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

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SUMMARY AND APPENDICES

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SUMMARY AND DISCUSSION

Osteoarthritis (OA) is a disease involving all tissues of the synovial joint, leading to pain, stiffness and functional impairment of the joint. Its prevalence is increasing with age, which leads to a large social and economic burden in the ageing population. The hand is one of the predilection sites of OA, where mostly the distal and proximal interphalangeal (DIP and PIP) and thumb base joints are affected. Despite this, hand OA is rarely studied. Several factors possibly add to this, such as its multi-joint involvement, its slowly progressive and variable disease course and a lack of disease-modifying treatment options and standardized outcome measures. In order to develop new and better treatments and to recognize patients who will benefit most, it is pivotal to identify modifiable factors that play a role in the disease process and that associate with core disease outcomes. Therefore, in this thesis we aimed to evaluate such factors for their association with hand OA disease status and progression of hand OA (**part I**). Furthermore, clinimetric properties of outcome measures were assessed (**part II**).

The HOSTAS cohort

This thesis is based on data from the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort. HOSTAS is an ongoing observational cohort study aimed at investigating determinants of outcome, utility of clinimetric instruments and the role of MRI-defined inflammation in primary hand OA. Between June 2009 and October 2015, 538 patients from the Leiden University Medical Center (LUMC) rheumatology outpatient clinic were included. Primary hand OA was diagnosed according to the clinical judgement of the rheumatologist. Hand OA is a clinical diagnosis; hence inclusion was based on the diagnosis of the treating rheumatologist and not on classification criteria such as the American College of Rheumatology hand OA criteria, which are widely used in research. From January 2011 on, a number of extended questionnaires was added to the study protocol and from March 2011 to October 2012 eligible patients received contrast-enhanced hand MR imaging. Patient underwent a study visit (including physical examination, radiographs and MR imaging) every two years and filled out questionnaires yearly.

Chapter 2 describes the complete HOSTAS cohort of 538 patients with their baseline clinical characteristics. Patients in different disease stages and subsets were enrolled, yet the mean age of 61 years and the percentage of women of 86% are reflecting an average hand OA patient. Our population concerns patients with hand OA recruited from an outpatient clinic in a secondary and tertiary referral center. These patients are probably a selection of patients with more symptoms and worse hand OA than patients from a primary care or general population and therefore results should be extrapolated with

caution. However, patients with hand OA in secondary care might be the patients that are in need of, and benefit most from, treatment and are therefore a target population for hand OA research. Large cohorts with patients with hand OA were scarce until recently[1–3]. For HOSTAS as a large, varied and well-documented cohort assessing different outcome measures, including MRI, and with available follow-up data, it is valuable in hand OA research.

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

First, we evaluated non-OA-related patient factors in disease status and progression in hand OA. In **chapter 2** that is comorbidity and in **chapter 3** that is illness perceptions.

Comorbidity (i.e., any additional disease co-occurring with a primary disease) is a patient-specific factor that is associated with increased disease burden in many chronic (musculoskeletal) diseases. Since many patients with hand OA are elderly, comorbidity is likely to occur. Yet, the role of comorbidity in hand OA disease burden is unclear. Therefore, in **chapter 2** we described prevalent comorbidities in HOSTAS and looked into the relationship between comorbidities and disease burden, concerning both general burden (health-related quality of life, HRQoL) and disease-specific burden (hand pain and function) and assessed the clinical relevance of this role. More than half of the patients in HOSTAS had comorbidity present. Obesity was the most prevalent comorbidity, followed by cardiovascular and pulmonary disease. We choose to consider obesity as a comorbidity, being aware that hand OA and obesity might not be two entirely separate diseases, for obesity is associated with a larger risk of OA including hand OA[4]. We did this because we feel that obesity is a medical condition on itself and is one of the most important preventable causes of death worldwide. Our point of view is supported by a large body of literature. On the other hand, one can view 'obesity' as a proxy for several comorbidities such as cardiovascular disease. However, we think that patients with, for example, cardiovascular disease *and* obesity have a larger comorbidity burden than patients with only one of these two. Therefore, we choose to consider obesity as a separate comorbidity.

