Mortality and other outcome measures in osteoarthritis

Liu, R.

Chapter 8

Summary and discussion

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder characterized by degradation of cartilage and changes in subchondral bone, which are accompanied by synovial involvement. It can affect any joint, but the knee, hand and hip joints are most frequently affected. It results in pain, disability and is associated with substantial morbidity. Its societal impact is considerable, since in a world of which the population is ageing, it is associated with a rapidly growing medical and financial burden. Whether it also leads to increased mortality is unclear.
In this thesis we evaluated both mortality and morbidity due to OA. With regard to the latter, we focused on the disease course with respect to the outcomes pain, disability, aesthetic damage and structural damage, especially in patients with hand OA. To investigate whether we can modify these outcomes we also investigated its determinants, including those that can be modified.

DISEASE COURSE AND ITS DETERMINANTS OF OUTCOME IN HAND OSTEOARTHRITIS IN SECONDARY CARE

In the first part of this thesis the focus is on hand OA. This thesis capitalises on the results from the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort study in which more than 500 patients with hand OA have been enrolled since 2009. Participants were included when they had consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and when these hand complaints had been diagnosed as primary hand OA. Baseline and 1-year and 2-year follow-up data have been used.
In **chapter 2** we investigated hand disability at baseline and after 1 year follow-up, and the role of both joint-specific and non-joint specific determinants. Disability was assessed by the Functional Index for Hand OA (FIHOA). We were especially interested in the role of coping strategies in patients with hand OA, which were assessed by the Coping with Rheumatic Stressors (CORS) questionnaire.
First, we showed that disability was associated with the number of painful hand joints and of hand joints with limitations in motion. Next, we investigated coping strategies in patients with hand OA. Coping strategies, next to illness perceptions, are determinants of health outcomes, according to Leventhal's common sense model (CSM). In the CSM model, patients' symptoms may be interpreted and elaborated upon to form into representations or illness perceptions, subsequently guiding coping responses and leading ultimately to the appraisal of outcomes.
The strategy 'optimism', with a median score of 16 (maximal potential range 5-20),

is a strategy to cope with limitations and this was the most often used coping strategy. Of the strategies to cope with pain, the strategy 'comforting cognitions' was the most frequently used. Finally, the coping strategy 'consideration' was more used by patients as a strategy to cope with dependency.
The strategy 'decreasing activity', a strategy to cope with hand pain, and the strategy 'pacing', a strategy to cope with limitations due to hand OA, were associated with disability at baseline and after 1 year follow-up. These associations remain present when adjusted for joint-specific factors. A likely explanation for these associations could be that limitation of activity may result in deterioration of muscular strength and endurance and patients who use 'limiting' activity as a way of coping with pain are more at risk of developing disability, regardless of disease status.
At baseline patients who used the strategy 'comforting cognitions' less often to cope with pain, reported more disability than those who used this strategy more often. However, the use of this strategy at baseline was not associated with disability after 1 year. This finding could suggest that disability drives the use of the coping style 'comforting cognitions'.
In previous studies, it has been demonstrated that education about OA may improve clinical outcomes. Early evidence is now available for the efficacy of psychological interventions such as pain coping strategies skills training in OA patients.[1-3] Our study has shown which coping strategies may influence physical limitations, thereby identifying potential targets for psychological interventions such as psychoeducation and cognitive restructuring.

