hand osteoarthritis (EHOA) [abstract]. *Ann Rheum Dis* 2017;76:122.
8. Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. *Stat Med* 1994;13:2465-76.
9. Bruynesteyn K, Boers M, Kostense P, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179-82.
10. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15:A1-56.
11. Haugen IK, Eshed I, Gandjbakhch F, et al. The longitudinal reliability and responsiveness of the OMERACT Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (HOAMRIS). *J Rheumatol* 2015;42:2486-91.
12. Lee KM, Lee J, Chung CY. Pitfalls and important issues in testing reliability using intraclass correlation coefficients in orthopaedic research. *Clin Orthop Surg* 2012;4:149-55.
13. Botha-Scheepers S, Riyazi N, Watt I, et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. *Ann Rheum Dis* 2009;68:1260-4.



CHAPTER 17

Summary and discussion



SUMMARY AND DISCUSSION

Osteoarthritis is a prevalent chronic rheumatic disease that is associated with a high personal and societal burden of disease.[1] The hand is one of the most commonly affected joint sites. Hand osteoarthritis leads to hand pain, stiffness, functional limitation, decreased grip strength and a reduced quality of life.[2-4] Clinical hallmarks of the disease include bony enlargement and deformities of the hand joints, at times accompanied by soft tissue swelling.[5] Despite the high prevalence and substantial disease-burden, there is an unmet need for effective therapies for patients suffering from hand osteoarthritis. Currently, available treatment options are limited. No disease-modifying treatments exist, and therapies to offer symptom relief are moderately effective at best.

While for a long time hand osteoarthritis was a "forgotten disease", it has gained more interest in recent years. But although the number of studies in the field has increased, thus far progress in finding new therapeutic options for patients with hand osteoarthritis has been disappointing. Several difficulties can be identified that stand in the way of a real breakthrough. An important challenge is that it is yet unclear which tissue to target by treatment, largely caused by omissions in our understanding of the underlying mechanisms leading to osteoarthritis development. Second, evidence is accruing that hand osteoarthritis is a heterogeneous disease, and that a differential approach is warranted for different hand osteoarthritis phenotypes. A third challenge lies in shortcomings in outcome measurement in hand osteoarthritis studies, precluding adequate assessment of potential treatment effects. In this chapter we will summarise the main findings of the studies described in this thesis, which addressed aspects of these challenges and made a start towards facilitating the development of new treatment options for patients with hand osteoarthritis.

Current treatment options in hand osteoarthritis

In **part I** of this thesis we wished to gain insight in the current state of treatment for patients with hand osteoarthritis. **Chapters 2-3** provide an overview of the currently available therapeutic options, which range from non-pharmacological to pharmacological and even surgical modalities. Data from multiple trials, summarised in these chapters, show that hand exercises and prolonged splinting of the thumb base are non-pharmacological therapies resulting in symptom relief. Additionally, single trials have shown positive results for joint protection strategies and the use of assistive devices (including for example cutlery with built-up handles, ergonomic pens and devices to facilitate opening bottles, cans or jars). Pharmacological therapies that most evidently proved to be efficacious in relieving symptoms were non-steroidal anti-inflammatory drugs (NSAIDs), both topical and oral preparations. Moreover, single trials have reported beneficial results for chondroitin sulfate and intra-articular injections of glucocorticoids in interphalangeal osteoarthritis.

Besides providing an overview of available therapies for patients with hand osteoarthritis, there are other important things to be learned from **chapters 2-3**. Although the number of trials since the previous evidence synthesis for the 2007 EULAR recommendations for the management of hand osteoarthritis had steeply increased (i.e., 39 out of 50 and 43 out of 64 included trials of non-pharmacological and pharmacological therapies in **chapter 3**, respectively, were published in 2007 or later), their quality was not consistent. The risk of bias in many trials was judged to be high, especially in trials of non-pharmacological therapies, mainly due to a lack of blinding or the use of an inadequate method of randomisation. Evidence from trials with a high risk of bias should be interpreted with caution, since bias in a trial can produce misleading results.

Furthermore, effect sizes of effective therapies were modest. For example, the effect of oral NSAIDs on pain was the largest consistent effect observed, yet the effect size only reached 0.4, which is generally regarded a small effect.[6] Only the effects of prolonged thumb base splinting, oral NSAIDs and intra-articular glucocorticoid injections in interphalangeal joints, the last only evaluated in one study, crossed the margin of clinical meaningful difference. Moreover, almost all trials focussed on symptom alleviation, and the few trials that did investigate structure modification found no evidence for disease-modification.

Finally, this data synthesis did not only show us what evidence had been collected, but also what is lacking. Indeed, important questions remain, and, amongst others, well-performed (placebo-controlled) trials of paracetamol and surgical interventions are warranted, as are replications of the single positive trials of, for example, topical NSAIDs, intra-articular glucocorticoid injections in interphalangeal joints and chondroitin sulfate. An example of a trial that could answer a combination of research questions would be a three-armed trial comparing paracetamol, topical NSAIDs and placebo. This type of trial would be a good example of an efficiency study ("*doelmatigheidsonderzoek*"), a research type becoming more and more important with the rising demand for care and increasing costs. While paracetamol is a cheap and commonly used analgesic in daily clinical practice, through prescription by health care providers but definitely also by self-care by patients, it has barely been investigated in clinical trials, limiting the ability to properly advise on its use in treatment recommendations (**chapter 4**). Furthermore, topical NSAIDs are now advised as first-line drug treatment to relieve hand osteoarthritis symptoms based on efficacy in one placebo-controlled trial (**chapter 4**), but it is unknown whether its benefits outweigh the higher costs of these drugs, and since the advice is based on only one trial, it needs to be replicated.

Because of the large number of new trials performed since the first EULAR recommendations for the management of hand osteoarthritis published in 2007, it was timely to update these with the newly accrued evidence. **Chapter 4** presents the 2018 update of the EULAR recommendations for the management of hand osteoarthritis, based on a review of the literature (**chapter 3**) and expert opinion from an international task force of experts in the field. The task force, consisting of 19 physicians, health care professionals and patients from 10 European countries, agreed upon five overarching principles and 10 recommendations. The overarching principles covered treatment goals, information provision, individualisation of treatment, shared decision-making and the need to consider multidisciplinary and multimodal (non-

pharmacological, pharmacological and surgical) treatment approaches. The role of different non-pharmacological therapies is covered in the first three recommendations, where the provision and use of education and assistive devices is discussed (#1), as well as hand exercises (#2), and orthoses (#3). Several pharmacological therapies are the topic of recommendations 4-8. Topical treatments are preferred over systemic treatments, with topical NSAIDs as the first-line choice (#4), while oral analgesics, particularly NSAIDs, are to be considered for symptom relief, as long as the risk-benefit-ratio is taken into account and prescription is of limited duration (#5). Chondroitin sulfate may be considered for symptom relief (#6). Intra-articular injections of glucocorticoids are generally not recommended, except in particular cases, for example in patients with painful interphalangeal osteoarthritis (#7). Prescription of conventional or biologic disease-modifying antirheumatic drugs is discouraged (#8). Considerations for surgery are discussed in recommendation #9. The last recommendation (#10) pertains to follow-up.

The recommendations presented in **chapter 4** provide up-to-date guidance on the management of patients with hand osteoarthritis. The major changes in comparison with the 2007 recommendations show that we have gained new insights into the management of this disease in the last decade. Recommendations and guidelines are important tools to facilitate the integration of research findings into daily clinical practice. However, in order to substantially influence daily clinical practice and care for patients with hand osteoarthritis, dissemination and implementation of recommendations is crucial. Uptake of guidelines in clinical practice has proven to be a challenge. While there are many published guidelines for osteoarthritis, research has shown that a gap exists between the care that is recommended versus the care that patients receive.[7-9] This problem is not unique for the field of osteoarthritis: the same holds true for the uptake of recommendations in other chronic rheumatic diseases, such as rheumatoid arthritis.[10]

When comparing recommended with delivered health care in daily clinical practice, an interesting paradox becomes apparent: the failure to deliver needed services, while continuing to deliver unnecessary services. These two concepts are referred to as "underuse" and "overuse" of health care.[11] It has been shown that underuse of simple and effective interventions, as well as overuse of ineffective services occur often and simultaneously.[12,13] Both concepts are equally problematic: underuse leads to avoidable suffering from disease, while overuse may lead to avoidable physical harms from adverse events and financial harms from wasted resources. Underuse can arise from several sources, including poor access to health care, lack of availability in the health care system, failure of providers to deliver the service and failure of patients to use it.[13] Factors that drive overuse are also numerous, including, for example, effects of money flow on incentives and integration of care, knowledge gaps, misleading psychological tendencies and erroneous beliefs.[14] Examples of under- and overuse can also be found in osteoarthritis health care.

A compelling example of underuse in osteoarthritis care was demonstrated in a trial in which health care providers caring for patients with hip or knee osteoarthritis were randomised to receiving evidence-based treatment recommendations by a study team versus usual care.[15] While many providers in the intervention group were recommended by the study team to provide simple interventions such as physical therapy (49%), knee braces (41%) or topical

NSAIDs (50%), only part of the providers actually advised or prescribed these to the patient in question (physical therapy: 20%, knee brace: 36%, topical NSAIDs not reported) and even fewer patients actually received the treatment (7%, 9% and 15%, respectively). The same authors found similar results in a larger trial with a similar intervention.[16] These results illustrate how underuse originates from multiple sources, increasing the magnitude of the problem: recommended care was not provided by the health care provider and patients failed to adhere to the prescribed care. While the first can likely be improved by efforts in dissemination and implementation of recommendations, the second deserves at least as much attention, and is crucial for any treatment to succeed.

As an example of overuse in osteoarthritis care, the same trials also showed that the number of patients in whom joint injections were provided outnumbered the instances in which injections were actually recommended.[15,16] Other studies have reported the rate of inappropriate total knee replacement in Spain and the United States to be 26% and 34%, respectively.[12] More indirect evidence of overuse within osteoarthritis health care comes from otherwise unexplained inter- and across country variations in certain interventions, such as a 13-fold regional variation in the rate of arthroscopic knee lavage in England.[12]

Examples of steps that have already been taken to gain awareness of the updated recommendations presented in **chapter 4** are presentations by members of the task force at national and international rheumatology conferences. In addition, a EULAR Health Professional project that aims at implementing best practice for hand osteoarthritis, for example by making short instruction videos which hand exercises patients can do, is ongoing. Other methods to aid dissemination of these recommendation to health care providers who see patients with hand osteoarthritis in daily clinical practice in the Dutch situation could encompass publication of a Dutch translation by relevant national societies, such as the Dutch rheumatology society (Nederlandse Vereniging voor Reumatologie, NVR) but also the Dutch general practice society (Nederlandse Huisartsen Genootschap, NHG). Ideally, this should not only be a literal textual translation, but also a translation to Dutch clinical practice, acknowledging barriers for implementation of the recommended care. For example, while topical NSAIDs are advised as first-line pharmacological treatment in these new recommendations, in the current Dutch health care system topical NSAIDs are not available free of charge. For some patients paying for medication will be an important barrier to adherence, and a risk for underuse.

In conclusion, updating the recommendations for the management of hand osteoarthritis alone is not enough. Care should be taken to support the uptake of these recommendations in daily clinical practice, and to be aware of over- and underuse in osteoarthritis care.

Inflammation as treatment target

From the studies in **part I** we learned that available treatment options for hand osteoarthritis are currently unsatisfactory, and new treatment options are warranted. To develop novel therapies, it is crucial to know which tissue to target by treatment. However, at this moment important omissions in our understanding of the aetiology of hand osteoarthritis hamper the search for such a treatment target.

Studying the pathogenesis of hand osteoarthritis is difficult for several reasons. Due to the localisation of the disease in the small hand joints, it is difficult to obtain samples of diseased tissue for researchers, and the quantities of obtained tissue are small. Also, existing animal models of osteoarthritis are more reflective of osteoarthritis of weight-bearing joints, such as the knees or hips, than of the hands, of which no animal models exist. Our understanding of hand osteoarthritis pathogenesis therefore largely comes from epidemiological studies of genetic data, advanced imaging data and clinical trials. In the next paragraphs, we will focus on the latter two.