Presence of comorbidity was associated with higher disease burden, both for musculoskeletal comorbidities such as connective tissue disease as well as for nonmusculoskeletal comorbidities including pulmonary or cardiovascular disease and depression/anxiety. When compared with minimal clinical important improvement/difference and to population-based reference values this higher burden was clinically relevant. Our results suggest that comorbidities should be considered as contextual factors when interpreting core disease outcomes such as HRQoL, hand function

and hand pain and in patient management and they are therefore highly relevant for future research in hand OA. These findings are in line with the Outcome MEasures in Rheumatology (OMERACT) hand OA working group identifying comorbidities as possible core contextual factor[5].

Psychosocial factors are also potential modifiable patient-specific factors that influence patient-reported outcomes such as disability. Knowledge about these factors could help explain variability in disease course and is of importance to design patient-tailored treatment strategies. Therefore, one of these factors, i.e., illness perceptions, was studied in **chapter 3** for its association with self-reported disability both cross-sectionally and longitudinally over two years. When patients are confronted with (symptoms of) an illness they build a mental model to make sense of and manage their health problem. These cognitive and emotional representations and beliefs, so-called illness perceptions, influence a patient's coping, health behaviour and health outcomes. We found that at baseline strong associations were present between negative illness perceptions and high disability. However, baseline perceptions were, after adjustment for baseline disability, not associated with high disability after two years. The strong relationship between baseline illness perceptions and baseline disability suggests that by improving baseline illness perceptions disability could also improve. For illness perceptions to be a relevant treatment target change should be possible and this change should be relevant. Our results support that illness perceptions could indeed be such a target; perceptions changed in two years to less negative and more chronic and for several perceptions this change was associated with increase in self-reported disability.

The results of **chapter 2 and 3** support the relevance of disease management with a holistic view taking into account all contextual patient factors. Comorbidity and illness perceptions are important factors for their relationship with disease burden. They are potentially modifiable and therefore might serve as a treatment target. For illness perceptions, intervention studies in other chronic disease showed promising results[6–8].

If analyses are done on patient level, patient factors should be taken into account when interpreting outcomes. Therefore, based on the knowledge from **chapter 2,** we included comorbidity in the analyses in **chapter 3**. Considering psychological factors, we showed in both **chapter 2 and 3** that presence of psychological symptoms (depression/anxiety and negative illness perceptions, respectively) was associated with increased hand disability compared with absence of these symptoms. In line with this, it was shown in people with musculoskeletal hand problems that increased depression or anxiety scores are associated with negative illness perceptions[9]. These studies stress the importance of the role of psychological factors in disease outcome.

The role of MRI-defined inflammatory features

As a next step, we looked into disease-related factors in disease status and progression by investigating the role of MRI-defined inflammatory features in hand OA in **chapters 4 to 7**.

Radiographs are widely used to assess structural damage in OA. However, this structural damage reflects changes in the bone and cartilage, which are progressive, irreversible and markers of late disease stages. On the contrary, visualization of the disease in an earlier stage will aid understanding of which processes are involved in pathophysiology and could facilitate identification of modifiable factors. MRI is an imaging modality visualizing all joint structures including synovial inflammation and lesions in the subchondral bone (bone marrow lesions [BML]). The few ultrasound studies in hand OA and MRI studies in knee OA and late-stage hand OA revealed that inflammatory features are clinically important for their association with pain and radiographic progression[1,10,11]. The clinical role of MRI-defined inflammatory features, especially BMLs, in hand OA was scarcely studied and therefore further investigation of this role was one of the aims of this thesis.

MRI inflammatory features are associated with increased hand joint pain

Hand pain is a major symptom in hand OA and can lead to decreased quality of life. Therefore it is important to understand the underlying mechanisms attributing to pain. In **chapter 4** we investigated the role of MRI-defined inflammatory features, and the co-occurrence and interaction of BMLs and synovitis in hand pain. We did this in a subgroup of HOSTAS including 105 patients who received contrast-enhanced MRI**.** BMLs and synovitis were present in more than half of (56%) and in almost all (90%) the patients. BMLs and synovitis were associated with pain in the same joint, but flexor tenosynovitis and extensor tendon involvement were not. Stratified analyses showed that BMLs did not associate with pain in the absence of synovitis, whereas synovitis was associated with pain in the absence of BMLs. Interaction was seen between BMLs and severe synovitis (grade 2 or 3). These results show that in patients with hand OA, severe synovitis is associated with joint pain, which is worsened when BMLs co-occur, suggesting synovitis as primary target in treatment of pain.

