Doctor, why does my hand hurt? The nature, course and treatment of pain in hand osteoarthritis

Meulen, C. van der

CHAPTER 11

SUMMARY AND DISCUSSION

C. van der Meulen

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Hand osteoarthritis is a common and debilitating disease, with pain as the main symptom. (1-3) The disease is characterized by bony swelling of the hand joints, primarily the distal interphalangeal (DIP), proximal interphalangeal (PIP) and first carpometacarpal (CMC-I) joints, often accompanied by soft swelling and deformation. (3) Curation or disease modification are currently not possible, leaving symptom reduction as the main aim of treatment. (4, 5)

Treatment is often unable to fully alleviate pain in hand OA. To improve and expand the selection of available treatments, research is currently being undertaken. Difficulties encountered in research include a lack of knowledge on natural disease progression and determinants thereof, which makes it difficult to select the right patient group and the correct interventions to conduct efficient trials. Secondly, much is unknown regarding the nature of hand OA pain and mechanisms underlying it. This further complicates the targets of potential interventions. A third challenge is the correct measurement of the effects in trials. Imperfections in our currently available tools potentially cause inefficiency in research, and could lead to false results or unnecessarily large trials.

This chapter summarizes and discusses the findings presented in this thesis, which addresses these issues with the aim of improving healthcare for hand OA patients.

Part 1: The natural course of hand OA

Much remains unknown regarding the natural course of hand OA, especially the course of pain symptoms. Information on this topic can aid in efficient and effective research, and can be used to inform patients and may aid in the development of new treatments. Of particular interest is the potential existence of subgroups who experience different pain trajectories. The existence of such subgroups was investigated in **chapter 2**, using latent class growth analysis. We first investigated which factors were associated with pain at baseline. This showed that the level of pain experienced was cross-sectionally associated with demographic, social, psychological and disease-related factors, reaffirming the need to view pain in hand OA through a biopsychosocial model. (6) We also found associations with specific coping styles and illness perceptions. Previous studies similarly showed associations between disability and coping styles and illness perceptions in hand OA. (7-9) These findings in particular might be used to develop psychosocial interventions for hand OA pain in the future. Through the LCGA we found three classes of patients with hand OA, differentiated based on their pain trajectories over four years. The three classes all showed a stable level of pain over time on average,

with differences in the level of pain at which the average was stable. This by itself is a valuable result to communicate with patients, who are frequently under the impression that hand OA invariably gets worse with time. Subsequent analyses into factors associated with these classes showed that classes of higher pain levels were positively associated with BMI, tender joints at baseline, symptom duration, signs of depression, impairments in hand function, and negatively physical health-related quality of life and education level, compared to the class with the lowest pain level. Many factors were associated both with baseline pain and the pain trajectory, even after adjustment for baseline pain. This shows these factors influence pain both cross-sectionally and over time. Our findings here are also in concordance with previous LCGA studies in hip and knee OA. (10-12)

LCGA analysis shows only average pain trajectories per derived class. Within these classes patients may still be highly heterogeneous in their pain development. This was clear when inspecting the individual patient trajectories that made up the averages of the classes (chapter 2, figure 1). To disentangle these groups we again investigated the development of pain in patients with hand OA over four years in **chapter 3**, this time classifying patients based on the minimal clinical important improvement. This yielded groups that improved, deteriorated or remained stable in their pain. We also investigated which patients had a good clinical outcome after four years, defined as a pain score lower than the patient acceptable symptom state (PASS). Over four years, 38% of patients experienced an improvement in their pain, 30% deteriorated and 32% remained stable. These findings are congruent with **chapter 2** as well as with earlier studies indicating that the average pain level of the entire group of hand OA patients is likely to remain stable, with the changes averaging each other out. (13-15) The high percentage of people whose pain remained stable or even improved also reaffirms the message that pain in hand OA need not get worse. Compared with patients with stable levels of pain, patients whose pain deteriorated on average had a higher BMI, used comforting cognitions as a coping style more often and perceived they had a better understanding of the disease. Patients whose pain improved on average had better hand function and mental wellbeing at baseline, and perceived less consequences of their hand OA. Both improvement and deterioration groups were more frequently employed and experienced less negative emotions due to their hand OA than the group with stable pain. The results support our findings in **chapter 2.** Both studies indicate a multifactorial nature of pain in hand OA cross-sectionally and over time. Almost half of the patients had a good clinical outcome after four years. On average, these patients had better hand function and less tender joints at baseline. They also attributed less symptoms to their hand OA.