Since the introduction of ultrasound and magnetic resonance imaging (MRI) our knowledge of hand osteoarthritis has vastly increased. In contrast to conventional radiographs, these imaging modalities provide us with the opportunity to visualise other joint structures than bone, including the collateral ligaments, cartilage and synovium, and on MRI the subchondral bone can be assessed. Studies using ultrasound and MRI showed that inflammatory changes are often present in hand joints affected with osteoarthritis.[17-19] Inflammatory signs that can be assessed on ultrasound include synovitis, effusion and power Doppler signal (PDS; a sign of increased vascularisation). Synovitis can also be assessed on MRI. Besides that, bone marrow lesions (BMLs; ill-defined lesions in the subchondral bone with high signal intensity on T2-weighted fat-suppressed images) can be seen with MRI, which in osteoarthritis may primarily be a sign of increased bone remodelling.[20] Subsequent studies have demonstrated that these inflammatory signs are associated with clinical features, particularly joint tenderness.[17-19,21] Furthermore, longitudinal studies have demonstrated that presence of inflammation in a joint was associated with radiographic progression,[22-25] as well as erosive progression in the same joint.[23,26,27] Interestingly, inflammation was associated with radiographic progression even after adjustment for the amount of radiographic damage at baseline, which is known to be a predictor for future radiographic damage.[28] Finally, it was also shown that an increase in inflammatory signs on MRI is associated with the development of joint tenderness, independent of structural progression.[29,30] Interestingly, one of these studies also demonstrated the opposite: an association between decreasing synovial inflammation and less joint tenderness.[30]

Evidence from these imaging studies led us to believe that inflammation plays an important role in hand osteoarthritis, and that it may be a viable target for treatment.

To investigate this hypothesis, we set up a proof-of-concept study. In the HOPE study, a fourteen-week placebo-controlled randomised clinical trial, we investigated the effectiveness of short-term low-dose oral prednisolone in patients with painful hand osteoarthritis who had evidence of synovial inflammation. The well-known potent anti-inflammatory characteristics of prednisolone provided us with the opportunity to investigate whether inflammatory signs in patients with hand osteoarthritis can be modulated, and whether this consequently has beneficial effects on their signs and symptoms. In this trial, of which the results are presented in **chapter 5**, we found that six-week treatment with prednisolone led to a substantial improvement in finger pain, which was our primary outcome. Secondary outcome measures of pain and function were also consistently more improved in the prednisolone group, and a remarkable higher proportion

of patients in the intervention group fulfilled the OMERACT-OARSI responder criteria. To put these results into context, we can compare the effect sizes of different therapies. The effect size is a way to quantify the magnitude of an effect. Cohen's d, a commonly used type of effect size, is calculated by dividing the difference of the mean of the two intervention groups by the standard deviation. As described in **part I**, most therapeutic options in hand osteoarthritis that are considered to effectively relieve pain, have an effect size of around 0.2, which can be considered a small effect.[6] NSAIDs have one of the largest effects, with an effect size of 0.4 on pain. In the HOPE study, we found an effect size of 0.7 on pain. The same comparison can be made for function, for which the effect size of 0.6 in the HOPE study substantially exceeds the effect sizes of all other interventions, which lie around 0.2.

Another, at least as important finding, is the effect we found on clinical and imaging measures of inflammation. Showing that inflammation in hand osteoarthritis can be modulated is an important first step towards targeted treatment in hand osteoarthritis. Interestingly, while prednisolone had a significant beneficial effect on ultrasound synovitis and MRI BMLs, between-group differences in the other imaging parameters of inflammation (ultrasound PDS, MRI synovitis) were small. Possibly, the prevalence, particularly of PDS, was too low to detect change. Alternatively, PDS and MRI synovitis may not be sensitive-to-change, which can either be a characteristic of the feature itself or a shortcoming in the scoring method that was used, and these imaging features may represent different aspects of inflammation. Another noteworthy finding was that in contrast to the other imaging features, the between-group difference in MRI BMLs primarily stemmed from a deterioration in the placebo group. Few other studies assessed the effects of anti-inflammatory therapies on inflammation on ultrasound or MRI in hand osteoarthritis, generally with negative results.[31-34] None of the studies that included MRI synovitis as an outcome measure could detect a change in this feature,[31,33,34] while one trial observed a significant decrease in MRI BMLs.[33] The trials that used ultrasound were all negative, though variable quality of ultrasound machines and a generally limited reproducibility of scores hindered the detection of between-group differences by ultrasound in many studies.[32,33] Furthermore, it is important to realise that comparison with these studies is hampered by the concurrent negative results for clinical outcome measures of those studies. In other words: those interventions were not effective in the first place, so a change in joint inflammation may also not be expected.

After tapering the study medication, beneficial effects on signs and symptoms were not sustained and resumed baseline values. While the observed symptomatic effect at week six was substantial, it is unknown whether continued treatment with prednisolone would have led to further improvements. Future studies to investigate the optimal dosage and duration of treatment are warranted. This could be done in trials employing treat-to-target strategies. One could for example consider to perform a trial with multiple arms with a range of initial prednisolone dosages to find an optimal dosage, but also trial designs with a step-down-step-up protocol dependent on the fulfilment of a certain definition of low and high disease activity as treatment target are of interest, and possibly a combination of these. Trials with treat-to-target strategies are highly dependent on the choice of a suitable definition for low and high disease activity on which treatment decisions are subsequently based, so this would first warrant further investigation, possibly using data acquired in the HOPE study.

The HOPE study provides evidence for the efficacy and safety of short-term treatment with low-dose prednisolone in patients who experience a flare of their disease. Prednisolone is an inexpensive, widely available drug, providing ample opportunity to directly apply these findings in daily clinical practice. However, we included hand osteoarthritis patients with specific characteristics, and therefore the results of this study cannot be generalised to all patients with hand osteoarthritis. It is likely that joint inflammation is a prerequisite for the effectiveness of prednisolone. While in clinical practice confirmation of presence of inflammation on ultrasound is impractical for many reasons, such as the availability of an ultrasound machine, time constraints, and lack of expertise, doctors who consider prescribing prednisolone to a patient with hand osteoarthritis should at least confirm that there is clinical evidence of joint inflammation. Also, this study only provides evidence for treatment for a short and clearly limited period of time.

Besides the interesting results of the efficacy and safety of prednisolone, the HOPE study also taught us other, more general lessons regarding clinical trials in hand osteoarthritis.

We employed stringent inclusion criteria and selected a specific subset of hand osteoarthritis patients. While this could be viewed as a limitation, since it limited the generalisability of the results as discussed above, it is also an important strength of the study. Osteoarthritis is a heterogeneous disease. Clear patient stratification is therefore essential to select patients who will most likely benefit from treatment. Failure to select the appropriate patient population may have been a reason that so many previous trials in hand osteoarthritis were negative. Moreover, the proof-of-concept nature of the trial, to evaluate inflammation as treatment target, made it essential to include patients with evidence of joint inflammation. In other words, we performed an explanatory trial, as opposed to a pragmatic trial, a distinction first proposed by Schwartz and Lellouch.[35] Explanatory trials are designed to confirm a physiological or clinical hypothesis, whereas pragmatic trials inform clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice.[36] While explanatory or mechanistic trials often have higher internal validity, pragmatic trials often have the advantage of improved external validity. Therefore, the ideal time to perform a pragmatic trial would be during the implementation stage of an intervention, and only after we have any real understanding of treatment benefit and potential adverse effects.

One of our inclusion criteria was the presence of a flare in hand pain after analgesic washout of at least 20 mm on a visual analogue scale (VAS). It has been suggested that flare designs, which are especially common in NSAID trials, are efficient, because it would lead to larger treatment effects and selection of patients with an "inflammatory" phenotype. However, during the course of the HOPE study, the flare criterion appeared difficult to assess and a reason for ineligibility of a substantial number of patients, despite a clinical presentation with "inflammatory" hand osteoarthritis and fulfilling other inclusion criteria. Therefore, during the course of the trial we decided to also include patients who did not experience a flare after analgesic washout. In accordance with a study published at that time, sensitivity analyses excluding those patients led to highly comparable between-group differences in the primary endpoint as the main analysis.[37] In hindsight, it is debatable whether a flare design was needed in our trial.

Finally, observed differences in the HOPE study between the results of different instruments all measuring the same domain, for example, comparing the treatment effect on pain measured by the VAS or by the Michigan Hand outcomes Questionnaire (MHQ) pain subscale, stresses the necessity of using instruments that are sensitive-to-change, as will be further discussed in one of the next paragraphs of this chapter.

While we were able to demonstrate an effect on pain and inflammation on the short-term, a question that remained unanswered in the HOPE study was whether suppression of inflammation may also modify the disease course of hand osteoarthritis on the long-term. Radiographic progression is a slow process, so to investigate whether suppression of inflammation may retard radiographic progression, studies with long-term follow-up are needed. Future studies investigating long-term effects of treatment with prednisolone on radiographic disease progression are therefore of interest, although, in comparison with short-term studies, the risk-benefit-ratio of prolonged glucocorticoid treatment becomes even more important to consider.

Systemic blockade of tumour necrosis factor (TNF) is also a potent method of suppressing inflammation, which is widely used in other chronic rheumatic diseases, such as rheumatoid arthritis. TNF-alpha is an important proinflammatory cytokine, produced in the inflamed synovium in osteoarthritis and implicated in several processes of osteoarthritis pathophysiology.[38] The clinical efficacy of TNF-inhibitors in patients with hand osteoarthritis has been investigated in several randomised clinical trials.[31,33,39,40] Generally, these trials failed to show beneficial effects on symptom relief, which suggests that, in contrast to for example rheumatoid arthritis, targeting a single cytokine may not be sufficient in osteoarthritis.

Osteoarthritis does not only lead to signs and symptoms such as pain, functional disability and reduced grip strength, but also causes progressive structural joint damage. While short-term clinical trials are ideal to investigate the clinical effects of anti-inflammatory medication, studies with long-term treatment and follow-up are needed to evaluate effects on structural damage. To investigate long-term effects of anti-inflammatory treatment in hand osteoarthritis, we and others took the opportunity to use ten-year follow-up data from the BeST study.[41] The BeST study is a randomised clinical trial originally designed to compare the efficacy of four treatment strategies in recent-onset rheumatoid arthritis patients, including treatment with TNF-inhibitors. Hand osteoarthritis is often present in these patients, either due to co-occurrence of primary osteoarthritis (predominantly in the distal and proximal interphalangeal (DIP and PIP) joints) or due to secondary osteoarthritis (predominantly in the PIP joints). Using data from the BeST study, we analysed the effect of prolonged treatment with TNF-inhibitors on incidental and progressive radiographic osteoarthritis in DIP and PIP joints.[42] We found that treatment with TNF-inhibitors was associated with a reduced risk, albeit small, of osteoarthritis progression in DIP joints after 10-year follow-up in patients with recent-onset rheumatoid arthritis, in line with findings in the same cohort after three-year follow-up.[43] While the study design may not have been ideal, data from that study suggest a role for TNF in the development of joint damage in osteoarthritis.