In **chapter 4** the summated scores of BML and synovitis were not associated with self-reported hand pain on patient level. This is in line with studies that compared summated radiographic scores with global pain scores showing inconsistent strengths of association[12]. Pain is a subjective experience influenced by different factors in the individual; the patient effect. In patient level analysis it is not possible to adjust for this

patient effect. Therefore, analysis on joint level may expose relationships that are obscured when joint-specific symptoms are combined into global or summated scores[13]. However, it is important to note here that we only summated scores of the interphalangeal joints without taking into account the thumb base joint, while this is an important contributor to hand pain[14]. When the thumb base joint was included in the summated score (along with the interphalangeal and metacarpophalangeal joints), indeed associations for grey-scale synovitis and effusion with hand pain on patient level are found, as was shown in an ultrasound study by Kortekaas et al. [1]. Hence, when only information about a limited number of joints is available, as in our study, joint level analysis for subjective measures such as pain with site-specific features such as BMLs and synovitis might be more relevant than patient level analysis.

MRI effusion plays a clinical relevant role

From the study in **chapter 4** we learned that effusion, i.e., fluid in the joint, appeared often to be present. Whether it coincides with synovial thickening or stands on itself was not clear. This is also not easy to study since no specific score for MRI-defined effusion exists. In **chapter 5** we made an effort to define effusion on MR images and investigated its prevalence and its clinical role separately from synovial thickening. The study was performed in a subgroup of 87 patients from the HOSTAS cohort who received contrast-enhanced MRI at baseline and of whom physical examination and two-year follow-up radiographs were available. MR images were scored for enhanced synovial thickening (EST, here reflecting synovitis), effusion (EST and T2-high signal intensity [hsi]) and BMLs. Effusion was defined as: 1) T2-hsi>0 and EST = 0 or 2) T2-hsi = EST but in different joint locations. We demonstrated that effusion was present in 17% of joints, both with and without EST. That effusion was also present in the absence of synovitis is a remarkable finding as effusion is usually considered a side effect of synovitis. It is possible that with effusion synovitis is also present, but it is too small to visualize and score on MR images. Effusion without EST was not associated with pain or radiographic progression, although a protective effect seemed present. Contrary to our hypothesis the known association between synovitis and progression was attenuated by the presence of effusion. We can only speculate about the mechanism behind this protective effect, which possibly comes about through a reduction of mechanical stress, by anti-inflammatory or repair-aiding substances in the fluid or by the reflection of another disease phase. Our results are a first indication that MRI-effusion is present in interphalangeal joints, can be defined as a separate feature and that it is of clinical importance. This study supports previous studies investigating joint effusion in finger joints in rheumatic diseases including hand OA, indicating clinical importance and validity of this feature[1,15–17].

MRI inflammatory features are associated with increased radiographic progression

We learned in **chapter 4** that synovitis and BMLs are clinically relevant. Therefore, the longitudinal aspect of their relevance was explored in **chapter 6** where we assessed the association between synovitis and BMLs and radiographic progression after two years in the same subgroup as in **chapter 5**. Further, we explored the role of MRI-defined inflammatory features in onset and progression of radiographic osteoarthritic damage separately and we investigated progression on patient level. Our results revealed that both BMLs and synovitis showed severity-dependent associations with radiographic progression. This was on joint level as well as on patient level and for onset as well as progression of radiographic damage. Results mean that the more severe the inflammatory state is, as can be assessed in just one hand, the higher the risk of progression in both hands. This study, together with **chapter 5**, indicates that all joint tissues, including BMLs, are important in the disease course of hand OA. Furthermore, it illustrates the use of MR imaging in detecting hand OA in and early stage and detection of joints and patients prone to progress. In contrast to **chapter 4,** where the subjective measure pain was used, **chapter 6** revealed that when more objective outcome measures like radiographic damage were assessed, summated scores were associated with radiographic progression. These findings are in line with **chapter 2 and 3** showing that on patient level other factors play a role than on joint level.

