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

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CHAPTER 1

GENERAL INTRODUCTION

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Hand osteoarthritis

Societal burden

Osteoarthritis is "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity", according to the Osteoarthritis Research Society International. (1) This complex disorder can affect any synovial joint. Of the various types of OA, hand OA is one of the most prevalent. In the population-based Rotterdam study, 67% of women and 55% of men aged 55 and older had radiographic signs of hand OA in at least one joint. (2) Radiographic signs of hand OA are not invariably accompanied by hand OA symptoms: symptomatic hand OA occurs less frequently. However, in women over the age of 70 the prevalence still has been estimated at 26%. (3) Due to, amongst others, the ageing population the prevalence of hand OA is expected to increase even further, up to an increase of 48% by 2050. (4) In the Netherlands, loss of work-related income due to hand OA has been estimated at almost 2500 euros per patient per year. (5)

Risk factors

Numerous risk factors for hand OA have been reported. The most important amongst these are age (particularly age >40) and sex. Particularly women over 50 who are in the climacteric transition are prone to hand OA development. (6) Other risk factors are genetic predisposition, obesity, bone mineral density, and various biomechanical factors, consisting of forearm muscle strength, laxity of the joints in the hands, previous traumatic damage to the hand through injury and biomechanical load on the joint, incurred through e.g. sports and physical work. (6-9) It should be noted that these risk factors need not be risk factors for progression of hand OA as well. Less is known about risk factors for progression, in part due to methodological difficulties in studying these. (10, 11) This knowledge gap contributes to the difficulty in treating hand OA.

Pathophysiology

Osteoarthritis has a complex pathogenesis, much of which remains unclear. It is currently known to be a disease of the joint, involving tissues therein and surrounding it. In the joint it affects the cartilage, subchondral bone, synovium, and periarticular tissues affected include muscle and tendon. (12) Cartilage degradation is considered an important feature of osteoarthritis. (13) Cartilage is continually modified by chondrocytes synthesizing molecules to replace degraded extracellular matrix molecules. This gives cartilage a high capacity for withstanding repeated mechanical stress. However,

cartilage has a limited capacity for healing of even minor injuries, making it susceptible to degeneration. (14) OA is currently thought to arise from biomechanical forces putting joints under inordinate levels of stress, leading to joint destabilization, working in tandem with genetic, environmental and systemic factors (including metabolic factors and inflammatory mediators). All these factors together disrupt the balance between synthesis and degradation of cartilage. This results in synovial inflammation, remodeling of bone (including formation of osteophytes and sclerosis of subchondral bone) and neurovascular changes. The damage to the joint and the decreased functionality of the cartilage turns into a vicious cycle, exacerbating the condition. Clinical OA symptoms such as pain and reduced motion and bony swelling are the result. (12)

Clinical presentation

Patients with hand OA often present with pain, stiffness, and functional impairment. Secondary consequences of hand OA include aesthetic complaints, loss of quality of life and impairment in work and social activities. Clinically, the condition is characterized by bony swellings, deformation of joints, pain upon palpation and occasionally soft swelling of the joints. On X-rays osteophyte formation, joint space narrowing and subchondral sclerosis are common. Bone marrow lesion may be found on MRI scans and synovial inflammation can be seen either on MRI or ultrasound. Typically, the distal interphalangeal (DIP), proximal interphalangeal (PIP) or first carpometacarpal (CMC-I) joints are affected. (6)

Subtypes

Several subtypes of hand OA are recognized, either divided by anatomical location or by pathologic features. Based on location we discern thumb base OA and interphalangeal OA. Based on pathology seen on imaging, erosive hand OA is recognized as a subtype. (6) Furthermore, a distinction can also be made between symptomatic and radiographic OA.

Natural course

Despite its high prevalence, studies on the natural course of hand OA are still scarce. This concerns studies on pain in hand OA, and to a lesser extent studies on structural progression in hand OA. Information on the natural course of hand OA is vital for informing patients about their prospects, but can also help in the development of new treatments. Subgroups with faster than average progression may be exposed to modifiable risk factors, and intervening on such risk factors may help prevent worsening of OA. Furthermore, patients with rapid progression are an ideal group to include in studies, as larger effects can be expected from interventions in that group, making studies more efficient. This would reduce the burden for patients as well as the research costs. (15)

Studies that have been done on the course of pain in hand OA indicate that, on average, pain remains stable over the entire patient group. However, subgroups of patients experiencing stable, increasing or decreasing pain may underly this larger pattern. (16-18) Knowledge of which patients constitute such subgroups is valuable for both patients, clinicians and researchers.