Interestingly, two clinical trials with a longer follow-up have performed subgroup analyses of the effect of anti-TNF in joints with active joint inflammation at baseline, and demonstrated a reduction in erosive progression after one year in inflamed joints of patients in the active treatment

arm compared to placebo, supporting our observations in the BeST cohort.[33,40] One of these trials further showed that BMLs decreased upon anti-TNF treatment, though no treatment response was seen on synovitis.[33] Further stratification revealed that this reduction of BMLs was primarily present in joints with synovitis at baseline. This apparent contradiction – no effect on synovitis itself, but a more pronounced reduction of radiographic erosive damage and BMLs in joints with inflammation – suggests that the interrelation between synovitis, subchondral bone marrow changes and structural damage is not straightforward. It suggests interplay between synovitis and the subchondral bone, possibly via cytokines like TNF-alpha. There are several pathways through which TNF-alpha can affect the subchondral bone, for example by induction of the production of other proinflammatory cytokines such as IL-6 and IL-8, through induction of the synthesis of matrix metalloproteinases (MMP) by chondrocytes and synovial cells, by activation of the cyclooxygenase-pathway, and by upregulation of the production of nitric oxide.[38] In a biomarker substudy of this trial, MMP-3 was indeed suppressed in the anti-TNF treated group.[44] Furthermore, in-vitro studies have shown that TNF-alpha can induce bone resorption by osteoclasts, and treatment with anti-TNF appeared to improve subchondral bone structure in animal models of osteoarthritis.[45,46] If it is true that TNF produced by inflamed synovium is a link between synovitis and bone processes in osteoarthritis, then inhibition of TNF may have an effect on the subchondral bone without impacting synovitis. Following this line of thought, it is conceivable that omnipotent suppression of inflammation through prednisolone (**chapter 5**) may reduce synovitis, subsequently decrease TNF production, and in this way also have an effect on subchondral bone. Moreover, observational studies have suggested that BMLs have an additive effect on pain when present in combination with synovitis, but that in absence of synovitis, BMLs have little effect on pain.[21,30] If synovitis is the main driver of pain in hand osteoarthritis, this would further explain why an intervention that does not impact synovitis but does reduce BMLs (anti-TNF) does not lead to clinical improvements, while an intervention that impacts synovitis as well as reducing BMLs (prednisolone) does invoke substantial symptom relief.

Future studies are warranted to elucidate this proposed interaction between the synovium and subchondral bone in hand osteoarthritis. As discussed above, while long-term studies of treatment with glucocorticoids would be of interest in this respect, prolonged glucocorticoid treatment is known to be associated with adverse effects that may outweigh the possible benefits. Other interventions also capable of general suppression of inflammation are the recently developed group of janus kinase (JAK) inhibitors, of which the first are now approved for the treatment of several chronic inflammatory rheumatic diseases. JAK inhibitors interfere with cytokine signalling by inhibiting the activity of one or more enzymes of the JAK family, which are crucial for signal transduction of several cytokine receptors. Since this signalling pathway is involved in many different cytokines, the activity of multiple cytokines is suppressed simultaneously. Therefore, a long-term clinical trial with a JAK inhibitor may be an interesting alternative.

In **chapter 9** we zoomed out, and looked at the role of inflammation in osteoarthritis from a completely different perspective, focussing on the systemic low-grade inflammation as is known to be present in obesity. Previous studies had provided evidence that not only mechanical, but also systemic factors are involved in the observed association between obesity and osteoarthritis

(figure 1, **chapter 1**). In the study described in **chapter 9**, we investigated the role of adipokines, bioactive factors produced by adipose tissue, as one of these systemic factors. We observed that increased leptin levels were associated with higher odds of knee and hand osteoarthritis, while adiponectin levels were not associated with osteoarthritis. Thereafter, we performed mediation analyses to investigate whether leptin could be one of the systemic factors connecting adiposity and osteoarthritis. In other words, we questioned whether part of the observed association between adiposity and osteoarthritis was in fact explained by a pathway of associations going from adiposity via leptin to osteoarthritis. Here, leptin is the so-called mediator. We found that leptin was a partial mediator in the association with knee and hand osteoarthritis. Sex-stratified analyses showed that the interrelations between adiposity, leptin and osteoarthritis were generally stronger in women than in men. These sex differences are in line with previous research showing that the aetiology of knee osteoarthritis in men is mainly biomechanical in nature, while in women there is a larger systemic or inflammatory component.[47,48] Another interesting observation was that when we adjusted the knee osteoarthritis analyses for body weight, as a proxy for the mechanical component of adiposity, the mediating effect of leptin only remained present in the lowest weight category. This suggests that in participants with a high body weight the detrimental effect of increased load is the most important determinant of osteoarthritis, while in those with a lower body weight the biomechanical effect is smaller and systemic effects play a larger role. Though this study supports the growing body of evidence for systemic effects of adipose tissue in osteoarthritis, adipokines are likely not the sole systemic factors by which adiposity contributes to osteoarthritis, but just one of the many mechanisms activated in the systemic inflammatory state that is present in obesity.

Thumb base osteoarthritis: a distinct hand osteoarthritis subset

Evidence is accruing that hand osteoarthritis is a heterogeneous disease. Any hand joint can be affected, though it most commonly occurs in the DIP, PIP and first carpometacarpal (CMC-1) joints. Besides the localisation of osteoarthritis in the hand, other factors that can vary between patients include, for example, the associated symptoms, speed of progression, and development of joint erosions. The heterogeneity of the disease is one of the challenges in hand osteoarthritis research.

Different hand osteoarthritis subsets have been proposed, based on their association with distinct risk factor profiles and disease outcomes.[49] The most important subsets include interphalangeal osteoarthritis (with or without nodes), thumb base osteoarthritis and erosive osteoarthritis. Data from studies described in **chapter 6-8** provide support for thumb base osteoarthritis as a distinct hand osteoarthritis subset, as will be discussed below.

A widely used intervention for thumb base osteoarthritis is intra-articular injection with glucocorticoids. However, from a meta-analysis of studies comparing these injections with placebo, presented in **chapter 6**, we had to conclude that intra-articular injection with glucocorticoids is not efficacious in thumb base osteoarthritis. Although the glucocorticoid and placebo groups both improved from baseline, there was no between-group difference. However, a placebo-controlled study of intra-articular glucocorticoid injections in interphalangeal joints did show promising effects on pain upon movement and joint swelling

in the injected joint, although not all endpoints were met.[50] Since the main mechanism of action of glucocorticoids is based on its anti-inflammatory properties, as discussed earlier in this chapter, we hypothesised a different role of inflammation in thumb base compared to finger osteoarthritis.

To explore this hypothesis, we investigated the relation between inflammation, radiographic damage and pain in thumb base osteoarthritis (**chapter 7 and 8**). We observed that, like in other hand joints with osteoarthritis, inflammatory signs on ultrasound and MRI were often present in the thumb base (**chapter 7**). While these inflammatory features were associated with joint tenderness, radiographic damage was a more important determinant, and after adjustment for radiographic damage the relation between inflammation and pain attenuated considerably. This is in contrast to what has been found in interphalangeal osteoarthritis, where the association between inflammation and pain is independent of radiographic damage.[17,21] Yet, to conclude that inflammation is not important in thumb base osteoarthritis is too simple, because additional analyses showed that the combined presence of inflammation and structural damage in a thumb base joint had an additive effect on pain, or in other words: the whole is greater than the sum of its parts (**chapter 7**).

Next, we set out to investigate whether a change in inflammation affects the course of joint pain in the thumb base. From interphalangeal osteoarthritis we knew that more synovitis was associated with more pain, and that vice versa less synovitis was associated with less pain, and also that fluctuation in BMLs amplified this effect of synovitis on change in pain.[29,30] In the thumb base we saw that an increase in synovitis and BMLs was associated with an increase in pain, particularly in joints with osteophytes at baseline (**chapter 8**). The number of joints with decrease in synovitis was too small to assess its relation to decrease in pain. A decrease in BMLs was associated with a decrease in pain.

Taking the results of **chapters 7 and 8** together, radiographic damage is the most important predictor of pain in thumb base osteoarthritis cross-sectionally, yet a change in inflammatory features may still be relevant. This is of interest for clinical trials. The inclusion criteria used in the trials of intra-articular glucocorticoid injections in thumb base osteoarthritis focussed on the presence of radiographic damage and/or pain, disregarding whether inflammation was present. If the trials would have selected patients with radiographic damage and concurrent joint inflammation, the trials may have led to different results. In the HOPE study (**chapter 5**) we deliberately excluded patients with predominantly thumb base complaints. Still, we observed an improvement in thumb base pain in the prednisolone group compared with placebo, albeit less than the observed effect on finger pain. This difference with the trials of intra-articular glucocorticoids may have been caused by the selection of patients with an "inflammatory" osteoarthritis phenotype, and therefore a higher prevalence of inflammation in the thumb base. It is also likely that patients in the HOPE study had less severe thumb base osteoarthritis, especially less radiographic damage, than the patients included in the trials of intra-articular glucocorticoid injections, which has an important influence on (change in) pain as we saw in **chapters 7 and 8**. Since the analyses described in **chapter 8** were hampered by the low amount of change in both inflammatory features and pain, it would be interesting to repeat these analyses in a positive clinical trial such as the HOPE study.

Even though inflammation also plays a role in thumb base osteoarthritis, it seems to be of less importance than in interphalangeal osteoarthritis, and intertwined with radiographic damage. Differences in underlying aetiology may explain this. The thumb base is a unique joint complex within the hand. It has to bear higher loads than finger joints and has a significantly larger, multidirectional range of motion, at the cost of joint stability.[51] Results from several studies have demonstrated the importance of these mechanical factors. For example, CMC-1 subluxation, higher maximal grip strength and hypermobility are all associated with CMC-1 osteoarthritis, but not with DIP osteoarthritis.[52-55] In the development of thumb base osteoarthritis these mechanical influences likely play a crucial role.

The studies described in **chapter 6-8** underline the importance of separate assessment of hand osteoarthritis subsets. If the relative effect of structural damage on pain is so much larger than that of inflammation in thumb base osteoarthritis, it is reasonable to focus on other types of interventions in thumb base osteoarthritis than those targeting inflammation. It may well be true that assessment of hand osteoarthritis as a whole, with disregard of the existence of specific subsets or phenotypes, has a large effect on study results. Pooling effects of heterogeneous subgroups may lead to null findings, despite a true intervention effect in one of the subgroups included.

While some trials have investigated interventions in certain hand osteoarthritis subsets, such as thumb base splints in thumb base osteoarthritis and anti-inflammatory type medication in so-called "activated" (interphalangeal) osteoarthritis,[56,57] many hand osteoarthritis trials use a clinical diagnosis of hand osteoarthritis or ACR classification criteria as their main inclusion criterion.[58] The ACR classification criteria, however, do not distinguish between osteoarthritis in interphalangeal and thumb base joints. Even more so, patients with isolated thumb base osteoarthritis, without concurrent involvement of interphalangeal joints, do not fulfil the ACR criteria for hand osteoarthritis. Currently, no separate classification criteria for thumb base and interphalangeal osteoarthritis exist. Separate classification criteria for interphalangeal and thumb base osteoarthritis could aid the development of therapies directed specifically at patients suffering from either one of these subsets. However, it is important to realise that osteoarthritis of the interphalangeal and thumb base joints often co-occurs and hand osteoarthritis subsets regularly overlap.[59]

Besides consideration of including the intended patient group in a study, it is important to be able to measure relevant outcomes in these patients. For example, the development of an MRI scoring system for interphalangeal osteoarthritis fuelled our ability to study the role of inflammation in the DIP and PIP joints, which led to increased insights in the disease.[60,61] Investigation of thumb base osteoarthritis with MRI, however, had rarely been done up to recently. This was, among other reasons, due to lack of an MRI scoring system for thumb base osteoarthritis. While ultrasound has been available, MRI has specific advantages over ultrasound in the case of the thumb base, including the ability to evaluate less superficially located joints and the ability to visualise both the radial and ulnar side of the joint. In addition, with MRI the subchondral bone can be assessed. Therefore, we developed the Outcome Measures in Rheumatology

(OMERACT) Thumb base Osteoarthritis MRI Scoring system (TOMS) in collaboration with the OMERACT MRI working group (**chapters 15-16**). The studies presented in **chapter 7 and 8** could only have been performed after development of the OMERACT TOMS.

Outcome measurement

As described in **chapter 1** of this thesis, high-quality outcome measurement is another prerequisite to advance our understanding of this disease. Below are two examples from studies described in **part I and II** of this thesis to illustrate this.