For these two chapters, an important caveat is that the data are derived from an observational study. Although it concerns a large cohort and statistical methods were applied to minimize confounding, it is unlikely that no residual confounding remains. As such, caution should be exercised in interpreting these results in a causal manner. By comparing these results with data from other large hand OA cohorts (e.g. the DIGICOD and NOR-hand cohorts) (16-18) these factors may be validated. After such validation they can inform future research and new hypotheses. It is also likely that these data lack the granularity needed to fully capture the pain experienced by hand OA patients. This pain is known to fluctuate over short periods, and such fluctuations may be missed when pain is measured annually.

Structural damage and pain need not progress together, as even cross-sectional associations are weak. (1, 19) Thus, we separately investigated (rapid) progression of radiographic damage and its determinants in **chapter 4**. We used data from the HOSTAS, from baseline to year 2. Radiographs were scored for presence of osteophytes (OP) and joint space narrowing (JSN) at both timepoints, and change in these radiological markers was used to classify patients as progressors or stable, based on the sum score of the hand joints. Determinants of being a progressor were then assessed with logistic regression. Of the participants, 65% showed progression of OP and 32% showed progression in JSN. Most progression was seen in the DIP joints, followed by the joints in the thumb base and the PIP joints. Radiographic damage at baseline was associated with progression of both OP and JSN. Erosive disease at baseline was also associated with OP progression. Furthermore, increases in AUSCAN pain from baseline to year two were associated with JSN progression. Analyses were also stratified by hand OA subtypes according to the 2023 EULAR criteria. (20) In interphalangeal hand OA strong associations were found between baseline erosive disease or bone marrow lesions and OP progression, and in thumb base OA between female sex and OP progression. Further evaluation of the association of baseline OP sum score with change in OP revealed that this effect was strongest in the youngest tertile of women in our cohort and attenuated with age. The association of baseline damage with progression of damage may be an indication that patients with more baseline damage represent those patients with faster progression of pain, rather implying positive feedback cycle of structural damage. Other underlying risk factors would then be the cause of the rapid progression. This requires further study. However, until these underlying factors are found, more baseline damage in otherwise similar patients may already be useful as a proxy to select patients for trials.

For all three studies presented in part 1, it is possible that associations were missed. Cohorts constructed based on the presence of a disease are at risk of collider stratification bias, in which the associations between risk factors are distorted, usually towards

the null. This has been described as a particular challenge in studying risk factors for progression of OA. (21, 22)

What is collider stratification bias?

Collider stratification bias occurs in samples collected based on the presence of a disease or similar outcome. Consider for example attendance of a prestigious university (the "disease" in this example). Students can attend this university either through a sports scholarship or through high average grades. Studies within this population might show a false negative association between being good at sports and being good at studying. In real life, more than two causes will be involved, and they need not be mutually exclusive, so the effects of the bias will be more subtle. However, there is still a tendency for effects to be biased towards the null.

In overview, part 1 of this thesis provides data on the natural course of hand OA and shows a number of potential risk factors. After replication and validation in other cohorts, these data may be used to inform future trials, both for patient selection and to develop new interventions. It would be particularly interesting to see whether psychosocial interventions will be useful in treating pain in hand OA. It may even be that part of the pain in hand OA can be reduced or even prevented by addressing widely held health beliefs or social inequality. In the meantime, these results are vital for accurate patient information and can help set their expectations.