Aesthetically unattractive appearance of the hands, or aesthetic damage, is an outcome that is reported by patients with hand OA to be of importance. This outcome is also included in the latest Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) endorsed core set of domains that have to be assessed when performing clinical trials and observational studies in hand OA. Aesthetic damage has been included as a subdomain, that is part of the domain structural damage. Though aesthetic damage in hand OA has been described previously, the impact of dissatisfaction with hand appearance on daily life remains unclear. **Chapter 3** focused on the prevalence of aesthetic dissatisfaction in hand OA patients, its impact on daily life and their determinants. To assess both aspects (dissatisfaction in itself and the impact on daily life) of aesthetic damage the Michigan Hand Outcomes Questionnaire(MHQ) was used, a reliable and validated questionnaire which includes a scale for the aesthetics of the hands.
Only 63 (26%) of the 247 studied patients were aesthetically dissatisfied, while even fewer patients (33 (13%)) reported impact on daily life due to dissatisfaction. Patients with deformed hand joints were at higher risk to be dissatisfied with

the aesthetic appearance of their hands. A previous French study, in which 34% of hand OA patients reported high aesthetic concern, reported a relationship between bony enlargements and aesthetic dissatisfaction.[4] Although we found a graded ('dose response') relationship between bony joint enlargements and aesthetic dissatisfaction in univariate analyses, the association was attenuated in multivariate analysis, which could be due to collinearity between deformed joints and bony joint enlargements. In accordance, radiographic damage as assessed by the Kellgren-Lawrence grade was associated with aesthetic dissatisfaction. Furthermore, patient-reported hand pain or disability was not associated with aesthetic dissatisfaction.

In contrast, the impact of aesthetic dissatisfaction was associated with hand pain and disability. Dose response relationships were also seen between deformed joints, bony joint enlargements and radiographic severity and impact due to aesthetic dissatisfaction, although the associations were not all statistically significant in multivariate models. Moreover, patients who reported impact, also reported more depression and negative illness perceptions, than those who did not report impact.

In line with our expectations, aesthetic dissatisfaction especially depends upon joint-specific determinants and less on psychosocial determinants. However, patients with more symptoms, a higher depression score and negative illness perceptions experienced more impact. These results demonstrated the influence of psychosocial factors on outcome measures in hand OA patients. The incorporation of self-management training could be considered as a part of treatment in hand OA patients, as patients with negative illness perceptions may benefit from these programs.

Chapters 4 and 5 focused on joint-specific determinants that can be assessed by Magnetic Resonance (MR) imaging and their association with joint pain and radiographic progression.

Activity in the subchondral bone, identified as bone marrow lesions (BMLs) on MR images, have been widely investigated in knee OA and have been shown to play a role in knee pain.[5] Also synovitis has been reported as a process that plays a role in osteoarthritic pain; also in hand OA in ultrasonographic studies. Studies investigating BMLs in patients with hand OA are sparse. MR imaging offers the possibility to investigate both the presence of BMLs and synovitis, thus enabling us to determine what is the contribution of BMLs and synovitis separately and which target is most promising for treatment.

Chapter 4 focused on the occurrence and interaction between BMLs and synovitis with respect to pain in patients with hand OA that had undergone contrast-enhanced MR imaging. A total of 840 interphalangeal joints from the right hands

in 105 hand OA patients were scored for MR features following a modified version of the Oslo hand OA MR imaging scoring system. The MR imaging features BMLs, (teno)synovitis, tendon inflammation and cysts were frequently seen. The features BMLs and synovitis on joint level were both associated with site specific pain upon palpation, when adjusted for age, sex, BMI, Kellgren-Lawrence grade and patients being present with multiple joints in the analysis. A clear interaction between BMLs and synovitis was seen, with a joint effect larger than the sum of the separate effects. We also found that severe synovitis alone was associated with pain while BMLs alone was not. Site specific pain upon palpation was observed in 53% of joints with BMLs and moderate to severe synovitis. A nearly 7-fold increased risk for pain was found in these joints when compared to interphalangeal joint without BMLs or synovitis.

We therefore concluded that in hand OA patients severe synovitis in the interphalangeal joints is associated with joint pain, which is worsened when BMLs co-occur. These results suggest that synovitis could be a target for treatment.

However, summarized scores of BMLs or synovitis for the total patient were not associated with self-reported pain on questionnaires and this might be explained by an inability to correct for patient effect such as psychosocial factors, that are of great influence on self-reported pain in patients, but also due to the lack of involving the finger joints of the left hand and the thumb base joints in the analyses.

