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

Meulen, C. van der

CHAPTER 9

SENSITIZATION AND PAIN PHENOTYPES IN HAND OSTEOARTHRITIS (SENSOA) STUDY

Coen van der Meulen, Lotte A. van de Stadt, Marieke Niesters,
Anne V.E.M. Olde Meule, Frits R. Rosendaal, Margreet Kloppenburg

ABSTRACT

Background

Pain is a common and difficult to treat symptom in patients with hand osteoarthritis (OA). The exact nature and cause of pain in hand OA are unknown. We hypothesize that in its pathophysiology, besides nociceptive triggers such as inflammation and mechanically induced pain, small fibre pathology and alterations in central pain mechanisms play a role.

Objectives

We present a study protocol with the aim to investigate the pain phenotype of patients with hand OA, including the prevalence of fibromyalgia, neuropathic pain symptoms and central sensitization. A further aim is to investigate factors associated with the presence of various pain types in patients with painful hand OA by questionnaires and physical examinations. Furthermore, we will assess the presence of small- and large fibre pathology and central sensitization as measured with quantitative sensory testing (QST) and cornea confocal microscopy (CCM). The validity of screening tools for the assessment of signs of central sensitization will be evaluated.

Study design

Observational study.

Study population

Patients with hand OA, recruited from the Leiden University Medical Center Rheumatology outpatient clinic, aged 18-80 and fulfilling hand pain criteria. Patients with known or suspected presence of rheumatic musculoskeletal diseases or laboratory findings suspect for other inflammatory rheumatic musculoskeletal diseases are excluded.

Examinations

Patients will undergo physical examination including a short quantitative sensory testing (QST) set and fill in questionnaires. Patients who do not have conditions known to cause neuropathic or nociplastic pain other than hand OA are invited to undergo further investigations, which consists of ultrasonography of the hands and an extensive QST test, as well as confocal cornea microscopy.

Main study endpoints

Pain phenotypes in patients with hand OA.

Secondary study endpoints

Determinants of sensitization, neuropathic pain symptoms, generalized small fiber pathology in patients with hand OA. Prevalence of fibromyalgia, and small fiber pathology in patients with hand OA. Validity of short QST test set, pressure pain threshold and the painDETECT questionnaire in hand OA compared to other pain parameters. Associations of synovitis and biomarkers with non-nociceptive pain and small fiber pathology.

Conclusion

Current knowledge of the aetiology of pain in hand OA is incomplete. By measuring pain phenotypes with QST tests and questionnaires, and measuring various possible causes of pain, we will be able to increase this knowledge. This provides a unique opportunity to gain insights into what causes and drives pain in hand OA.

INTRODUCTION

Osteoarthritis (OA) is a common disorder that can affect any joint site. A highly prevalent subtype is hand OA, with a lifetime risk of around 40%. (1) It results in bony enlargements and cartilage loss in finger and thumb base joints, and is often accompanied by overt inflammation. Pain is the most common symptom. Unfortunately, the exact aetiology of osteoarthritic joint pain is still unclear and it is not fully explained by the structural changes, inflammation or other known causes. This lack in understanding hampers effective treatment of pain in patients with OA in general, including those with OA in the hands. (1)

In general, the International Association for the study of Pain (IASP) defines three mechanistic pain descriptors: Nociceptive pain (pain arising from actual or threatened damage to non-neural tissue and due to activation of nociceptors), neuropathic pain (pain caused by a lesion or disease of the somatosensory nervous system) and nociplastic pain (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). Of these, nociplastic pain was the most recent addition, added in 2017. (2-4)

It was long thought that pain in OA was nociceptive in nature, and that it arises in response to inflammatory or mechanical stimuli. Recently it is increasingly recognized that other mechanistic types of pain may also be involved. (5-7) This is supported by findings of knee and hip OA patients reporting hyperalgesia (increased responsiveness of nociceptive neurons to their normal input) or allodynia (a pain response to inputs that are normally below the pain threshold), as well as "referred pain" (pain felt in a loca-

tion other than the location where the lesion causing the pain is situated). (8, 9) These symptoms can be indicative of neuropathic or nociplastic pain. Similarly, in data from the HOPE trial we found indications of neuropathic pain characteristics and changes in central pain processing in 16% of the hand OA patients, based on the painDETECT questionnaire. (10-12) Studies in other countries reported similar findings, although the reported prevalence of such symptoms varies. (13-17)

How neuropathic or nociplastic pain mechanisms are activated in hand OA is not yet clear. It could be an effect of chronic (inflammatory) pain, described to lead to changes in the nervous system which stimulate the recruitment of immune cells to the affected dorsal root ganglia and dorsal horn of the spinal cord. The recruited immune cells in turn release mediators which create a positive feedback loop which leads to further pain. (18) This may cause a disturbance in the facilitation and inhibition of pain, and an increased responsiveness of nociceptive neurons, also called sensitization. (3) This mechanism could provide an explanation for the pain symptoms found in hand OA.