Part 2: Pain and pain treatment in hand OA

The nature of pain will be key in determining the best treatment for patients with hand OA. After finding a strong effect of prednisolone on pain in inflammatory hand OA, the question arose why some patients did not respond to the treatment. (23) A secondary analysis was performed in **chapter 5**. The PainDETECT questionnaire was used to investigate and classify signs of neuropathic or nociplastic pain in the trial population. Subsequently, factors associated with high PainDETECT scores including quality of life, the response of the PainDETECT score to prednisolone treatment and potential interaction of PainDETECT scores with visual analogue scale (VAS) pain response were studied. Neuropathic or nociplastic pain was likely in 16% of patients based on the painDETECT, more frequently in females, patients with a higher comorbidity load and with less radiographic damage. Presence of neuropathic or nociplastic pain symptoms was also associated with physical health-related quality of life. The symptoms of neuropathic or

nociplastic pain did not decrease with prednisolone, but their presence did also not weaken the response of VAS pain to prednisolone.

Our study adds to a new but growing body of evidence for the presence of neuropathic or nociplastic pain in hand OA. Other studies had similarly reported its presence, often with even higher prevalence. (24-27) The best way to measure non-nociceptive pain in hand OA is currently unknown. The associations found may represent potential risk factors, and are largely in line with other literature. (27, 28) The association with lower quality of life emphasizes the importance of different pain mechanisms, as they can be indicative of different disease burdens. Whether neuropathic or nociplastic pain causes lower quality of life, or whether other factors underlying low quality of life (e.g. psychological problems) predispose patients for the development of non-nociceptive pain requires further investigations. This information is essential to improve healthcare for these patients. The lack of response of neuropathic or nociplastic pain symptoms to prednisolone was as expected. (29) In the future, separate treatments for different pain mechanisms may be required for hand OA patients. This was further supported by the data showing that the response of VAS pain to prednisolone was not attenuated by the presence of neuropathic or nociplastic pain.

Research into therapies aimed at the nerves, as a potential addition to the therapies aimed at nociceptive pain, inflammation and the joint structure, is already ongoing. An example is surgical denervation of joints. This procedure severs the nerves innervating the joint, disturbing pain transmission. It operates on similar principles as radiofrequency ablation, conditionally recommended for knee OA by the American College of Rheumatology (ACR) guidelines. (4) In **Chapter 6** we conducted a systematic literature review to summarize the available evidence and determine the efficacy and safety of surgical denervation for pain in hand OA. Based on 16 case series and one trial, all with significant risk of bias, we found that surgical denervation may decrease pain, improve hand function and be satisfactory for patients. However, adverse events were frequent, there was large heterogeneity in the techniques used and it was impossible to determine how surgical denervation compares with usual care, other methods of denervation or placebo. As such, we concluded that more and higher-quality evidence is needed before it could be recommended as a treatment.

Part 2 showed that neuropathic or nociplastic pain is important to address in hand OA. It mainly raises new questions to be addressed through future research, along with a number of challenges. First, the need for proper tools to establish the presence of neuropathic or nociplastic pain in hand OA, both for research and for diagnosis purposes. Second, the need to specify which type of pain it concerns specifically. Following these

questions, it is important to investigate specific treatments to combat this type of pain, as these are currently lacking in hand OA. Some other approaches are already being investigated, such as the use of pregabaline. (30) Other therapies used in neuropathic pain treatment may similarly become candidates to study in hand OA. Examples include anti-depressants and cognitive behavioral therapy. (28) Ultimately, a broader arsenal of therapies aimed for the different types of pain will need to be developed in order to fully alleviate pain symptoms for hand OA patients.