The overview of the available hand osteoarthritis trials (**chapter 2 and 3**) shows that outcome measurement in trials in hand osteoarthritis is still diverse and of variable quality. When several studies investigate the same intervention, but measure either different endpoints or use different instruments to measure the same endpoint, it becomes difficult to synthesise the evidence. In **chapter 3**, despite the inclusion of many trials, meta-analysis was often not possible for this reason. Trials that are performed, but of which results cannot be used, may be considered a form of research waste. Development of core domain sets is a way to reduce this research waste, if they are consistently used. Therefore, it is important to determine the uptake of a core domain set (and avoid that it becomes research waste itself). Although generally the recently published trials included in the systematic review (**chapter 3**) often assessed a larger part of the OMERACT core domain set for hand osteoarthritis than older studies did, uptake of the core domain set in hand osteoarthritis trials has not been formally investigated before, as has been done in some other rheumatic diseases.[62,63]

Another example of the importance of outcome measurement comes from the clinical trial described in **chapter 5**. In this trial we assessed several endpoints with multiple instruments. For example, pain was assessed using the VAS, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) and the MHQ. While the VAS pain and the AUSCAN pain showed a large between-group difference in pain in favour of the intervention group, the between-group difference on the MHQ pain was much smaller. Expressed as a percentage relative change from baseline, the patients in the prednisolone group improved by around 40% on the VAS and AUSCAN, while they relatively improved around 16% on the MHQ. This demonstrates that the choice of measurement instrument can have a large influence on the conclusions of a study. When a trial with an effective intervention uses a measurement instrument that is less sensitive-to-change to measure its primary outcome, effective interventions may be overlooked.

The underlying aim of the studies described in the last part of this thesis was therefore to further outcome measurement in the field of hand osteoarthritis. Research in outcome measurement can roughly be divided into two aspects, which are highly interrelated. First, meaningful endpoints have to be chosen to measure relevant outcomes, which should then be measured in all studies. For this purpose the OMERACT hand osteoarthritis working group presented a core domain set of outcomes to be measured in three settings: clinical trials of symptom modification, clinical trials of structure modification, and observational studies (figure 2, **chapter 1**).[64] Secondly, suitable instruments to measure these endpoints (core domains) have to be chosen and subsequently used in all studies. Before a decision can be made which instrument is most

suitable, the properties of potential instruments have to be compared. The studies in **part III** of this thesis primarily focussed on this second aspect of outcome measurement.

Chapter 10 presents age- and sex-specific reference curves for the AUSCAN, developed in analogy to the famous growth curves for children, in an effort to better interpret scores of this frequently used questionnaire for hand pain, function and stiffness. The reference curves can for example be used to compare AUSCAN scores across different populations, to compare scores of the same population on different occasions or to detect aberrant individual scores.

In **chapter 11 and 12**, we compared the clinimetric properties of several instruments that measure the core domains pain and function (**chapter 11**), and hand mobility (**chapter 12**), in preparation of selection of the most suitable instruments for these domains, as explained earlier in this paragraph. In these studies, assessment was guided by the OMERACT filter, evaluating truth ('Does the instrument measure what it intends to measure?'), discrimination ('Can the instrument discriminate across disease stages?', 'Can the instrument identify change over time?' (often referred to as responsiveness), 'Can the instrument pick up difference between treatment groups in a clinical trial?'), and feasibility ('Can the instrument be applied easily, given constraints of time, money, and interpretability?').[65]

In **chapter 11** we evaluated the MHQ, a questionnaire of hand complaints that was not validated for use in hand osteoarthritis before, and showed that it has several advantages justifying its use in hand osteoarthritis studies. It consists of multiple subscales, which measure different domains. Some of these subscales measure unique domains (work performance, aesthetics and satisfaction), other subscales assess the domains pain and function. The three domains unique for the MHQ were demonstrated to be valid, and can provide useful insights in aspects which are likely of importance for patients with hand osteoarthritis, but are currently understudied in absence of valid measurement instruments. The subscales measuring pain and function were compared to more widely used pain and function questionnaires in hand osteoarthritis (AUSCAN, Functional Index for Hand Osteoarthritis (FIHOA), VAS). Comparison of the individual items of the different questionnaires revealed that each assessed partly the same, but partly also rather different aspects of pain and function. With respect to discrimination and responsiveness, the MHQ generally performed at least as good as the reference instruments. An important advantage of the MHQ with respect to feasibility is that it is freely available, in contrast to the AUSCAN. Disadvantages are that the questionnaire is longer, and that different directions of effect of different subscales may negatively impact its interpretability. Taking all aspects together, none of the instruments was clearly superior to another. In the setting of the cohort in which the analyses of **chapter 11** were performed, sensitivity-to-change could not be investigated. Interestingly, as discussed above, in **chapter 5** we could see that the MHQ pain subscale, as well as the MHQ function subscales, were not as good in discriminating between the treatment groups as other pain and function instruments. This observation warrants a more detailed investigation.

We compared several instruments to measure hand mobility in **chapter 12**, including the Hand Mobility in Scleroderma test (HAMIS), fingertip-to-palm distance during maximal finger flexion and modified Kapandji index, and concluded that HAMIS had slightly more favourable properties. The reliability, feasibility and correlations with other outcome measures were similar

for the various hand mobility tests. However, although all tests could measure finger mobility, only HAMIS could distinguish between patients with and without reduced thumb mobility. HAMIS also appeared the most responsive, though generally the change in hand mobility over the two-year timeframe that was assessed, was small for all tests. The observed low progression rate in hand mobility could mean that the tests are not sensitive enough to measure change over time, in other words, that it is a problem of the instrument. On the other hand, it could also indicate that changes in hand mobility do not occur within a two-year timeframe, which is a problem of the domain. The latter would suggest that this domain is not useful to assess in (usually short-term) clinical trials. To further investigate these remaining research questions, we can again take advantage of data collected in the HOPE study (**chapter 5**), which included assessment of hand mobility, where we know that a change over time occurred in the intervention group in other domains.

In contrast to **chapters 10-11**, **chapter 12** focussed on a domain for clinical trials of structure modification. Besides hand mobility, structural damage, which includes subdomains radiographic damage, aesthetic damage, bony damage and deformity, is another domain intended to be measured in clinical trials of structure modification. From the studies described in **part I** of this thesis, we learned that few trials in hand osteoarthritis so far focussed on structure modification, and those that did found no evidence for disease-modification. In light of the studies on outcome measurement discussed here, it is important to realise that, although it may well be true that these interventions do indeed not have a structure modifying effect, it could also be a problem of the used measurement instruments. This is illustrated by the results presented in **chapter 12** for the domain hand mobility, as discussed above, but the same holds true for the domain structural damage. Put differently, as long as we do not have good measurement instruments to assess the domains of structure modification, finding a disease-modifying drug will be difficult.

When the OMERACT core domain set for hand osteoarthritis studies was endorsed in 2014, a preliminary proposal for suitable instruments was also presented.[64] Those instruments included VAS or numeric rating scale (NRS) to measure pain, FIHOA to measure function, tender joint count to measure joint activity and grip or pinch strength to measure hand strength. However, for several domains (patient global assessment, health-related quality of life, hand mobility) no instrument could be proposed, and several aspects of the proposed instruments also needed to be investigated further before these could be selected as core instruments for those domains. Therefore, a research agenda was compiled, in which the working group summarised the work that still needed to be done to progress selection of instruments for each of the core domains. **Chapter 13** presents the report of the progress made by the OMERACT hand osteoarthritis working group in instrument selection for each of the core domains since that time, as discussed at the 2018 OMERACT conference. Besides an overview of the progress in instrument selection, it presents an updated research agenda to guide future research. An important next step for this working group is to present a set of suitable instruments for domains for which enough data has accrued to be able to compare the properties of the available instruments and make a well-informed decision. Likely, the domains pain and physical function will be the first domains for which instruments can be selected.

One of domains for which instrument development would likely advance hand osteoarthritis research, but which at the same time is one of the most difficult domains to select an appropriate instrument for, is the domain 'joint activity'. Insufficient knowledge about the underlying pathophysiological process and lack of a well-accepted definition for this domain are the main problems hampering instrument development. Nevertheless, the ability to measure whether there is an active osteoarthritis disease process going on in a joint, may be pivotal in interfering in the disease before irreversible joint damage occurs. It could also be helpful in selection of suitable patients for clinical trials. Potential instruments that have been proposed and/or researched for this domain include inflammation on imaging (ultrasound or MRI), joint pain upon palpation ("joint tenderness"), self-reported joint pain, soft tissue swelling and pain while gripping. While individually none of these instruments were satisfactory, it is possible that these instruments complement each other and that a combination of (some of) these instruments may be a better reflection of joint activity. Future studies to investigate combinations of instruments to measure joint activity are warranted. Taking prediction of radiological progression as an anchor to assess suitable instruments may be a useful approach in these studies.

In contrast to the other chapters in **part III** of this thesis, evolving around the investigation of properties of existing measurement instruments, the studies in **chapter 14-16** describe the work done in development of the OMERACT TOMS. As discussed in one of the previous paragraphs of this chapter, thumb base osteoarthritis is an important hand osteoarthritis subset, which deserves separate attention. The development of this MRI scoring system made it possible to investigate the role of inflammation in thumb base osteoarthritis, and to increase our understanding of osteoarthritis in this unique hand joint (**chapter 7 and 8**). Besides the development (**chapter 14**) of the scoring system, in collaboration with the OMERACT MRI working group, we also investigated the reliability of scoring MRIs with this system cross-sectionally (**chapter 14**) and longitudinally (**chapter 16**), and developed an atlas to facilitate the use of the scoring system (**chapter 15**). To further validate the scoring system, a study comparing thumb base MRI with other imaging methods (ultrasound, radiography) that can (partly) visualise similar features would be of interest. Due to the differences in imaging techniques, it is conceivable that MRI is more sensitive than radiography. Whether features, for example small osteophytes or erosions, that can be seen on MRI but not on radiography, are of interest (i.e., can predict disease progression or are associated with complaints) has to be subject of investigation.

Future perspectives

In this chapter we summarised and discussed the findings of the studies described in this thesis, and addressed some of the major challenges in hand osteoarthritis research. First of all, this thesis provides an overview of the current state of treatment options in hand osteoarthritis, including a set of up-to-date recommendations for the management of this disease in daily clinical practice. Furthermore, this thesis contributes to the development of new treatment options for patients with hand osteoarthritis by providing evidence for inflammation as a suitable target for

treatment. Ultimately, this may contribute to the development of treatments that can alter the disease course of osteoarthritis. Moreover, this thesis advances the optimisation of outcome measurement in hand osteoarthritis research.

The HOPE study (**chapter 5**) is at the center of this thesis, and a unique trial in hand osteoarthritis. Besides its clinical application, providing evidence for a new treatment option to relieve symptoms of patients with hand osteoarthritis, this trial also advances the field in two other aspects. Not only does it provide more insights in the disease pathogenesis, showing that inflammation can be modulated in hand osteoarthritis, for many of the proposed follow-up studies, especially those with regard to outcome measurement, data collected in the HOPE study are invaluable.

Although the studies described in this thesis provide us with new insights in different aspects of hand osteoarthritis, many questions remain or were raised by the studies that were conducted, warranting future research. Throughout this chapter we have discussed how these studies may affect our current thinking about pathophysiology and clinical care for patients with hand osteoarthritis, and how they may provide guidance to future studies.