Several studies have investigated radiographic progression of hand OA, showing that progression strongly increases with time, with up to 94% of patients experiencing some form of structural progression after twelve years. (16-20) As with pain, the rate of progression may vary between patients. It remains unclear which patients are most likely to experience rapid progression, and we have no current set of criteria to identify these patients.

Pain in hand OA

Pain is, as can be glanced from the classification criteria, a key symptom in hand OA. Generally speaking, pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". (21) Pain can be divided into mechanistic pain descriptors: nociceptive, neuropathic and nociplastic pain, with the last of these defined only in 2017. These mechanistic descriptors are based on the mechanisms thought to underly the various types of pain, irrespective of the disease that invokes these mechanisms. An overview of the mechanisms with examples of conditions which may cause each type of pain is given in table 1. (21-23) These mechanistic descriptors can then be divided further, as demonstrated in the International Association for the study of Pain (IASP) classification of chronic pain. (24) Within this framework, OA pain has been classified by the WHO as a chronic secondary musculoskeletal pain. The types of pain also present differently, with symptoms such as allodynia (pain in reaction to non-painful stimuli) and hyperalgesia (increased response to painful stimuli) being associated with neuropathic and nociplastic pain, as opposed to nociceptive pain. (25) These and other symptoms associated with the mechanistic pain descriptors can be used to perform quantitative sensory testing (QST). This is a class of tests consisting of amongst other testing of the pressure pain threshold (PPT, the level of pressure which first becomes painful) and temporal summation (repeat administration of stimuli with a pinprick to see if the intensity of the pain invoked increases). An often use, extensive validated protocol for QST has been described by the German Research Network on Neuropathic Pain. (26)

Table 1. Mechanistic pain descriptors as defined by the IASP (21)

	Nociceptive pain	Neuropathic pain	Nociplastic pain
Description	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.	Pain caused by a lesion or disease of the somatosensory nervous system.	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.
Examples	Bruises, burns, cuts, inflammation	Carpal tunnel syndrome, phantom pain, diabetic neuropathy	Fibromyalgia, complex regional pain syndrome, chronic low back pain

Hand OA, and OA in general, was long thought to cause only nociceptive pain, originating from the affected joint. There are various tissues in the joint that contain sensory receptors. Two types of these sensory receptors (I and II, forming the corpuscular organs), are found in the capsule and ligaments (and in the knee, the meniscus). They are mechanoreceptors that respond to pressure and traction. Type III sensory receptors are present on the surface of ligaments. These respond to strong mechanical stimuli, having a higher threshold than types I and II, and also respond to thermal stimuli. Finally, type IV receptors are found in all tissues in and surrounding the joint, except the cartilage itself. Type IV receptors are activated by mechanical, thermal and chemical stimuli, but only in pathological conditions such as in inflammation caused by OA. Types III and IV have been described to be involved in pain sensations. The cartilage itself is not innervated, and thus cannot contribute to the pain signal directly. (27) All other tissues can contribute to pain signaling, for example in response to inflammatory signaling, deformation of the joint and increased synovial fluid, exerting pressure on the capsule.

There is an increasing understanding that more pain mechanisms than just the nociceptive mechanism are likely to be involved in hand OA pain. (27-29) Part of this is the increased recognition that neuropathic or nociplastic pain may also be present in hand OA, through findings of lowered PPTs and the presence of temporal summation. (30-32) Given that no evident neurological lesions are thought to arise from hand OA, nociplastic pain may be more likely. Sensitization, the process in which synaptic plasticity results in changes in the nervous system (either centrally or peripherally), leading to increased responsiveness of neurons, has been proposed as a possible cause of neuropathic or nociplastic pain in hand OA. (33) The exact nature of the pain in hand OA, which patient subgroups experience which kind of pain and what causes this is still unknown.

Table 2. ACR 1990 criteria for hand OA (42)

Mandatory	3/4 of the following
Hand pain, aching or stiffness	Hard tissue enlargement of 2 or more of 10 selected joints
	Hard tissue enlargement of 2 or more DIP joints
	Fewer than 3 swollen MCP joints
	Deformity of at least 1 of 10 selected joints

The ten selected joints are: Second and third DIP, second and third PIP and CMC-I joints of both hands.
DIP = Distal interphalangeal. PIP = Proximal interphalangeal. MCP = Metacarpophalangeal. CMC-I = first carpometacarpal.