Various methods exist to measure pain and its phenotypes, including sensitization, such as Quantitative Sensory Testing (QST). QST is a standardized approach used to profile patients with chronic pain. An often-used extensive validated QST protocol was developed by the German Research Network on Neuropathic Pain, which can be used to quantify the somatosensory function on a local and central level. (19) It is based on measuring participant's responses to calibrated external stimuli, including mechanical, thermal or electrical stimuli, and provides information on gain and loss of function of amongst others small- and large fibers, the presence of hyperalgesia, allodynia and sensitization. To obtain valid results, QST has to be performed in a standardized and reliable way. In many OA studies to date, only one test of the QST test set is performed to explore sensitization, the PPT (Pressure Pain Threshold). (20, 21) This particular test solely investigates the presence of hyperalgesia rather than the full breadth of non-nociceptive pain symptoms.

Some studies have applied QST in patients with hand OA; however, these studies had limitations. Many studies were small (13, 16, 17), most only investigated or reported QST directly on hand joints, (13, 15, 16), their test-retest reliability was limited, (14) and only one used the validated QST set of the German Research Network on Neuropathic Pain. In future studies the use of shorter protocols or even questionnaires as screening tools would be preferable; however, these are currently not validated against a validated test set. Both these issues can be addressed by collecting more data in hand OA patients using the validated German test set.

A difficulty in the interpretation of pain measured by these methods is that a variety of conditions may underlie the pain. Comorbid fibromyalgia, which is characterized by chronic widespread pain without identifiable nociceptive input, could distort measurements in hand OA. (22) Small fiber pathology might play a role in the pain generated in fibromyalgia, and was previously detected in fibromyalgia patients with cornea confocal microscopy (CCM), (23) a validated non-invasive technique. Small fiber pathology may similarly influence pain in hand OA. Similarly, diabetes mellitus and metabolic syndrome may affect hand OA pain. (24) Knowledge of the prevalence of these conditions in the hand OA population and their possible association with specific pain mechanisms will be invaluable.

Disregarding comorbidities, hand OA itself is not a fully homogenous disease, with some patients exhibiting more inflammatory phenotypes than others, which may also influence pain. Previous studies at our department have shown that ultrasonography is a valid approach to assess inflammation in hand OA. (25) The investigation of associations between QST outcomes and ultrasonography findings may help to further explain the role of inflammation in hand OA pain.

So, our understanding of hand OA pain is far from complete. The protocol outlined here aims to investigate the pain phenotype of patients with hand OA, the prevalence of central sensitization, fibromyalgia, small fiber pathology and other comorbidities in this group, as well as assessing potential screening tools for central sensitization.

METHODS

Design and setting

The SensOA is an observational, cross-sectional cohort study, consisting of 2 visits with a maximum of 4 weeks between them.

Patient population

Consecutive patients with symptomatic hand OA will be screened and recruited from the Rheumatology outpatient clinic at the LUMC by their rheumatologist or other health professional. Additional patients will be informed about the study at the Alrijne Zorggroep, and then referred to the study physician in the LUMC for further information and potential inclusion. Additionally, patients included in the Hand OSTeoarthritis in Secondary Care (HOSTAS) cohort, with known hand osteoarthritis, will be sent an invitation to receive further information.

The study population consists of adult men and women, aged 18-80, with hand osteoarthritis according to the American College of Rheumatology criteria for clinical hand OA, (26) pain during more than half of the days of the previous six weeks and a minimal pain score of 30 out of 100 on a Visual Analogue Scale. Exclusion criteria are applied sequentially: For the first visit of the SensOA study, they comprise an inability to understand the Dutch language, presence of psoriasis or a chronic inflammatory rheumatic disease, or presence of rheumatoid factor of anti-CCP.