REFERENCES

1. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437-41.
2. Marshall M, Watt FE, Vincent TL, et al. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. *Nat Rev Rheumatol* 2018;14:641-56.
3. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
4. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
5. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
6. Cohen J. *Statistical power analysis for the behavioral sciences*, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
7. Denoeud L, Mazieres B, Payen-Champenois C, et al. First line treatment of knee osteoarthritis in outpatients in France: adherence to the EULAR 2000 recommendations and factors influencing adherence. *Ann Rheum Dis* 2005;64:70-4.
8. Porcheret M, Jordan K, Jinks C, et al. Primary care treatment of knee pain--a survey in older adults. *Rheumatology* 2007;46:1694-700.
9. Steel N, Bachmann M, Maisey S, et al. Self reported receipt of care consistent with 32 quality indicators: national population survey of adults aged 50 or more in England. *BMJ* 2008;337:a957.
10. Gvozdenovic E, Allaart CF, van der Heijde D, et al. When rheumatologists report that they agree with a guideline, does this mean that they practise the guideline in clinical practice? Results of the International Recommendation Implementation Study (IRIS). *RMD Open* 2016;2:e000221.
11. Saini V, Brownlee S, Elshaug AG, et al. Addressing overuse and underuse around the world. *Lancet* 2017;390:105-07.
12. Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet* 2017;390:156-68.
13. Glasziou P, Straus S, Brownlee S, et al. Evidence for underuse of effective medical services around the world. *Lancet* 2017;390:169-77.
14. Saini V, Garcia-Armesto S, Klemperer D, et al. Drivers of poor medical care. *Lancet* 2017;390:178-90.
15. Allen KD, Yancy WS, Bosworth HB, et al. A combined patient and provider intervention for management of osteoarthritis in veterans: a randomized clinical trial. *Ann Intern Med* 2016;164:73-83.
16. Allen KD, Oddone EZ, Coffman CJ, et al. Patient, provider, and combined interventions for managing osteoarthritis in primary care: a cluster randomized trial. *Ann Intern Med* 2017;166:401-11.
17. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
18. Keen HI, Wakefield RJ, Grainger AJ, et al. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum* 2008;59:1756-63.
19. Kortekaas MC, Kwok WY, Reijnierse M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367-9.
20. Loef M, van Beest S, Kroon FPB, et al. Comparison of histological and morphometrical changes underlying subchondral bone abnormalities in inflammatory and degenerative musculoskeletal disorders: a systematic review. *Osteoarthritis Cartilage* 2018;26:992-1002.
21. Liu R, Damman W, Reijnierse M, et al. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. *Osteoarthritis Cartilage* 2017;25:1093-99.
22. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-17.
23. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. *Ann Rheum Dis* 2016;75:117-23.
24. Kortekaas MC, Kwok WY, Reijnierse M, et al. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. *Ann Rheum Dis* 2015;74:1720-4.
25. Mathiessen A, Slatkowsky-Christensen B, Kvien TK, et al. Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years. *Ann Rheum Dis* 2016;75:825-30.
26. Mancarella L, Addimanda O, Pelotti P, et al. Ultrasound detected inflammation is associated with the development of new bone erosions in hand osteoarthritis: a longitudinal study over 3.9 years. *Osteoarthritis Cartilage* 2015;23:1925-32.

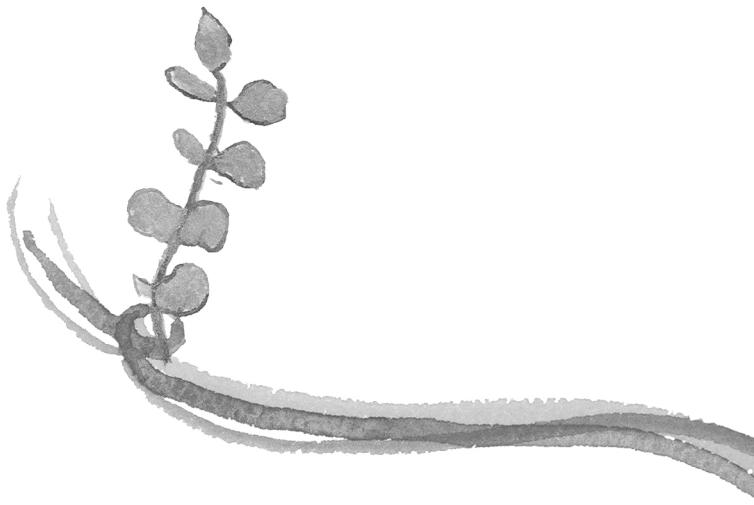
27. Kortekaas MC, Kwok WY, Reijnierse M, et al. Brief report: association of inflammation with development of erosions in patients with hand osteoarthritis: a prospective ultrasonography study. *Arthritis Rheumatol* 2016;68:392-7.
28. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.
29. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Ann Rheum Dis* 2016;75:702-8.
30. Van Beest S, Damman W, Liu R, et al. In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study. *Osteoarthritis Cartilage* 2019;27:1048-56.
31. Aitken D, Pan F, Laslett L, et al. A randomised double-blind placebo-controlled crossover trial of humira (adalimumab) for erosive hand osteoarthritis: the HUMOR trial. *Osteoarthritis Cartilage* 2017;25:S9.
32. Keen HI, Wakefield RJ, Hensor EM, et al. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. *Rheumatology* 2010;49:1093-100.
33. Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:1757-64.
34. Wenham CYJ, Hensor EMA, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* 2012;51:2286-94.
35. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis* 1967;20:637-48.
36. Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016;375:454-63.
37. Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic review and meta-analysis. *Ann Rheum Dis* 2016;75:1971-78.
38. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011;7:33-42.
39. Chevalier X, Ravaud P, Maheu E, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697-705.
40. Verbruggen G, Wittoek R, Vander Cruyssen B, et al. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891-8.
41. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406-15.
42. Loef M, Kroon FPB, Bergstra SA, et al. TNF-inhibitor treatment is associated with lower risk of hand osteoarthritis progression in rheumatoid arthritis patients after 10 years. *Rheumatology* 2018;57:1917-24.
43. Güler-Yuksel M, Allaart CF, Watt I, et al. Treatment with TNF-alpha inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. *Osteoarthritis Cartilage* 2010;18:1256-62.
44. Kroon F, Bay-Jensen AC, Wittoek R, Verbruggen G, Smolen JS, Kloppenburg M, Ramonda R. Etanercept therapy leads to reductions in matrix metalloproteinase-3 in patients with erosive hand osteoarthritis. *Scand J Rheumatol* 2020;49:167-68.
45. Bertolini DR, Nedwin GE, Bringman TS, et al. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;319:516-8.
46. Ma CH, Lv Q, Yu YX, et al. Protective effects of tumor necrosis factor-alpha blockade by adalimumab on articular cartilage and subchondral bone in a rat model of osteoarthritis. *Braz J Med Biol Res* 2015;48:863-70.
47. Kellgren JH, Lawrence JS. Osteo-arthrosis and disk degeneration in an urban population. *Ann Rheum Dis* 1958;17:388-97.
48. Visser AW, de Mutsert R, Loef M, et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. *Osteoarthritis Cartilage* 2014;22:197-202.
49. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
50. Spolidoro Paschoal Nde O, Natour J, Machado FS, et al. Effectiveness of triamcinolone hexacetonide intraarticular injection in interphalangeal joints: a 12-week randomized controlled trial in patients with hand osteoarthritis. *J Rheumatol* 2015;42:1869-77.
51. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
52. Chaisson CE, Zhang Y, Sharma L, et al. Grip strength and the risk of developing radiographic hand osteoarthritis: results from the Framingham Study. *Arthritis Rheum* 1999;42:33-8.

53. Hunter DJ, Zhang Y, Sokolove J, et al. Trapeziometacarpal subluxation predisposes to incident trapeziometacarpal osteoarthritis (OA): the Framingham Study. *Osteoarthritis Cartilage* 2005;13:953-7.
54. Jonsson H, Valtysdottir ST. Hypermobility features in patients with hand osteoarthritis. Osteoarthritis Cartilage. *Osteoarthritis Cartilage* 1995;3:1-5.
55. Jonsson H, Valtysdottir ST, Kjartansson O, et al. Hypermobility associated with osteoarthritis of the thumb base: a clinical and radiological subset of hand osteoarthritis. *Ann Rheum Dis* 1996;55:540-3.
56. Talke M. Treatment of Heberden and Bouchard types of finger osteoarthritis. Comparison between local etofenamate and oral indomethacin. *Therapiewoche* 1985;35:3948-54.
57. Zacher J, Burger KJ, Farber L, et al. Topical diclofenac versus oral ibuprofen: A double blind, randomized clinical trial to demonstrate efficacy and tolerability in patients with activated osteoarthritis of the finger joints (Heberden and/or Bouchard arthritis). [German]. *Aktuel Rheumatol*. 2001;26:7-14.
58. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
59. Marshall M, Peat G, Nicholls E, et al. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. *Osteoarthritis Cartilage* 2013;21:1674-84.
60. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. *Ann Rheum Dis* 2011;70:1033-8.
61. Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386-91.
62. Bautista-Molano W, Navarro-Compan V, Landewé RB, et al. How well are the ASAS/OMERACT core outcome sets for ankylosing spondylitis implemented in randomized clinical trials? A systematic literature review. *Clin Rheumatol* 2014;33:1313-22.
63. Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 2017;357:j2262.
64. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190-7.
65. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198-9.



CHAPTER 18

Nederlandse samenvatting



NEDERLANDSE SAMENVATTING

Artrose is een veelvoorkomende chronische reumatische aandoening die geassocieerd is met een hoge persoonlijke en maatschappelijke ziektelast. De gewrichten in de handen zijn hierbij vaak aangedaan. Handartrose leidt tot pijn en stijfheid, functionele beperkingen, verminderde grijpkracht en een verminderde kwaliteit van leven. Klinische kenmerken van de ziekte zijn benige zwellingen en vergroeiingen van de handgewrichten, van tijd tot tijd gepaard gaand met zachte zwelling en roodheid.

Ondanks de hoge prevalentie en substantiële ziektelast, zijn de behandelingsmogelijkheden van handartrose beperkt. Er bestaan geen behandelingen die het beloop van de ziekte kunnen beïnvloeden, en behandelingen om de symptomen te verlichten zijn op zijn best matig effectief. Lang was er weinig aandacht voor handartrose, maar dit is aan het veranderen. Hierdoor is het aantal studies naar handartrose toegenomen, maar toch is de voortgang in het vinden van een goede behandeling vooralsnog teleurstellend. Er zijn meerdere zaken die een echte doorbraak in de weg staan.

Ten eerste is het nog onduidelijk op welk doelwit behandelingen zich moeten richten (een zgn. 'treatment target'). Dit komt grotendeels door tekortkomingen in onze kennis van de onderliggende ziekteprocessen die leiden tot het ontstaan van artrose. Artrose werd voorheen beschouwd als een degeneratieve ziekte die vooral het kraakbeen aantast ('slijtage'). Dit beeld is echter aan het veranderen. De laatste jaren is er steeds meer bewijs dat ontsteking een belangrijke rol speelt in het ziekteproces van artrose. Met onderzoeken met echografie en magnetic resonance imaging (MRI) ontdekte men dat gewrichtsontsteking bij handartrose regelmatig voorkomt, en dat dit gepaard gaat met gewrichtspijn en de ontwikkeling van gewrichtsschade. Dit alles is een reden om te denken dat ontsteking zou kunnen dienen als behandeldoel.

Een ander probleem wordt gevormd door tekortkomingen in het meten van uitkomstmaten in onderzoek naar handartrose. Het goed kunnen meten van uitkomsten, zowel in studies als in de klinische praktijk, is essentieel om een behandeleffect adequaat te kunnen beoordelen. Hierbij zijn verschillende aspecten van belang. Allereerst om relevante uitkomsten te meten, en ook dat iedereen dezelfde uitkomsten meet. Deze standaardisatie van te meten uitkomsten kan worden gefaciliteerd door het opstellen van een set van 'kern uitkomsten' (zgn. 'core outcome sets'). Vervolgens moeten deze kern uitkomsten gemeten worden door gestandaardiseerde, valide en betrouwbare meetinstrumenten. Handartrose heeft een aantal specifieke aspecten die de ontwikkeling van uitkomstmaten en meetinstrumenten compliceren. Zo bestaat de hand uit vele individuele gewrichten, waarvan meestal meerdere gewrichten tegelijk zijn aangedaan. Ook is er steeds meer bewijs dat handartrose een heterogene ziekte is, met verschillende uitingsvormen ('fenotypen' of 'subsets') die geassocieerd zijn met andere risicofactoren en uitkomsten en mogelijk ook een andere behandeling behoeven.