Pain in OA is considered a multifactorial problem. In hand OA, there is increasing attention to pain as seen through a biopsychosocial model. (34-36) In such models, biological factors such as joint pathology and inflammation are regarded as part of a complex system, in which psychological (coping, tendency for catastrophizing, illness perceptions), and sociological (social support, occupation, education level) factors are also included. (36, 37)

Based on the multifactorial nature of pain in hand OA, it is likely there are patient subgroups with different pain phenotypes, which may require different treatment regimens. Currently, the search for the correct division of OA pain phenotypes is receiving a lot of attention, with various groups investigating this question in different types of OA. (35, 38, 39)

Treatment

There are currently no curative or disease-modifying treatments (Disease Modifying Osteoarthritis Drugs, DMOADS) available for hand OA. This leaves clinicians with symptom relief as the aim of treatment, with pain relief as primary aim. Current guidelines by the ACR and EULAR recommend non-pharmaceutical interventions as the first step. This can consist of exercise, education and assistive devices including braces. Should these fail, pharmaceutical interventions can be considered. Pharmaceuticals of choice are non-steroidal anti-inflammatory drugs (NSAIDs), preferably applied topically to prevent systemic side effects. If these also fail, surgical interventions can be considered, consisting of trapeziectomy for thumb base OA and arthrodesis or arthroplasty for interphalangeal OA. (40, 41)

Despite these options, many patients will not be fully relieved of their symptoms. Given the new insights into osteoarthritic pain outlined above, treatments aimed at the nervous system instead of the joint may constitute an avenue to improve treatment outcomes. Some initial work has been done in this regard, but there are no clear evidence-based interventions aimed at nerves available as of yet. (31) This is a field which requires further investigation.

Table 3. EULAR 2023 criteria for hand OA (43), scores are summed to derive a classification as shown in the legend

Interphalangeal hand OA[1]		Thumb base OA[2]		Overall hand OA[3]	
Age		**Age**		**Age**	
Below 45 years	0	Below 45 years	0	Below 45 years	0
45-54 years	1	45-54 years	1	45-54 years	1
55-64 years	2	55-64 years	2	55-64 years	2
65 years and above	3	65 years and above	3	65 years and above	3
Duration of morning stiffness in DIP, PIP and IP joints		**Duration of morning stiffness in CMC-I joints**		**Duration of morning stiffness in DIP, PIP, IP and thumb base joints**	
Long (>30 minutes)	0	Long (>30 minutes)	0	Long (>30 minutes)	0
None	1	None	1	None	1
Short (30 minutes or less)	2	Short (30 minutes or less)	2	Short (30 minutes or less)	2
Numbers of DIP, PIP and IP joints with osteophytes		**Number of CMC-I joints with osteophytes**		**Numbers of DIP, PIP, IP and thumb base joints with osteophytes**	
None	0	None	0	None	0
1-2 joint(s)	2	1 joint	2	1-2 joint(s)	2
3-5 joints	3	2 joints	4	3-5 joints	3
6 or more joints	4			6 or more joints	4
Numbers of DIP, PIP and IP joints with JSN		**Number of CMC-I joints with JSN**		**Numbers of DIP, PIP, IP and thumb base joints with JSN**	
None	0	None	0	None	0
1-2 joint(s)	1	1 joint	2	1-2 joint(s)	1
3-5 joints	2	2 joints	3	3-5 joints	2
6 or more joints	3			6 or more joints	3
Symptom-structure concordance*		**Symptom-structure concordance***		**Symptom-structure concordance****	
No	0	No	0	No	0
Yes	3	Yes	3	Yes	3

1: Target population: Person with pain, aching and/or stiffness in at least one target joint (DIP, PIP and IP joints) on most days of the previous 6 weeks, and no other disease or acute injury that can explain the symptoms. Diagnosis on a score of at least 8/15.

2: Target population: Person with pain, aching and/or stiffness in at least one target joint (DIP, PIP, IP and CMC-I joints) on most days of the previous 6 weeks, and no other disease or acute injury that can explain the symptoms. Diagnosis on a score of at least 9/15.