Part 3: OA research methodology

To perform the future research described, valid and reliable outcome measures are required. We have to be able to identify various processes in hand OA, such as structural damage and inflammation, as well as measure pain accurately. Currently, the Australian Canadian osteoarthritis hand index (AUSCAN) is an often-used questionnaire to measure pain changes in trials. (31, 32) It can be used both as a continuous score and with well-defined cutoffs, based on the minimal clinical important improvement (MCII). (33) In **chapter 7** we investigated how changes in the AUSCAN compare with changes in pain as recalled by patients, by comparing it with an anchor question. The AUSCAN MCII was originally derived based on an almost identical anchor question. However, we found that there is very low concordance between changes on the AUSCAN and the recalled change in pain, both for increases and decreases in pain. We investigated this both in the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort and in the Hand Osteoarthritis Prednisolone Efficacy (HOPE) trial, allowing us to compare trial data with cohort data. In the trial, a majority of patients answered that pain had improved. In the cohort the majority answered that pain had worsened. In both settings the concordance was low. Based on this result it is possible that treatments with positive results in trials will not lead to satisfactory pain relief experienced by patients. Part of the discordance might be due to recall bias, and thus influenced by the duration between measurements. Both the 6-week period in the trial and the yearly period in the cohort performed badly. This raises the question what the optimal interval to study pain is. We did not find association between mental wellbeing or illness perceptions and whether patients answered the two methods concordantly.

As inflammation, specifically synovitis, has been associated with joint pain in hand OA, it is vital we measure this correctly. (34-36) In rheumatoid arthritis (RA), synovitis can be measured with the new Global OMERACT/EULAR ultrasound synovitis score (GLOESS). (37) In **chapter 8** we investigated the performance of this score in hand OA. We compared the composite GLOESS score, calculated from ultrasound scores for synovial thickening and doppler signal, with the separate ultrasound features used to calculate the GLOESS, as well as with effusion. We used data from the HOPE trial, in which ultrasonography was

performed at baseline, week 6 and week 14. The primary publication had shown that synovitis responds to prednisolone treatment. (23) We found the same for the GLOESS score, with a similar magnitude. No responsiveness was seen for Doppler signal or effusion. Cross-sectional associations between joint tenderness and ultrasound features was seen for all separate features and for the GLOESS score. In the direct comparison, we found no evident benefits for the GLOESS score. This may be due to the relatively low prevalence of synovitis in hand OA compared with RA. Potential benefits include higher interobserver reliability between different investigators and ultrasound machines than separate ultrasound features, and the GLOESS may provide a higher specificity than the separate ultrasound features. Such benefits were not proven in this chapter and require future investigations.

Part 3 showed through both chapters that hand OA research still faces methodological difficulties. It highlights the importance of ongoing evaluation of the tools we use, updating them as necessary based on new insights. Especially for pain, more tools are required. Pain is recognized as part of the core outcomes for hand OA research by the Outcome Measurements in Rheumatoloy (OMERACT). (38) A VAS or numeric rating scale (NRS) was considered a preliminary tool for pain measurement in hand OA by the OMERACT in 2018. (39) A general scale may not provide insight into the full breadth of hand OA pain, which concerns both severity and nature, as demonstrated in **chapter 5.** Together with **chapter 7** this shows a need for new pain measurement tools. It may be necessary to develop an entirely new tool, or it may be possible to combine existing tools.

Part 4: Future research directions

Throughout this final chapter, a number of directions for future research have already been described. During the making of this thesis, two new projects were started to aid in this future research.

The first project concerns the SensOA study, described in **chapter 9.** SensOA is an observational study with the aim to investigate the nature of pain in hand OA, the risk factors for various types of pain found in patients with hand OA, and to validate tools which measure pain types in hand OA. This cohort may also be used to validate recent studies from the NOR-hand study, in which phenotypes of hand OA pain are investigated. (40) Patients in the study undergo physical examination of the joints, including the hands, hips and knees, and a short set of quantitative sensory testing (QST) examinations is performed. They fill in questionnaires on demographics, pain, illness perceptions, coping styles, their tendency to catastrophize pain, and other factors related to pain. Patients in whom other potential causes of neuropathic or nociplastic pain have been excluded

further undergo ultrasonography of the hands and the extensive QST protocol. (41) The results from this study will be used to validate several tools for the detection of non-nociceptive pain, which can then be used in research or even in the clinic. This study will be the first to perform the full German QST protocol in patients with hand OA, providing the most comprehensive investigation on the nature of pain in hand OA to date.