Decrease in MRI inflammatory features goes with a decrease in joint tenderness

Since in **chapter 4** and **chapter 6** synovitis and BMLs appeared to have a clinically relevant role, predicted disease course and are in potential modifiable factors, as a next step we investigated in **chapter 7** longitudinal MRI data over two years. We were especially interested whether decreasing synovitis/BML scores were associated with loss, or at least attenuation, of joint tenderness since this would make them a relevant treatment target. We found that already after two years a decrease in synovitis, but not in BMLs, was associated with attenuated tenderness. On the contrary, an increase in synovitis and osteophytes was associated with increased tenderness. Through stratification it became apparent that BMLs acted as an effect-modifier of the association between synovitis and tenderness. Our findings are in line with another study in hand OA suggesting an association between decreasing/resolving MRI-defined synovitis and loss of joint tenderness[18]. A key consideration in our study was to select joints that had both the determinant (i.e., the MR feature under investigation) and the outcome (i.e., tenderness)

present at baseline. This is different from the other study that selected joints based only on the outcome (i.e., tenderness)[18]. This is an important difference; when selecting joints with potential in the determinant (in other words; inflammation is present that can be reduced) it is possible to see whether that inflammation can be targeted to reduce pain. Our results, together with **chapter 4**, confirm that synovitis is the most relevant target in reducing hand joint pain.

In the methodology of scoring we made an important choice to score in scrambled and masked time order. We did this because the standard, a chronological time order, could result in biased scoring as readers might assume worsening over time. Our results revealed that indeed progression cannot be assumed: synovitis and BMLs increased as well as decreased over two years in different patients. Therefore, we think that when scoring MR images over time, scoring in masked time order should always be considered. When following the HOAMRIS score[19] simple rules can be applied to prevent inflation of the score from a 4-point to a 7-point scale.

Conclusions of chapters 4-7

We showed that inflammatory MR features play an important role in the disease course in hand OA. These results are in line with another hand OA study with MRI[11,20]. Together with ultrasound studies studying inflammation[1,21], this supports the current-day view that hand OA, like other forms of OA, is an inflammatory disease[22]. Unfortunately, up till now this vision has not yet been translated into treatment, for studies on treatment with anti-inflammatory drugs such as biologicals and corticosteroids have largely been unsuccessful[23]. In the future perspectives we will further elaborate on recent studies that assessed anti-inflammatory medication.

While our results in **chapter 4** and **chapter 7** suggested that synovitis is the most relevant target with regards to pain, the results in **chapter 5 and chapter 6** revealed that synovitis, effusion and BMLs are interesting targets with regards to radiographic progression. Hence, it depends on the treatment goal which target is most relevant. On the short term a physician would want to reduce symptoms and could focus on pain relief probably by reducing synovitis. For the long term, however, radiographic damage is associated with more symptoms[3,13]. Therefore, progression should be prevented and serves as a treatment target.

Overall conclusions of part I

Overall, in **part I** we showed that in our well-defined and large secondary/tertiary care cohort of patient with primary hand OA, both patient factors (comorbidity and illness

perceptions) and joint-specific factors (MRI-defined inflammation) were associated with disease burden and progression. Hence, an optimal treatment strategy for hand OA addresses both patient factors and OA disease factors.

Already after two years, which could be the term of a clinical trial, relevant change had taken place and this change was associated with the determinants that we investigated. Comorbidity, illness perceptions and MRI-inflammation could all serve as potential modifiable factors and hence are interesting as treatment targets.

Part II: clinimetric properties of outcome measures in hand OA

Hand pain and structural damage are important outcome measures in hand OA disease status and disease course. Hand OA research is in need of disease-specific validated instruments to measure such outcomes[5]. Therefore, in **part II** of this thesis we evaluated validity and responsiveness of new instruments to measure hand pain, joint activity and cartilage loss.

Self-reported painful joint count could be used to measure hand pain

In **chapter 8** we investigated the metric properties of self-reported painful joint count compared with assessor-reported tender joint count to measure hand pain. Contrary to our hypothesis that correlations between these measures would be at least moderate, they were found to be of weak strength, as were convergent correlations of both joint counts to other measures of pain. Hence, assessor-reported tender joint and self-reported painful joint counts do not measure entirely the same construct of hand pain. Self-reported painful joint was consistently higher than assessor-reported tender joint count. Agreement between patients and assessors was highest in joints with low prevalence of pain/tenderness, while overall agreement was low due to most agreement derived from non-tenderness. We concluded that self-reported painful joint count and assessor-reported tender joint count cannot be used interchangeably. However, both measures performed equally so there is no preference for one measure over the other. If our results could be confirmed, self-reported painful joint count seems a useful and feasible instrument in measuring hand pain.