Huidige behandelingsmogelijkheden bij handartrose

In **deel I** van dit proefschrift hebben we de huidige behandelingsmogelijkheden bij handartrose geëvalueerd. **Hoofdstuk 2 en 3** geven een overzicht van alle beschikbare studies naar de verschillende behandelmogelijkheden, variërend van niet-farmacologische tot farmacologische en zelfs chirurgische behandelingen. Gegevens van meerdere studies laten zien dat handoefeningen en langdurig dragen van een duimspalk effectieve niet-farmacologische therapieën zijn die symptomen kunnen verlichten. Daarnaast laten afzonderlijke studies positieve resultaten zien voor strategieën gericht op gebalanceerd belasten van gewrichten ('joint protection') en het gebruik van hulpmiddelen (zoals aangepast bestek, ergonomische pennen of blikopeners). De farmacologische behandeling die het meest effectief bleek in het verlichten van symptomen was behandeling met 'non-steroidal anti-inflammatory drugs' (NSAID's), zowel topicale als orale preparaten. Afzonderlijke studies rapporteerden positieve effecten van chondroïtine sulfaat en gewrichtsinjecties met glucocorticoïden in de interfalangeale gewrichten.

Alhoewel er uit **hoofdstuk 2** en **3** bleek dat er in de afgelopen jaren veel nieuwe studies naar de behandeling van handartrose zijn gepubliceerd, was de meerderheid van de onderzochte behandelingen niet effectief en bleek de effectiviteit van behandelingen die dat wel waren op zijn best matig. Bovendien onderzochten slechts enkele onderzoekers of een behandeling het beloop van de ziekte kon beïnvloeden, door te kijken naar het effect van een behandeling op gewrichtsschade, en was er geen behandeling die hierin slaagde.

Vanwege een groot aantal publicaties sinds het verschijnen van de eerste richtlijn voor de behandeling van handartrose door de Europese reumatologie vereniging (EULAR) in 2007, was het nodig deze richtlijn te actualiseren. De update van deze richtlijn, gepresenteerd in **hoofdstuk 4**, is gebaseerd op een systematisch literatuuroverzicht (**hoofdstuk 3**) en de mening van een internationale groep experts op het gebied van handartrose, waaronder artsen, paramedici en patiënten. Er werden vijf zgn. 'overarching principles' (overkoepelende principes die worden geacht aan de basis te liggen van de behandeling van patiënten met handartrose) en tien 'recommendations' (aanbevelingen) geformuleerd.

Ontsteking als doelwit van behandeling

Van de studies in **deel I** van dit proefschrift hebben we geleerd dat de behandelingsmogelijkheden bij handartrose momenteel tekortschieten. Om nieuwe behandelingen te onderzoeken, is het cruciaal om te weten waar deze behandeling zich op moet richten, met andere woorden, wat het behandeldoel of 'treatment target' is. In **deel II** van dit proefschrift hebben we onderzocht of ontsteking, waarvan in eerdere studies aan het licht is gekomen dat het een belangrijke rol speelt bij handartrose, een geschikt behandeldoel zou kunnen zijn.

Om dit te onderzoeken hebben we een gerandomiseerde dubbelblinde studie opgezet, waarin we patiënten met handartrose die pijnklachten hadden en ook ontsteking van één of meer handgewrichten zes weken lang behandelden met een lage dosering prednisolon (een sterke onstekingsremmer) of placebo. Na zes weken werd de studiemedicatie in twee weken afgebouwd en vervolgden we alle deelnemers nog eens zes weken zonder dat ze studiemedicatie gebruikten. De resultaten van de Hand Osteoarthritis Prednisolone

Efficacy (HOPE) studie worden in **hoofdstuk 5** beschreven. We zagen dat behandeling met prednisolon ten opzichte van placebo leidde tot een substantiële verbetering in vingerpijn (onze belangrijkste uitkomstmaat). Ook secundaire uitkomstmaten van pijn en functie verbeterden meer in de prednisolon groep, en er was een groot verschil in het aantal patiënten dat een behandelrespons liet zien. Om deze resultaten in de context van huidige behandelingsmogelijkheden bij handartrose te zetten, kunnen we de grootte van de behandeleffecten ('effect size') van verschillende behandelingen vergelijken. De meeste effectieve behandelingen bij handartrose hebben een behandeleffect van rond de 0.2, wat we meestal zien als een klein effect. Grofweg het grootste effect dat we kennen op pijn is dat van NSAID's, met een behandeleffect van 0.4. In de HOPE studie daarentegen, vonden we een behandeleffect van 0.7. Behalve een effect op pijn, vonden we ook een verbetering van tekenen van ontsteking in de vingergewrichten op echografie en MRI, en ook op klinische tekenen van ontsteking. Nadat de behandeling werd afgebouwd, verdwenen de positieve effecten van de behandeling geleidelijk weer. De resultaten van deze studie laten niet alleen zien dat een korte kuur prednisolon in lage dosering een effectieve behandelingsmogelijkheid is voor patiënten met handartrose die een opvlamming ('flare') van de ziekte hebben, maar ook dat ontsteking bij handartrose kan worden beïnvloed. Dit laatste is een belangrijke eerste stap is in doelgerichte behandeling bij handartrose.

In **hoofdstuk 9** hebben we vanuit een heel ander perspectief gekeken naar de rol van ontsteking bij handartrose, door ons te concentreren op de systemische laaggradige ontsteking die aanwezig is bij mensen met overgewicht. Een interessante observatie uit eerder onderzoek is dat mensen met overgewicht niet alleen een hoger risico hebben op de ontwikkeling van knieartrose, maar ook op het ontwikkelen van handartrose. Alhoewel de ontwikkeling van knieartrose bij overgewicht goed zou kunnen ontstaan door de verhoogde krachten op het kniegewricht, is dit voor handartrose onwaarschijnlijk (we lopen immers niet op onze handen). Deze opmerkelijke observatie leidde tot verder onderzoek, waaruit bleek dat overgewicht niet alleen via toegenomen mechanische belasting van een gewricht leidt tot artrose (vnl. in de knie), maar ook via systemische effecten die overgewicht heeft op het lichaam (vnl. in de hand). In **hoofdstuk 9** hebben we onderzocht of adipokines, stofjes uitgescheiden door vetcellen, een van deze systemische factoren zouden kunnen zijn, en zo een schakelrol spelen in de relatie tussen overgewicht en artrose. Deze schakelrol noemen we met een ander woord 'mediatie'. We onderzochten twee bekende adipokines: leptine en adiponectine. Leptine bleek een mediator te zijn in de relatie tussen overgewicht en artrose, maar adiponectine niet. Alhoewel onze studieresultaten laten zien dat leptine één van de systemische factoren is die een rol speelt bij het ontwikkelen van artrose in mensen met overgewicht, zijn er naast adipokines hoogstwaarschijnlijk nog veel andere factoren aanwezig in mensen met overgewicht die belangrijk zijn in dit geheel.

Artrose in de duimbasis: een apart fenotype

Zoals eerder besproken in dit hoofdstuk, is het van belang om te onderkennen dat handartrose een heterogene ziekte is met verschillende uitingsvormen of fenotypen, en dat deze fenotypen van belang kunnen zijn bij de behandeling. De belangrijkste fenotypen waar we onderscheid

tussen maken zijn interfalangeale artrose (met of zonder noduli), duimbasisartrose en erosieve artrose. In **hoofdstuk 6-8** hebben we ons gericht op duimbasisartrose, en laten we zien dat dit inderdaad een apart fenotype betreft binnen de handartrose.

De duimbasis is een bijzonder complex van gewrichten binnen de hand, dat essentieel is voor goede handfunctie. De duimbasis bestaat uit twee gewrichten: het carpometacarpale-1 (CMC-1) en het scaphotrapeziotrapezoïd (STT) gewricht. In tegenstelling tot de interfalangeale gewrichten, wat scharniergewrichten zijn, is de duimbasis een zadelgewricht. Dit zorgt ervoor dat het gewricht een grotere bewegingsvrijheid heeft, maar leidt er ook toe dat het gewricht instabieler is. Bovendien staan er grote krachten op de duimbasis.

Uit een systematisch overzicht van de literatuur naar de effectiviteit van gewrichtsinjecties bij handartrose (**hoofdstuk 6**), bleek dat injecties met glucocorticoïden bij duimbasisartrose niet effectiever zijn dan een injectie met placebo. Een studie die keek naar gewrichtsinjecties met glucocorticoïden bij interfalangeale artrose daarentegen, vond veelbelovende effecten op pijn tijdens bewegen en gewrichtszwelling. Hieruit ontstond de hypothese dat ontsteking een andere rol speelt bij duimbasisartrose dan in vingerartrose.

Dit hebben we verder onderzocht door de relatie tussen ontsteking, radiografische schade en pijn bij duimbasisartrose te bekijken (**hoofdstuk 7 en 8**). We zagen dat, in overeenkomst met de vingergewrichten, tekenen van ontsteking op echografie en MRI regelmatig voorkwamen in de duimbasis (**hoofdstuk 7**). Alhoewel deze tekenen van ontsteking geassocieerd waren met gewrichtspijn, bleek radiografische schade een belangrijke determinant van pijn, en na correctie voor radiografische schade werd de relatie tussen ontsteking en gewrichtspijn aanzienlijk kleiner. Dit is in tegenstelling tot wat eerdere studies bij interfalangeale artrose hebben laten zien, waarin de associatie tussen ontsteking en pijn onafhankelijk was van de aanwezigheid van gewrichtsschade. Wanneer zowel ontsteking als gewrichtsschade in de duimbasis aanwezig waren, had dit een supra-additief effect op pijn, of met andere woorden, het geheel is meer dan de som der delen (**hoofdstuk 7**). Vervolgens wilden we weten of verandering in ontsteking het beloop van gewrichtspijn beïnvloedt in de duimbasis. Van studies bij interfalangeale artrose was bekend dat een toename in ontsteking geassocieerd was met een toename in gewrichtspijn en vice versa. In **hoofdstuk 8** beschrijven we het beloop van tekenen van ontsteking op de MRI over twee jaar en de relatie tussen veranderingen in ontsteking en veranderingen in pijn. Overeenkomstig de vingergewrichten, bleek een toename in ontsteking geassocieerd te zijn met een toename in pijn, met name in gewrichten waarbij op baseline gewrichtsschade te zien was. Het aantal gewrichten waarin ontsteking van het gewrichtskapsel ('synovitis') afnam was te klein om uitspraken over te doen, maar een afname van afwijkingen in het subchondrale bot ('beenmerglaesies') was geassocieerd met een afname in pijn.

In de **hoofdstukken 7 en 8** laten we dus zien dat radiografische schade in de duimbasis de belangrijkste voorspeller is voor pijn op dat moment, maar dat een verandering in tekenen van ontsteking wel relevante effecten op pijn kan hebben. Desalniettemin lijkt ontsteking bij duimbasisartrose van minder groot belang en meer verweven met gewrichtsschade dan bij interfalangeale artrose. Dit zou kunnen wijzen op verschillen in de onderliggende oorzaken van artrose in de duimbasis en de interfalangeale gewrichten. Zoals eerder uitgelegd, staan er op de duimbasis grote krachten en is het een gewricht met grote mobiliteit, maar ook grote kans

op instabiliteit. Studies hebben laten zien dat de invloed van deze mechanische factoren groter is bij duimbasis artrose dan bij interfalangeale artrose. Het is goed mogelijk dat mechanische invloeden een cruciale rol spelen in de ontwikkeling van duimbasisartrose.

Het meten van uitkomstmaten

Tenslotte hebben we ons in **deel III** van dit proefschrift gericht op het verbeteren van het meten van uitkomsten in studies naar handartrose. Zoals eerder besproken in dit hoofdstuk zijn goede uitkomstmaten essentieel om behandeleffecten adequaat te kunnen meten.

In 2014 werd door de Outcome Measures in Rheumatology (OMERACT) handartrose werkgroep een set van 'kern uitkomsten' ('core domain set') vastgesteld voor studies naar handartrose (figuur 2, **hoofdstuk 1**). Het ontbreekt echter nog aan een gestandaardiseerde set meetinstrumenten waarmee deze kern uitkomsten zouden moeten worden gemeten. Hiervoor was meer onderzoek naar verschillende beschikbare meetinstrumenten nodig, om vast te stellen of deze meetinstrumenten de juiste eigenschappen hebben om de beoogde uitkomst te meten. De studies in **deel III** van dit proefschrift richtten zich hierop.