The MR imaging features flexor tenosynovitis, extensor tendon inflammation and cysts were not associated with pain. Though a previous study found an association between flexor tenosynovitis and pain, these results were not replicated and this may be explained by a difference in study population and methods used.[6]

More studies will be necessary to investigate the feature extensor tendon inflammation for its association with clinical parameters. No association was found between extensor tendon inflammation and pain, but this feature may possibly be associated with other clinical properties, such as hand mobility. The reliability for the scoring of this feature was also lower than for other features scored and more studies may investigate whether it is perhaps a more difficult feature to define and whether an adaptation of the current definition is necessary.

Future studies could also analyze the DIP and PIP joints separately since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ between DIP and PIP joints.

The association between MR imaging features and both onset and progression of radiographic damage in hand OA were studied in **chapter 5**. Of 696 interphalangeal joints of the right hand in 87 patients with hand OA, 324 joints had no radiographic OA damage at baseline (Kellgren-Lawrence score=0). After two years of follow-up 78 joints had onset or progression of radiographic osteoarthritic damage. Our

results demonstrated that BMLs grade 2/3 were associated with Kellgren-Lawrence progression. BML grade 1 however was not associated. A graded association was found between synovitis and Kellgren-Lawrence progression. The association of these MR imaging features with osteophyte and JSN progression was similar.
Both BMLs and synovitis were associated with both onset and radiographic progression on joint level. In adjusted analyses the presence of BMLs decreased the strength of the association between synovitis and progression, while synovitis in turn also decreased the strength of the association between BMLs and progression.
We concluded that BMLs, next to synovitis, play a role in radiographic progression already after 2 years, and that therefore both joint tissues could be important targets for therapy.
One of the strengths of the study is that patients from early to severe stages of OA were included in this study. Furthermore, progression was not only investigated on joint level, but also on patient level. Crude associations were found between summated BMLs or synovitis score, but only synovitis remained associated after adjustment. Our results suggest that the more severe the inflammatory state is, the higher the risk of progression. This would mean that future randomized controlled trails could explore if anti-inflammatory medication like oral steroids could modify inflammatory MR imaging features. This study did not investigate whether MR imaging features are persistent or fluctuate in its occurrence. Future studies could focus on the persistent and fluctuant nature of these features and the progression of structural damage over time.

MORTALITY IN OSTEOARTHRITIS

A study by Nuesch et al reported that mortality was increased among subjects surveyed from the general population with hip and knee pain and radiographic OA signs.[7] A possible association between OA and mortality could be explained by factors such as atherosclerosis, diabetes, walking disability and use of NSAIDs. If an association is indeed present, this could mean that management of patients with OA should focus on effective treatment of cardiovascular risk factors and comorbidities in clinical practice.
In **chapter 6** we studied two observational cohorts of OA patients who consulted health care for their OA: The 'Genetics ARthrosis and Progression'(GARP) cohort comprised 192 Caucasian sibling pairs (384 patients) with symptomatic primary OA at multiple sites in the hand or in at least 2 of the following sites: hand, knee, hip or spine, that were diagnosed by rheumatologists, orthopaedic surgeons and general practitioners. The 'Osteoarthritis Care Clinic'(OCC) cohort consisted of

460 consecutive patients who were diagnosed by the rheumatologist with primary hand, knee or hip OA and referred to the clinical nurse specialist for education. We found no increased mortality rate when compared with the general population for either cohort. The factors male sex, increasing age and co-morbid condition of cancer were associated with mortality in GARP, as was expected, but OA was not. Hip OA was associated with mortality in univariate analysis, but this association was no longer present when adjusted for sex and age. Self-reported cardiovascular disease, physical function and body mass index were not associated with increased mortality.

Previous arthroplasty studies in hip and knee OA found prolonged survival in OA patients. Our results are in line with these studies.