3: Target population: Person with pain, aching and/or stiffness in at least one target joint (CMC-I joints) on most days of the previous 6 weeks, and no other disease or acute injury that can explain the symptoms. Diagnosis on a score of at least 8/15.

* Radiographic OA (osteophytes or JSN) in at least 50% of the target joints in which the person has experienced pain, aching and/or stiffness on most days of the previous 6 weeks.

** Radiographic OA (osteophytes or JSN)in at least 1 CMC-I joint with pain, aching and/or stiffness on most days of the previous week.

EULAR = European Alliance of Associations for Rheumatology. DIP = Distal interphalangeal. PIP = Proximal interphalangeal. IP = Interphalangeal. CMC-I = first carpometacarpal. JSN = Joint space narrowing.

Based on Haugen et al (43)

Methodological considerations

Classification criteria

In research, hand OA is usually defined according to the 1990 ACR criteria for hand OA (table 2). (42) These criteria were primarily developed to differentiate hand OA from rheumatoid arthritis (RA). Recently, a new set of criteria has been published, with the aim of setting a new standard for hand OA research and to allow for the stratification of subtypes of hand OA (table 3). (43)

Pain measurement

A related issue to the nature of pain is the measurement of pain. Pain is highly individual, and is ultimately determined by the patient experiencing the pain. Measuring nerve conduction is not sufficient, which can also be inferred from the biopsychosocial model. (21) This leaves researchers with questionnaires which allow patients to express the severity (visual analog scale (VAS), numeric rating scale (NRS)) and nature of their pain (e.g. PainDETECT). (44) Specific validated hand OA questionnaires are also available, with the Australian Canadian Hand Osteoarthritis Index (AUSCAN) used most frequently. (45, 46) However, each of the available questionnaires may capture a slightly different domain, and it remains unclear how well we can currently assess the full pain experience. This further complicates investigating pain, and directly affects our ability to investigate and develop new treatments.

Imaging

Another essential tool in hand OA research is imaging. The most commonly used modality is radiography, which can be scored using the Kellgren-Lawrence, OARSI or Verbruggen-Veys scoring systems. (47-49) The first two describe the severity of OA in the joint based on joint space narrowing (loss of cartilage as seen on radiographs) and osteophytes. The latter system offers a standardized method to score the presence of central erosions in the joint, thereby allowing the classification of erosive disease. They all allow staging of the disease, and tracking of progression when applied longitudinally.

It should be noted that the association between pain and structural damage measured on radiographs in hand OA appears to be positive, but variable and of limited magnitude. (50) Stronger associations have been found with ultrasonography, which allows the investigation of inflammation separately for each joint. On the joint level, presence of synovitis has been associated with pain in that same joint. (51, 52) In ultrasonography joints are scored semi-quantitatively for the presence of osteophytes, effusion, synovial thickening and Doppler signal, the latter three of which may be seen in inflamed joints. (53) Recently the Global OMERACT/EULAR ultrasound synovitis score (GLOESS) has been

introduced in RA, which combines synovial thickening and Doppler signal scores to enhance the scoring system. (54) It remains unclear which ultrasound feature or which combination of features serves best as an indicator of synovial inflammation in hand OA.

AIMS OF THIS THESIS

This thesis aims to:

1. Investigate the natural course of hand OA, particularly the natural course of pain symptoms in hand OA, and to describe subgroups of patients with different trajectories
2. To investigate the nature of pain in hand OA and potential treatments aimed at neuropathic or nociplastic pain mechanisms
3. To investigate the validity and reliability of outcome measures for pain and synovial inflammation in hand OA

Study populations

The research described in this thesis was performed with data from a double-blind, randomized, placebo-controlled clinical trial and a primary observational hand OA cohort study. This combination allowed the study of hand OA and study methodology both in a natural setting and in a trial setting.