Assessment of joint activity by tender joint count needs further development

Assessor-reported tenderness upon palpation is not only proposed to measure pain as an outcome, but also as in instrument to assess joint activity[24]. It was not known whether this instrument was also valid. In hand OA, joint activity reflects the activity of the underlying

osteoarthritic process and is therefore thought to include aspects of both pain and inflammation. Preliminary work already showed that assessor-reported tender joint count in the form of the Doyle index indeed correlated to both aspects[25]. In **chapter 8** joint activity is only partly reflected in each of the joint counts, as was shown by weak convergent correlations of both joint counts to other measures of pain and inflammation. Hence, painful/tender joints seem not valid enough as instruments to measure joint activity. Probably it is better when an instrument for this outcome domain is a composite score of pain and inflammation so that both aspects are taken into account.

Automatic joint space width measurements perform less than joint space narrowing scoring

Since bone can be visualized on radiographs but cartilage cannot, the joint space is used as a surrogate marker to measure thickness of cartilage and cartilage loss. Visual grading methods such as the OARSI atlas are considered the 'gold standard' to assess joint space. However, such methods are reader-dependent and limited in number of grades. Cartilage loss in hand OA over short time periods is through its small changes particularly difficult to assess and hence more objective and sensitive methods are preferred. Automated methods such as JSW measurements could serve this goal. In **chapter 9** we assessed sensitivity-to-change and validity of longitudinal quantitative semi-automatic joint space width (JSW) measurements and compared this with semi-quantitative joint space narrowing (JSN) scoring. Data from the ECHO study, a longitudinal observational study in patients with hand OA, were used[15]. Patients in the ECHO study were also recruited from our outpatient clinic and were similar in age and sex to HOSTAS patients. At the time, the ECHO had the advantage over HOSTAS in that we could assess validity by associations of JSW/JSN with an external standard, i.e., baseline inflammation.

Our study revealed that the JSW method is able to detect small changes over 2.6 years, but especially in a severe hand OA population due to measurement error results should be interpreted with caution. Furthermore, the JSW method classifies other joints with progression and shows weaker associations with baseline inflammatory features than the JSN method. Hence, performance was less with JSW than with the JSN method. However, JSW measurements could be useful to detect subtle changes in early-stage disease. Joint margins are better defined in early-stage OA requiring less user interaction, and the fingers are not flexed and no erosive disease is present leading to less measurement error. We found that the variation in JSW in the group with normal JSN was the largest, but the semi-quantitative JSN method is not able to differentiate within this group. The JSW method could make it possible to measure a decrease in JSW in early-stage disease.

Overall conclusions of part II

Overall, in **part II** we evaluated clinimetric properties of two new instruments: self-reported painful joint count and semi-automatic JSW measurement. Both these new methods have an advantage in feasibility over the standard methods they are compared with for being less time-consuming and less assessor-dependent. Self-reported painful joint count seems a promising instrument to measure hand pain, although results should be confirmed in future studies. JSW measures performed less well than JSN scoring and seem therefore, in our population, not useful as new instrument.

Future perspectives

Hand OA research cohorts and outcome measures

This thesis describes results of baseline and two-year follow-up data in the HOSTAS cohort. We showed that already after two years relevant progression had taken place. Hand OA remains nevertheless a slowly progressive chronic disease with a fluctuating course of symptoms[26]. Hence, there is a need to assess the role of baseline features such as MRI-inflammation after longer than two years follow-up and to assess the disease course over time. In rheumatoid arthritis (RA), research cohorts exist that run for over 25 years (e.g., the Leiden Early Arthritis Cohort), providing valuable information about disease course. In hand OA such cohorts are rare[2,3]. One of these other cohorts is the only one also including MRI and it has five years follow- up, although this is a relatively small cohort with late-stage hand OA[3]. Therefore, recently, the follow-up of HOSTAS was extended to continue for eight years, providing a unique opportunity to study primary hand OA over an extended course. In this context it is necessary to think about how to keep patients motivated to participate in such long follow-up. A disadvantage in HOSTAS is that it is an observational study without disease-modifying treatment options. Hence, participation does not purport certain treatment benefits. Therefore, patients in HOSTAS are 'rewarded' with regular follow-up, MRIs of the hands that are not made in regular care, newsletters, Christmas cards and patient information days resulting in a good number (around 75%) of patients in follow-up.