So, although an association between OA and risk of death was reported by Nuesch et al, we could not replicate these results, which could be due to differences in study populations: their study included subjects with knee or hip OA recruited via a survey of the general population, whereas the patients in our OA cohorts actively consulted a medical specialist or general practitioner for their OA complaints. An explanation might be that our patients possessed personality traits which prompted them to actively seek health care. This personality trait might also be accompanied by a pursuit for healthy life-style and a search for early care in case of illness. Moreover, by consulting health care for their musculoskeletal complaints due to OA they could have received treatment for other known medical conditions as well. However, it is also possible that an opposite mechanism explained the findings of Nuesch et al, i.e., that those who respond to a survey and self-report knee or hip complaints, suffer from co-morbidities affecting life expectancy, which confounded the results. Since our study did not find a specific cause of death nor an effect of OA-related factors, these explanations seem more likely than an effect of OA per se on mortality.

Additional analyses were performed to preclude that our results might be explained by the exclusion of patients with a shortened life span in the GARP study. We did not find a 'healthy cohort' effect and this was supported by the replication of our results in the OCC study, where this exclusion criterion was not applied.

The reliability of the death certificates could be questioned, but possible misclassification of causes of death will occur for both OA patients and in the general Dutch population. This is therefore not a likely explanation of the results.

As evidence concerning mortality due to OA has been contradictory, we performed a systematic literature review to summarize and determine the true association between OA and mortality in **chapter 7**. A total of 33 articles, investigating 35 studies, reported on the association between OA and mortality. Studies could be distinguished in three clinical settings: patients receiving an arthroplasty, patients seeking care for their OA or participants from the general population. Seven high

quality studies investigating patients receiving an arthroplasty found an equal or lower overall mortality rate for OA patients when compared to the general population. In line, are the results of three high quality studies investigating patients seeking care for their OA, that also reported no association between OA and mortality. Finally, ten high quality studies investigated participants from the general population. We could perform a meta-analysis of six studies of these ten studies and found a pooled hazard ratio (HR) of 1.04 (0.91-1.18). Two of the four studies that were not included in the meta-analysis found an association between OA and mortality, while two did not. Separate analyses for radiographic and symptomatic OA did not result in an increased hazard ratio.

So, in conclusion, we did not demonstrate a clear association between the presence of OA and mortality nor does a pooled estimate of the literature suggests such an association.

Although we did not find an association between OA and mortality in OA patients who received a joint arthroplasty and in those who sought care from a health professional for their OA complaints, we cannot rule out that such an association between OA and overall mortality might exist in another clinical setting, since the results in population based studies were more varied. Factors which could influence these differences could be the 'healthy cohort' effect, the attitude of patients to take better care of themselves or possess a better general health, the OA subtype, adjustment for confounders and publication bias.

FUTURE PERSPECTIVES

This thesis has provided more knowledge on the disease course and its determinants of outcome in hand OA. Simultaneously, we have also uncovered topics which warrant future research.

We have shown that patients' perceptions of hand OA and the coping strategies that patients with hand OA use are important for patient-reported outcomes such as disability, not only at the same moment in time, but also after 1 year. Therefore, these coping strategies could serve as potential targets for interventions such as psychoeducation and cognitive restructuring. Additionally, these interventions could also be considered as a part of treatment in patients with negative illness perceptions. As we have shown patients with negative illness perceptions experience more impact due to aesthetic dissatisfaction. Though aesthetic damage has been suggested as a part of the domain structural damage, patients with negative illness perceptions seems especially influenced and could possibly also benefit from these interventions.

The 'Grip on pain' study is an ongoing trial performed in the department of Rheumatology of the Leiden University Medical Center, which will hopefully soon provide the first data on this topic. This randomized controlled trial aims to investigate the effectiveness of an online self-management intervention in patients with hand OA. Therefore, patients that have consulted a rheumatologist for their hand OA are either randomized to care as usual, comprising a consultation by the nurse specialist and occupational therapist, or to care as usual plus the online self-management intervention led by a health psychologist. The trial will not only increase our insight whether targeting psychosocial factors will improve quality of life and symptoms in patients with hand OA, but will, when positive, also supply a new treatment modality to improve the management for patients with hand OA.