The HOSTAS cohort

The observational Hand OSTeoArthritis in Secondary care (HOSTAS) cohort contains 538 patients with primary hand OA diagnosed by their treating rheumatologist. Consecutively referred patients were included. Exclusion criteria comprised secondary OA and other pathologies which could explain the symptoms of the hand. Patients were followed for up to 8 years. Data collection started in 2009 and finished in 2023. Patients filled in questionnaires yearly and underwent physical examinations every other year, at which time radiographs of the hands were also made. The questionnaires included demographic and clinical information, amongst which were the AUSCAN questionnaire, the Hospital Anxiety and Depression Scale (HADS), the Coping with Rheumatic stressors (CORS) and the Illness Perceptions Questionnaire (IPQ). (55)

The HOPE trial

The double-blind, randomized Hand Osteoarthritis Prednisolone Efficacy (HOPE) trial investigated the efficacy of 10mg prednisolone daily versus placebo over 6 weeks. Patients were eligible for inclusion if they had symptomatic hand OA fulfilling the ACR criteria, with signs of inflammation on ultrasound (defined as at least one DIP or PIP joint with soft swelling or erythema, at least one DIP or PIP joint with synovial thickening of grade at least 2) and finger pain of at least 30mm on a 0-100mm VAS. A flare-up after washout of NSAIDs was further required. Patients were excluded when their pain was present primarily in the thumb base, when there were conditions that compromised safety of the study medication, or when there were comorbidities that would interfere with out-

come measurements. Finally, patients were excluded when they used systemic or local immunomodulating drugs or hyaluronic acid injections in the thumb base in the past 90 days. Study medication was used for 6 weeks, and then tapered to cessation in 2 weeks. Patients were followed for 14 weeks, with clinical assessments made baseline and weeks 2, 6 and 14. At baseline and weeks 2, 4, 6, 8 and 14 patients filled in questionnaires, and ultrasonography of the hands was performed at baseline, week 6 and week 14. The primary outcome was change in pain measured on VAS. Questionnaires further included amongst others the painDETECT, Hospital Anxiety and Depression Scale, Coping with Rheumatic Stressors questionnaire, Illness Perceptions Questionnaire and AUSCAN. (56)

THESIS OUTLINE

Part 1: The course of hand OA

Part one of this thesis investigates the natural course of hand osteoarthritis, capitalizing on longitudinal data from the HOSTAS cohort. In **chapter 2**, a latent class growth analysis of data on pain in hand OA is described. This allows for the classification of the cohort into subgroups with different pain trajectories, and the subsequent characterization of those subgroups. Subgroups derived from such a data-driven approach may differ strongly from subgroups based on clinically determined cutoffs for progression. To compare this, we investigated subgroups of patients determined by the minimal clinical important improvement (MCII) in **chapter 3**. (57)

As described earlier, structural damage and pain need not coincide. The same also holds for the progression of radiographic progression and symptomatic progression. Thus, we separately investigated progression of radiographic damage and its determinants in **chapter 4**.

Part 2: Pain and treatment in hand OA

In part two we focus on the nature and treatment of pain in hand OA. We begin with an analysis of data from the HOPE trial, where we investigate the presence of neuropathic or nociplastic pain and its determinants. This is described in **chapter 5.** To add to the knowledge of treatment options and potential treatment targets, we have reviewed the evidence for surgical denervation to treat pain in hand OA in **chapter 6.**

Part 3: OA research methodology

In order to do reliable research, correct outcome measures that accurately reflect what the researcher aims to investigate are crucial. In the third part of this thesis we investigate the performance of such outcome measures. In **chapter 7** we compare changes in pain scored on the AUSCAN questionnaire with changes in pain as reported by the patient with a recall question, and we investigate the influence of illness perceptions and mental wellbeing on these methods yielding the same answer. **Chapter 8** compares the performance of the new GLOESS score with separate ultrasound features, to investigate whether this composite is suitable for use in hand OA research. We also investigate the association of the various ultrasound features and the GLOESS with pain on the joint level.

Part 4: Future research

In the final part of this thesis, we present two protocols describing ongoing studies. The first, the Sensitization and pain phenotypes in hand OsteoArthritis (SensOA) study

in **chapter 9**, describes a cross-sectional study aimed at phenotyping pain in hand OA, with quantitative sensory testing as the main method of investigation. **Chapter 10** describes the follow-up for the SensOA, the Pulsed Radiofrequency therapy for hand OsteoArthritis Pain (PROAP) trial. This trial investigates the efficacy of transcutaneous pulsed radiofrequency therapy for relieving pain in hand OA in patients that underwent QST during the SensOA study.

Concluding this thesis, **chapter 11** provides a summary and discussion of the findings presented in this thesis, including future perspectives. A Dutch summary is given in **chapter 12**. The **Appendices** contain I) a list of publications, II) a Curriculum Vitae, and III) acknowledgements in Dutch.

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