In order to run such a large cohort as HOSTAS, adjustments in research logistics are necessary to keep the process efficient. Such adjustments could mean a transition to digital questionnaires instead of paper. Also the number and usefulness of questionnaires involved should be evaluated. Therefore, we evaluated instruments, as described in this thesis, for their performance. Another instrument that we evaluated was the Michigan Hand Outcomes Questionnaire (MHQ)[27]. The first results show, that next to much used

questionnaires such as AUSCAN and FIHOA, MHQ has several useful aspects justifying its use in hand OA. However, MHQ, AUSCAN and FIHOA appear to measure different aspects of pain and function while using three questionnaires to assess a domain seems redundant. In this respect, there in an important role for the OMERACT hand OA working group in the coming years to determine which outcome measures are preferred for the different outcome domains[5]. With good instruments to measure hand disability available it might be considered to discard questionnaires measuring overall disability such as Health Assessment Questionnaire (HAQ). When responsiveness of instruments is assessed, anchor questions like we used in the MHQ study are useful[27].

Interventions on patient-specific factors

We evaluated patient factors that were associated with disease burden. First this was presence of comorbidity. Future research could build upon our results by studying the effect of comorbidity or its treatment (e.g., exercise or medication use) on hand OA disease burden over time. Second, we found that illness perceptions could be a potential treatment target to reduce disability. Intervention studies for illness perceptions in patients with hand OA have not been performed so far and could be a focus of future research. Such a study is the 'Grip on Pain' study, which is currently performed, and in which patients with hand OA participate. This eHealth program aims to implement and evaluate an online chronic pain treatment taking into account psychoneurobiologic factors.

Hand joint pain as an outcome measure

In several chapters we studied pain; in **chapter 4** we investigated the role of inflammatory MRI-features in joint pain and in **chapter 8** we evaluated the metric properties of self-reported painful joint count. The etiology of pain in hand OA is multifactorial and influenced by biological, psychological and social factors. Inflammation is an important contributor, but also other factors such as central sensitization are likely to contribute[28]. This makes assessment of pain in hand OA difficult. It remains partly unresolved which type of pain, or construct of pain, is addressed by self-reported painful joint count and whether this is a different construct than addressed by assessor-reported tender joint count. In HOSTAS no centralized pain measurements were performed. Therefore, future studies could also asses the centralized pain component to further the understanding of pain in (hand) OA. This could, for example, be done by quantitative sensory testing, neuroimaging or by questionnaires discriminating between nociceptive and neuropathic pain. In **chapter 2** it became also apparent that two-thirds of the Hostas patients used pain medication, mainly acetaminophen. Unfortunately, details about the use and dosage of

the medication were not recorded in detail and therefore its contribution to (relieve of) pain could not be studied. A more detailed recording could be valuable to evaluate the effect of this medication when studying pain.

Effusion as a separate inflammatory feature

In **chapter 5** we showed that MRI-defined effusion is present in interphalangeal joints of patients with hand OA and that it is, in line with previous studies, of clinical importance. Hence, research is warranted to confirm our results and to further study the role of effusion apart from synovitis in hand OA. Therefore, it could be considered to include effusion in MRI-scoring for hand OA as a separate feature. Our definition could serve as a framework for this, after confirmation of validity and reliability. For this, acquisition of MR images with contrast enhancement is necessary to make a distinction between synovitis and effusion. Furthermore, the reader should be aware that flexor tendon sheath fluid, which is highly prevalent in healthy volunteers, should not be mistaken for effusion in the small finger joints[16]. It could be that the protective effect of effusion that we found is explained by anti-inflammatory or repair-aiding substances in the fluid. This hypothesis could be further studied by assessing the fluid itself and by comparing this to joint fluids of healthy individuals.