Knowledge on the nature of pain should lead to new treatments. The patients who complete the entire study, including the ultrasonography and extensive QST, have been invited to participate in the Pulsed Radiofrequency therapy for hand OsteoArthritis Pain (PROAP) trial, described in **chapter 10.** In this trial the efficacy of transcutaneous pulsed radiofrequency (tPRF) for treating hand osteoarthritis pain will be investigated, in a double blind, sham controlled setting. tPRF is a treatment aimed at the nerve, rather than the joint, which is already applied to other types of chronic pain. This might be one of the future therapeutic options for patients with hand OA. As the trial is conducted with patients from whom all the information of the SensOA is available, it will be possible to investigate the effect of tPRF in great detail with high efficiency.

Future perspectives

This thesis has increased our knowledge of the natural course of hand OA, the nature and treatments of pain in hand OA, and our knowledge of the tools we use to investigate this condition. It also describes the work that has been started to generate further data on pain in hand OA and the treatment thereof. This thesis provides valuable information for researchers, clinicians and patients alike.

A number of future directions for research are discussed above. In short, potential risk factors for progression of pain and structural damage in hand OA need to be validated, the mechanisms underlying pain in hand OA require clarification, treatments for pain need further study, and the measurement tools for both pain and structural features of hand OA require further assessment. Etiological studies are needed to discover and classify the nature of pain in hand OA. Qualitative studies should be performed to identify the components that must be covered by pain measurement tools. Furthermore, by collecting multiple pain questionnaires in future studies, it would be easier to compare the various tools. All this can lead to new tools, which can then be used to research new treatments.

A crucial issue is how the pain in hand OA should be classified. This can be done through mechanistic descriptors, through the more extensive ICD-11 codes, or through pain phenotypes. (42-44) We should do what is necessary to achieve good treatments for all patients, without dividing the population in more subgroups than is necessary to

achieve that goal. Imagine for example ending up with 3 phenotypes, which all have the same mechanistic type of pain. These could potentially be treated with the same treatment, just different in dosage. This is by no means certain, but future researchers should be wary of creating a framework with too many phenotypes, which are all part of one group on a sliding scale.

A second question is whether these phenotypes should be unique to hand OA or developed for OA in general. Given that hand OA differs from knee and hip OA in that mechanical loading plays a different role (as the hands are not weight bearing), the pain phenotypes in hand OA may be unique. This question requires answering through future studies.

What we can already tell, however, is the importance of correct terminology. Strict adherence to agreed upon terminology allows for better comparisons between studies. Either the International Association for the Study of Pain (IASP) terminology could be used, or another terminology could be agreed upon, but harmonization might greatly benefit and speed up research.

To end this thesis, we return to the observation that pain is inherently subjective. This means that any tool we develop to measure pain will be subject to the way patients answer to questions and interpret their pain. For example, patients may be inclined to compare the pain caused by hand OA with other types of pain they have experienced. Based on what has occurred in their life up to that point, the answer may vary greatly. Sharply delineating what type of pain fits with a certain condition carries an inherent risk of reducing it too much to a biological fact, rather than appreciating the full complexity. We should always keep this in mind when investigating pain, lest we lose sight of the ultimate goal: achieving a satisfactory state for the patient.

This final chapter has put the studies in this thesis into the perspective of the wider body of evidence, and has provided suggestions on how to address the newly arising challenges, including two protocols for studies which are currently being conducted. By continuing to study pain and treatment thereof in hand OA, the scientific community will be able to keep on improving healthcare for patients with hand OA.

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