In the current studies we have investigated the disease course of hand OA over 2 years. However, hand OA is a chronic slowly progressive disease. Therefore, it would be highly relevant to extend the investigation of disease course and its determinants to a time-frame over 2 years. Since the HOSTAS study is an ongoing observational cohort with already patients with a follow-up duration of 8 years this would be valuable to evaluate. On the other hand, the HOSTAS study is a Dutch study, and therefore it could be that the results are not generalizable to hand OA patients in other countries. It could be that cultural differences exist for instance with an outcome as aesthetic damage. Therefore, it is important to collaborate with other cohorts, such as DIGICOD in France and Nor-Hand in Norway, to replicate results.

MR imaging is a promising method to evaluate diseases processes and outcomes in hand OA. The features BMLs and synovitis on joint level were both associated with site specific pain upon palpation and a clear interaction could also be seen. Other MR imaging features such as extensor tendon inflammation were not associated with pain. Since this was the first study to investigate the latter feature in OA, more studies will be necessary to investigate the association between this feature and other clinical parameters, such as hand mobility. Future studies could perform separate analyses of the DIP and PIP joints since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ. Since BMLs and synovitis were not associated with pain on the patient level, it will be challenging to discover which other known and unknown variables could contribute to the patient effect. Especially the role of the thumb base joints are highly relevant. Furthermore, it would also be interesting to see if MR imaging features change over time, which can be done by using the follow-up data from the HOSTAS study.

We showed that BMLs and synovitis were both associated with onset and radiographic progression after two years of follow-up. Therefore, future randomized double-blind placebo-controlled trials could explore if anti-

inflammatory medication could modify inflammatory MR imaging features and symptoms in patients with hand OA. One such trial is the Hand Osteoarthritis Prednisolone Efficacy (HOPE) study, whose main objective is to identify a possible new treatment to alleviate pain and diminish inflammation in hand OA patients.
A part of this thesis focused on the association between OA and mortality. We studied two observational cohorts of OA patients who consulted health care for their OA and found no association. In a subsequently performed systematic literature review we have shown that OA was not associated with mortality in patients receiving arthroplasty or seeking care, while this association has been reported in population-based OA studies. OA subtypes and other factors could play a role in this association and have not been sufficiently investigated till now. Large scaled population based studies, such as the Netherlands Epidemiology of Obesity (NEO) study, a population-based prospective cohort study which was started to investigate underlying mechanisms of the relationship between obesity and related diseases such as OA, can be used to further our understanding of the relations between OA, co-morbidities and mortality . Ideally, these large scaled studies will also aid us in our quest for treatment options.

REFERENCES

1 Keefe FJ, Blumenthal J, Baucom D, Affleck G, Waugh R, Caldwell DS et al. Effects of spouse-assisted coping skills training and exercise training in patients with osteoarthritic knee pain: a randomized controlled study. Pain 2004;110:539-49.

2 Hunt MA, Keefe FJ, Bryant C, Metcalf BR, Ahamed Y, Nicholas MK et al. A physiotherapist-delivered, combined exercise and pain coping skills training intervention for individuals with knee osteoarthritis: a pilot study. Knee 2013;20:106-12.

3 Broderick JE, Keefe FJ, Bruckenthal P, Junghaenel DU, Schneider S, Schwartz JE et al. Nurse practitioners can effectively deliver pain coping skills training to osteoarthritis patients with chronic pain: A randomized, controlled trial. Pain 2014;

4 Hodkinson B, Maheu E, Michon M, Carrat F, Berenbaum F. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. Ann Rheum Dis 2012;71:45-9.

5 Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70:60-7.

6 Haugen IK, Boyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK. 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 Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ 2011;342:d1165.