Hoofdstuk 10 presenteert leeftijd- en sekse-specifieke referentiecurves voor de Australian/Canadian Hand Osteoarthritis Index (AUSCAN), die werden ontwikkeld met een vergelijkbare methode als de beroemde groeicurves voor kinderen. Het doel van deze referentiecurves is het vergemakkelijken van de interpretatie van scores op de AUSCAN, één van de meest frequent gebruikte vragenlijsten voor handpijn, -stijfheid en -functie.

In **hoofdstuk 11 en 12** vergeleken we de eigenschappen van verschillende meetinstrumenten die de kern uitkomsten pijn en functie (**hoofdstuk 11**) en hand mobiliteit (**hoofdstuk 12**) kunnen meten, om zo tot een selectie te komen van het meest geschikte meetinstrument. In deze studies keken we naar aspecten uit de zgn. 'OMERACT filter': *truth* ('Meet dit instrument wat het beoogt te meten?'), *discrimination* ('Kan dit instrument onderscheid maken tussen ziektestadia?', 'Kan dit instrument verandering over de tijd onderscheiden?' (vaak 'responsiviteit' genoemd), 'Kan dit instrument verschillen tussen behandelgroepen onderscheiden in een klinische studie?'), en *feasibility* ('Kan dit instrument gemakkelijk toegepast worden, met het oog op beperkingen in tijd, geld en interpretatie?'). In **hoofdstuk 11** richtten we ons op de Michigan Hand outcomes Questionnaire (MHQ), een vragenlijst over handklachten die niet eerder gevalideerd was voor gebruik bij patiënten met handartrose. We lieten zien dat de MHQ verschillende voordelen had ten opzichte van bestaande vragenlijsten. Zo meet deze vragenlijst bepaalde domeinen die niet door andere vragenlijsten worden gemeten, namelijk prestaties op het werk, esthetiek en tevredenheid, en lieten we zien dat deze domeinen valide waren. Het onderdeel van de vragenlijst dat pijn en functie meet, werd vergeleken met regelmatig gebruikte vragenlijsten naar handpijn en -functie bij handartrose (AUSCAN, Functional Index for Hand Osteoarthritis (FIHOA) en een visueel analoge schaal (VAS) van pijn). De verschillende vragenlijsten die hetzelfde domein (pijn of functie) zouden moeten meten, maten inderdaad deels dezelfde, maar deels ook andere aspecten van dat domein. Op het gebied van *discrimination* presteerde de MHQ over het algemeen tenminste net zo goed als de referentie instrumenten. Een belangrijk voordeel van de MHQ is dat deze, in tegenstelling tot de AUSCAN, gratis verkrijgbaar is. Nadelen zijn dat het een langere vragenlijst is, en dat de score voor pijn mogelijk moeilijker te interpreteren is. Alles bij elkaar

genomen was er geen pijn- of functievragenlijst die duidelijk superieur was ten opzichte van de andere vragenlijsten. In **hoofdstuk 12** vergeleken we verschillende instrumenten die hand mobiliteit kunnen meten, waaronder de Hand Mobility in Scleroderma test (HAMIS), vingertop-palm-afstand en de gemodificeerde Kapandji index. Hierbij bleek de HAMIS wat gunstigere eigenschappen te hebben in vergelijking met de rest. De betrouwbaarheid, *feasibility* en correlatie met andere uitkomstmaten was vergelijkbaar voor alle instrumenten. HAMIS was daarentegen het enige instrument dat patiënten met en zonder verminderde mobiliteit van de duim kon onderscheiden. Bovendien leek de HAMIS het meest responsief, alhoewel de verandering in hand mobiliteit tijdens de vervolgperiode van twee jaar over het algemeen klein was voor alle testen, waardoor het onderzoeken van responsiviteit bemoeilijkt werd.

In **hoofdstuk 13** beschrijven we de voortgang van de OMERACT handartrose werkgroep in de vier jaar na het opstellen van de set van kerndomeinen in 2014. Daarnaast presenteren we in dit hoofdstuk een geactualiseerde onderzoeksagenda, om toekomstige studies op te baseren.

In **hoofdstuk 14-16** hebben we ons gericht op het ontwikkelen van een MRI scoresysteem voor duimbasisartrose, de OMERACT Thumb base Osteoarthritis MRI Scoring system (TOMS). Dit is het eerste MRI scoresysteem voor de duimbasis, en heeft ervoor gezorgd dat we voor het eerst studies met MRI konden gaan uitvoeren bij patiënten met duimbasisartrose, om zo onder andere meer te weten te komen over de rol van ontsteking bij duimbasisartrose. De studies uit **hoofdstuk 7 en 8** hadden niet uitgevoerd kunnen worden zonder de ontwikkeling van de OMERACT TOMS. We beschrijven de ontwikkeling van de OMERACT TOMS in **hoofdstuk 14**. Daarnaast hebben we ook de betrouwbaarheid van het scoresysteem onderzocht, zowel cross-sectioneel (**hoofdstuk 14**) als longitudinaal (**hoofdstuk 16**). **Hoofdstuk 15** presenteert een atlas met referentie afbeeldingen, om gebruik van het scoresysteem te faciliteren.

Toekomstperspectieven

In dit hoofdstuk hebben we de bevindingen van studies beschreven in dit proefschrift samengevat, en belangrijke uitdagingen in het onderzoek naar handartrose besproken. Dit proefschrift biedt een overzicht van de huidige behandelingsmogelijkheden voor patiënten met handartrose, waaronder ook een vernieuwde EULAR-richtlijn voor de behandeling van deze ziekte. Verder draagt dit proefschrift bij aan de ontwikkeling van nieuwe behandelingen voor patiënten met handartrose. Naast een nieuwe behandelmogelijkheid voor patiënten met handartrose die een opvlamming van de ziekte hebben, levert dit proefschrift bewijs dat ontsteking een geschikt behandeldoel is. Uiteindelijk zou dit ook kunnen bijdragen aan de ontwikkeling van behandelingen die het beloop van deze ziekte kunnen beïnvloeden. Daarnaast beschrijft dit proefschrift studies die bijdragen aan het optimaliseren van het meten van uitkomsten bij handartrose.

De HOPE studie (**hoofdstuk 5**) staat centraal in dit proefschrift, en is een unieke studie binnen het handartrose veld. Naast een directe klinische toepassing, zal deze studie het veld ook op twee andere manieren vooruitbrengen. De studie levert niet alleen nieuwe inzichten in het ziekteproces op, doordat het laat zien dat ontsteking beïnvloed kan worden bij handartrose, het is ook een schat van data om andere studies, met name die naar geschikte meetinstrumenten, uit te voeren.

Alhoewel de studies beschreven in dit proefschrift ons vele nieuwe inzichten hebben geboden in verschillende aspecten van handartrose, blijven er diverse vragen onbeantwoord en zijn er ook veel nieuwe vragen ontstaan, die aansporen tot verder onderzoek.

Zo blijkt uit **deel I** van dit proefschrift dat placebo-gecontroleerde dubbelblinde studies naar de effectiviteit van paracetamol en chirurgische interventies nog ontbreken. Ook zouden studies naar de effectiviteit van chondroïtine sulfaat, topicale NSAID's en intra-articulaire injecties met glucocorticoïden in de interfalangeaal gewrichten gerepliceerd moeten worden, omdat deze behandelingen nu slechts in één studie werden onderzocht. Een studie die meerdere onderzoeksvragen tegelijk zou kunnen beantwoorden, en een mooi voorbeeld van doelmatigheidsonderzoek, is een trial met drie interventiearmen waarin paracetamol, een topicale NSAID en placebo met elkaar worden vergeleken. Een ander belangrijk vervolg dat voortvloeit uit dit deel van het proefschrift, is het belang van de verspreiding en implementatie van de vernieuwde EULAR-richtlijn voor de behandeling van handartrose. In Nederland zou publicatie van een vertaling van deze richtlijn naar de Nederlandse situatie door beroepsorganisaties zoals de Nederlandse Vereniging voor Reumatologie (NVR) en de Nederlandse Huisartsen Genootschap (NHG) hiervoor heel waardevol zijn.

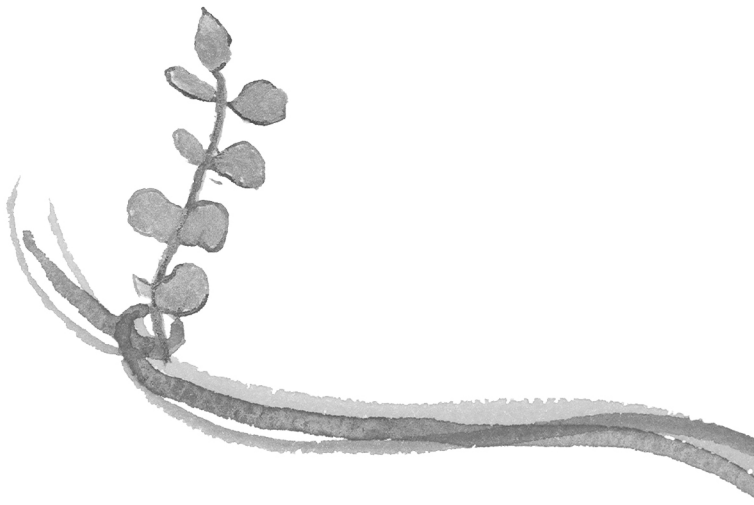
Vervolgonderzoek naar aanleiding van de opgedane kennis in **deel 2** van dit proefschrift omvat onder andere studies naar de lange termijn effecten van het onderdrukken van ontsteking. Dit zou kunnen worden onderzocht bij patiënten die voor langere periode worden behandeld met glucocorticoïden, maar omdat dit vaak bezwaarlijk is, zou hiervoor ook gedacht kunnen worden aan studies met nieuwe middelen die ontsteking kunnen onderdrukken, zoals janus kinase (JAK) inhibitors als interessant alternatief. Daarnaast is verdere studie naar de relatie tussen synovitis en pijn in de verzamelde data van de HOPE studie van interesse. Ook benadrukken de resultaten die laten zien dat duimbasisartrose een apart handartrose fenotype is, dat de ontwikkeling van aparte classificatiecriteria voor vinger- en duimbasisartrose van belang is.

Wat betreft vervolgonderzoek naar uitkomstmaten bij handartrose, waar in **deel 3** van dit proefschrift aandacht aan besteed wordt, is de HOPE studie, als positieve trial waarin veel uitkomsten werden gemeten met meerdere instrumenten, weer een belangrijke bron van waardevolle data. Zo kan deze data worden gebruikt om de sensitiviteit om verandering op de pikken van verschillende meetinstrumenten, die dezelfde uitkomst meten, te vergelijken. Een andere belangrijke vervolgstudie is de ontwikkeling van een geschikt meetinstrument voor het domein 'joint activity', mogelijk door meerdere bestaande instrumenten te combineren tot één score. Het uiteindelijke doel van het verder onderzoek naar meetinstrumenten is het ontwikkelen van een set van 'kern meetinstrumenten' ('core instrument set') passend bij de eerder vastgestelde set van 'kern uitkomsten'.

De studies beschreven in dit proefschrift dragen bij aan onze huidige denkwijze over de pathofysiologie en klinische zorg voor patiënten met handartrose, en kan handvaten bieden voor toekomstig onderzoek in dit veld.