Inflammatory features as a treatment target

From our results in **chapters 4-7** we concluded that MRI-defined inflammatory features are clinically important and could therefore serve as a treatment target. Especially synovitis seemed relevant as a target in reducing pain. We hypothesized that these inflammatory features could be modified by anti-inflammatory medication like steroids, which is to be further explored in future proof-of-concept trials. Such a trial, the HOPE study, studying the effect of low-dose prednisone on pain and inflammation, is running now in the rheumatology department of the LUMC.

Several studies have been performed recently as proof-of-concept trials to reduce inflammation in patients with erosive hand OA with inflammation. A randomized placebo-controlled trial (RCT) with etanercept, a blocker of the pro-inflammatory cytokine tumor necrosis factor (TNF), showed no effect over placebo on the primary endpoint of pain at 24 weeks. However, their per protocol analysis (i.e., in the patients that completed the study) suggested that etanercept was superior over placebo both on pain and structural damage, especially in joints with soft swelling and erythema[29]. Furthermore, treatment with etanercept inhibited BMLs, especially when severe synovitis was present at baseline. This suggests that TNF has a role in the pathophysiology of erosive OA[30]. However, another

crossover RCT with adalimumab, also a TNF-blocker, did not show any effect on pain, synovitis or BMLs of adalimumab over placebo after 12 weeks[31]. Two RCTs with another anti-inflammatory drug, hydroxychloroquine, in patients with symptomatic hand OA showed no effect on pain relieve over placebo[32,33]. These results are in contrast to effects of these medications in other inflammatory arthritides such as RA[34–36], suggesting that inflammation has a different role in OA than in other inflammatory diseases. In a recent review about underlying histological changes in subchondral bone abnormalities (BMLs), it was shown that BMLs correlate to various histological features and therefore it was suggested that BMLs could reflect different disease stages. The authors could not draw conclusions about underlying pathological processes in BMLs[37]. Hence, the precise role of inflammation in hand OA is yet to be further elucidated. How inflammation is targeted best remains a challenge; whether this is by steroids or by other disease-modifying drugs.

Studying the thumb base

In our MRI studies we assessed only interphalangeal finger joints; a choice based on the high prevalence of OA in these joints, the availability of a scoring system and on feasibility of the imaging protocol at the time. However, the thumb base is also affected in hand OA and is associated with considerable pain and disability[14]. Where MRI provided insight in the pathophysiology of OA in finger joints, MRI studies of the thumb base were lacking. Therefore, after October 2012, the MR acquisition protocol in HOSTAS was changed; contrast agent was no longer administered (for ethical and logistical reasons) and imaging of the thumb base was added. Using these images, recently the OMERACT thumb base osteoarthritis MRI scoring system (TOMS) was developed[38,39]. Studies using this score could reveal the role of inflammation in the thumb base. One study has indicated that inflammatory features play a different role in the thumb base than in the finger joints[40].

Feasible tests

From **chapter 8** we concluded that self-reported painful joint count is a promising instrument to measure hand pain. Also in **chapter 9** we concluded that semi-automatic joint space width measurements might be useful in early-stage OA. A large advantage of such measurements is the feasibility and necessity of little resources (e.g., no or fewer assessors) to perform the measurement. With rising costs of health care but also of medical research low-cost tests are warranted. Both instruments in **part II** are examples of relatively simple and low-cost tests. Another example of such tests are hand mobility tests that we evaluated outside this thesis[41].

A focus to hand OA in primary care

Where hand OA research in population-based cohorts and in secondary care is already scarce, hand OA research in primary care is even scarcer[32,42,43]. Meanwhile, we can assume that many patients stay in primary care. Moreover, in many countries there is a shift in health care from secondary to primary care. Therefore it is important to include primary care patients in hand OA research. Both instruments evaluated in **part II** could aid such research. Nevertheless, further validation of these tests in primary care patients would be necessary before implementation.

Main themes of future research

Based on this thesis, future hand OA research in general should focus on two main themes. The first is to further unravel the disease process in order to aid development of disease-modifying treatments. The second is to determine what the best care is for patients with hand OA; tailored to the individual and taking into account comorbidities, patients' wishes and expectations, joint inflammation and disease burden.

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