APPENDICES

List of publications
Curriculum vitae
Dankwoord



LIST OF PUBLICATIONS

Publications related to thesis

1. Van Beest S, Kroon HM, Reijnierse M, Rosendaal FR, Kloppenburg M, **Kroon FPB**. Two-year changes in MRI-features and pain in thumb base osteoarthritis. *Arthritis Care Res* 2020 Jun 17. doi: 10.1002/acr.24355 [Epub ahead of print]
2. **Kroon FPB**, Kortekaas MC, Boonen A, Böhringer S, Reijnierse M, Rosendaal FR, Riyazi N, Starmans M, Turkstra F, van Zeben J, Allaart CF, Kloppenburg M. Six-week treatment with prednisolone 10 mg in patients with hand osteoarthritis (HOPE): results from a randomised double-blind placebo-controlled trial. *Lancet* 2019;394:1993-2001.
3. **Kroon FPB**, Veenbrink AI, de Mutsert R, Visser AW, le Cessie S, Rosendaal FR, Kloppenburg M. Role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1761-67.
4. Wittoek R, **Kroon FPB**, Kundakci B, Abhishek A, Haugen IK, Berenbaum F, Conaghan PG, Ishimori ML, van der Heijde D, Kloppenburg M. Report from the Hand Osteoarthritis Working Group at OMERACT 2018: update on core instrument set development. *J Rheumatol* 2019;46:1183-87.
5. **Kroon FPB**, van Beest S, Gandjbakhch F, Peterfy C, Chen S, Conaghan PG, Eshed I, Foltz V, Genant HK, Haugen IK, Medema JK, Østergaard M, Zhang L, Levesque MC, Kloppenburg M. Longitudinal reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS). *J Rheumatol* 2019;46:1228-31.
6. Kloppenburg M*, **Kroon FP***, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019;78:16-24. (*co-first authorship)
7. **Kroon FPB**, van Beest S, Ermurat S, Kortekaas MC, Bloem JL, Reijnierse M, Rosendaal FR, Kloppenburg MI. In thumb base osteoarthritis structural damage is more strongly associated with pain than synovitis. *Osteoarthritis Cartilage* 2018;26:1196-1202.
8. **Kroon FPB**, Carmona L, Schoones JW, Kloppenburg M. Efficacy and safety of nonpharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *RMD Open* 2018;4:e000734.
9. **Kroon FPB**, Boersma A, Boonen A, van Beest S, Damman W, van der Heijde D, Rosendaal FR, Kloppenburg M. Performance of the Michigan Hand Outcomes Questionnaire in hand osteoarthritis. *Osteoarthritis Cartilage* 2018;26:1627-35.
10. **Kroon FPB**, Damman W, Liu R, Bijsterbosch J, Meulenbelt I, van der Heijde D, Kloppenburg M. Validity, reliability, responsiveness and feasibility of four hand mobility measures in hand osteoarthritis. *Rheumatology (Oxford)* 2018;57:525-32.
11. **Kroon FPB**, Peterfy C, Conaghan PG, Foltz V, Gandjbakhch F, Eshed I, Genant HK, Østergaard M, Reijnierse M, Bloem JL, Haugen IK, Kloppenburg M. Atlas for the OMERACT thumb base osteoarthritis MRI scoring system (TOMS). *RMD Open* 2018;4:e000583.
12. Kloppenburg M*, **Kroon F***. Management of hand osteoarthritis. In: UpToDate, Curtis MR (Ed). UpToDate. Waltham, MA, 2020 (Version 5.0). Available at: https://www.uptodate.com/contents/management-of-hand-osteoarthritis. (*co-first authorship)

13. **Kroon FP**, Conaghan PG, Foltz V, Gandjbakhch F, Peterfy C, Eshed I, Genant HK, Østergaard M, Kloppenburg M, Haugen IK. Development and reliability of the OMERACT thumb base osteoarthritis magnetic resonance imaging scoring system. *J Rheumatol* 2017;44:1694-98.
14. **Kroon FPB**, Ramiro S, Royston P, Le Cessie S, Rosendaal FR, Kloppenburg M. Reference curves for the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) in the middle-aged Dutch population. *Rheumatology (Oxford)* 2017;56:745-52.
15. **Kroon FPB**, Rubio R, Schoones JW, Kloppenburg M. Intra-articular therapies in the treatment of hand osteoarthritis: a systematic literature review. *Drugs Aging* 2016;33:119-133.

Publications outside thesis

16. Landewé RBM, Machado PM, **Kroon F**, Bijlsma JWJ, Burmester GR, Carmona L, Combe B, Galli M, Gossec L, Iagnocco A, Isaacs JD, Mariette X, Müller-Ladner U, Openshaw P, Rezza G, Smolen JS, Stamm T, Wiek D, Schulze-Koops H. EULAR provisional recommendations for the management of rheumatic musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis* 2020;79:851-8.
17. Haugen IK, Felson DT, Abhishek A, Berenbaum F, Bierma-Zeinstra S, Borgen T, Herrero-Beaumont G, Ishimori ML, Jonsson H, **Kroon FPB**, Maheu E, Ramonda R, Ritschl V, Stamm T, van der Heijde D, Wittoek R, Greibrokk E, Smeets W, Kloppenburg M. Development of classification criteria for hand osteoarthritis: comparative analyses of persons with and without hand osteoarthritis. *RMD Open* 2020;6:e001265.
18. Van de Stadt LA, **Kroon FPB**, Kloppenburg M. Measures of hand function. *Arthritis Care Res*. [In press]
19. Loef M, **Kroon FPB**, Böhringer S, Roos EM, Rosendaal FR, Kloppenburg M. Percentile curves for the Knee Injury and Osteoarthritis Outcome Score in the middle-aged Dutch population. *Osteoarthritis Cartilage* 2020 Apr 9. doi: 10.1016/j.joca.2020.03.014 [Epub ahead of print]
20. Liu R, Kortekaas MC, **Kroon FPB**, Schoones JW, Huizinga TWJ, Rosendaal FR, Kloppenburg M. Mortality in osteoarthritis: a systematic review. [Submitted]
21. **Kroon F**, Bay-Jensen AC, Wittoek R, Verbruggen G, Smolen JS, Kloppenburg M, Ramonda R. Etanercept therapy leads to reductions in matrix metalloproteinase-3 in patients with erosive hand osteoarthritis. *Scand J Rheumatol* 2020;49:167-68.
22. **Kroon FPB**, Damman W, van der Plas JL, van Beest S, Rosendaal FR, van der Heijde D, Kloppenburg M. Self-reported painful joint count and assessor-reported tender joint count as instruments to assess pain in hand osteoarthritis. *Rheumatology (Oxford)* 2019;59:1094-98.
23. Van Beest S, **Kroon FPB**, Kroon HM, Damman W, Liu R, Bloem JL, Reijnierse M, Kloppenburg M. Assessment of osteoarthritic features in the thumb base with the newly developed OMERACT magnetic resonance imaging scoring system is a valid addition to standard radiography. *Osteoarthritis Cartilage* 2019;27:468-75.
24. Kloppenburg M, Peterfy C, Haugen IK, **Kroon F**, Chen S, Wang L, Levy G, Fleischmann RM, Berenbaum F, van der Heijde D, Bansal P, Wittoek R, Feng S, Fang Y, Saltarelli M, Medema JK, Levesque MC. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and antiinterleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann Rheum Dis* 2019;78:413-20.

25. Kloppenburg M, Ramonda R, Bobacz K, Kwok WY, Elewaut D, Huizinga TWJ, **Kroon FPB**, Punzi L, Smolen JS, Vander Cruyssen B, Wolterbeek R, Verbruggen G, Wittoek R. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:1757-64.
26. Kloppenburg M, van Beest S, **Kroon FPB**. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
27. Loef M, van Beest S, **Kroon FPB**, Bloem JL, Dekkers OM, Reijnierse M, Schoones JW, Kloppenburg M. Comparison of histological and morphometrical changes underlying subchondral bone abnormalities in inflammatory and degenerative musculoskeletal disorders: a systematic review. *Osteoarthritis Cartilage* 2018;26:992-1002.
28. Loef M, **Kroon FPB**, Bergstra SA, van der Pol JA, Lems WF, Kerstens PJSM, Allaart CF, Kloppenburg M. TNF-inhibitor treatment is associated with lower risk of hand osteoarthritis progression in rheumatoid arthritis patients after 10 years. *Rheumatology (Oxford)* 2018;57:1917-24.
29. Damman W, Liu R, **Kroon FPB**, Reijnierse M, Huizinga TWJ, Rosendaal FR, Kloppenburg M. Do comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand Osteoarthritis in Secondary Care Cohort. *J Rheumatol* 2017;44:1659-66.
30. Gossec L, Portier A, Landewé R, Etcheto A, Navarro-Compán V, **Kroon F**, van der Heijde D, Dougados M. Preliminary definitions of 'flare' in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: an ASAS initiative. *Ann Rheum Dis* 2016;75:991-6.
31. **Kroon FP**, van der Burg LR, Ramiro S, Landewé RB, Buchbinder R, Falzon L, van der Heijde D. Nonsteroidal antiinflammatory drugs for axial spondyloarthritis: a Cochrane review. *J Rheumatol* 2016;43:607-17.
32. **Kroon FP**, van der Burg LR, Ramiro S, Landewé RB, Buchbinder R, Falzon L, van der Heijde D. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) [Review]. *Cochrane Database Syst Rev* 2015;7:CD010952.
33. **Kroon FPB**, van der Burg LRA, Ramiro S, Landewé RBM, Buchbinder R, van der Heijde D. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) [Protocol]. *Cochrane Database Syst Rev* 2014, Issue 1.
34. **Kroon F**, Staples M, Ebeling P, Wark J, Osborne R, Mitchell P, Wriedt C, Buchbinder R. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. *J Bone Miner Res* 2014;29:1346-55.
35. **Kroon F**, Landewé R, Dougados M, van der Heijde D. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2012;71:1623-9.
36. **Kroon FPB**, van der Burg LRA, Buchbinder R, Osborne RH, Johnston RV, Pitt V. Self-management education programmes for osteoarthritis [Review]. *Cochrane Database Syst Rev* 2014;1:CD008963.

CURRICULUM VITAE

Féline Pascale Bernadette Kroon werd op 16 september 1992 geboren in Nijmegen. Ze groeide op in Meerssen, waar zij in 2006 het VWO diploma voor de vakken Engels en Wiskunde behaalde aan het Stella Maris College. In 2008 behaalde ze aan dezelfde school het gymnasium diploma voor de overige vakken. In datzelfde jaar begon zij met de studie Geneeskunde aan de Universiteit Maastricht. Na het behalen van het bachelor diploma reisde zij een half jaar door China, Australië en Nieuw-Zeeland. In die periode woonde ze 14 weken in Melbourne (Australië), en deed hier wetenschappelijk onderzoek onder begeleiding van prof. dr. R. Buchbinder naar de effectiviteit van zelfmanagement programma's in artrose. In 2012 begon ze aan haar coschappen, terwijl ze wetenschappelijk onderzoek binnen de reumatologie voortzette en haar eerste wetenschappelijke artikelen publiceerde. Na het doorlopen van de vaste coschappen, een keuzecoschap op de afdeling interne geneeskunde (Laurentius ziekenhuis, Roermond), en buitenland ervaring in India (afdeling dermatologie, KMC Hospital, Manipal) en België (afdeling neurologie, Ziekenhuis Oost Limburg, Genk), sloot zij haar studie af met een semiartsstage op de afdeling reumatologie in het Zuyderland ziekenhuis te Heerlen. Tijdens dit afsluitende coschap maakte zij de definitieve keuze voor de reumatologie. In januari 2015 behaalde zij (cum laude) het artsexamen.

Vanaf februari 2015 was zij als arts-onderzoeker verbonden aan de afdeling reumatologie van het Leids Universitair Medisch Centrum. Onder begeleiding van prof. dr. M. Kloppenburg en prof. dr. F.R. Rosendaal werkte zij aan het onderzoek beschreven in dit proefschrift. Zij was de studiearts van een klinische trial, de Hand Osteoarthritis Prednisolone Efficacy (HOPE) studie, waarvan de resultaten worden gepresenteerd in dit proefschrift. Tevens heeft zij tijdens deze periode de cursussen in kader van de opleiding tot epidemioloog B via de afdeling klinische epidemiologie gevolgd. Daarnaast was ze actief betrokken bij de Outcome Measures in Rheumatology Clinical Trials (OMERACT) hand osteoarthritis working group en de OMERACT MRI working group. Ook was ze fellow bij een project van de European League Against Rheumatology (EULAR) om de richtlijnen voor de behandeling van handartrose te herzien. In 2016 kreeg ze een prijs voor beste orale presentatie op het jaarlijks congres voor de Nederlandse Vereniging van de Reumatologie (NVR Najaarsdagen).

In maart 2019 startte zij de opleiding tot reumatoloog in het Zuyderland ziekenhuis (opleider: dr. M. Starmans). Momenteel volgt zij aldaar de vooropleiding interne geneeskunde (opleider: dr. J. Buijs).

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