For the second visit of the SensOA, exclusion criteria are presence of fibromyalgia (American College of Rheumatology (ACR) 2011 criteria, (27)), neurologic disorders, carpal tunnel syndrome, history of chemo- or radiotherapy, spinal surgery or trauma with lasting damage, cognitive impairment, psychiatric conditions, pregnancy, breastfeeding, eye surgery for glaucoma or keratoconus or other corneal surgery in the preceding three months and presence of an implantable cardioverter-defibrillator (ICD), neurostimulator or pacemaker. This staggered approach allows us to both investigate the prevalence of other conditions potentially causing neuropathic pain or changes in central pain

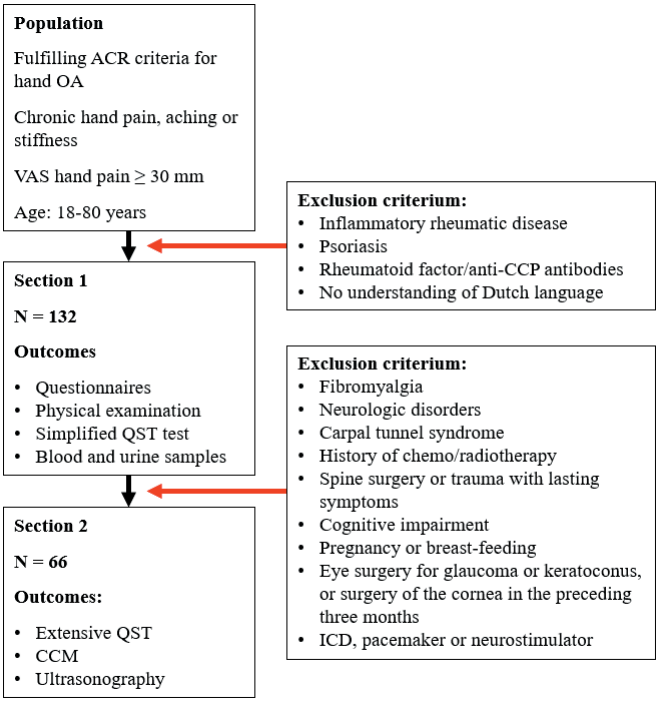

Figure 1. Flow scheme of patient selection. ACR = American College of Rheumatology. OA = Osteoarthritis. VAS = Visual Analog Scale. CCP = Cyclical Citrullinated Peptides. N = number of patients. QST = Quantitative Sensory Testing. CCM = Confocal Cornea Microscopy. ICD = implantable cardioverter defibrillator.

processing (first part), as well as the occurrence of these mechanisms due to hand OA alone (second part).

For an overview of the patient population, see figure 1.

Sample size

Sample size calculation is hampered by a lack of data for the prevalence of central sensitization and small fiber pathology in patients with hand OA. The performance of extensive QST and CCM in hand OA is completely new and exploratory. Based on previous studies using these methods in different diseases, we aim for 66 participants in section 2. (23, 28)

Based on data from Zhao et al on the prevalence of fibromyalgia in rheumatoid arthritis, and the observation by Haligoglu et al. and Slatkowsky-Christensen et al. that fibromyalgia was more common among patients with (hand) OA than among patients with rheumatoid arthritis, we expect that around 30 to 35% of the patients will suffer from fibromyalgia. (29-31) Finally, some additional patients will be excluded, due to the other described exclusion criteria, and we anticipate that some patients will refuse to participate in section 2. Therefore, in section 1 we will start with 132 patients.

Main study outcome

Determination of different pain phenotypes of patients with hand OA and associated factors

Secondary study outcomes

- Prevalence of fibromyalgia as measured by the ACR 2011 classification criteria (27)
- Determinants of fibromyalgia in patients with hand OA
- Prevalence of small fiber pathology as measured by QST and CCM
- Determinants of generalized small fiber pathology in patients with hand OA
- Prevalence of metabolic syndrome in hand OA as determined by a modified version of the International Diabetes Federation Metabolic Syndrome World-wide Definition (32)
- Association between severity of inflammation on ultrasonography of the hand joints and central sensitization and small fiber pathology
- Association between serum and urine biomarkers and central sensitization and small fiber pathology.
    - Validity of the simplified QST test set as a screening tool for neuropathic pain symptoms compared to the comprehensive QST

- Validity of the painDETECT questionnaire as a screening tool for neuropathic pain symptoms compared to the comprehensive QST

Physical examination

Participants will undergo physical examination by a study physician, consisting of examination of the hands (tender joint count, soft swollen joint count, bony enlarged joint count and deformity joint count), length, weight, blood pressure, middle circumference, and assessment of the elbows, shoulders, acromioclavicular joints, sternoclavicular joints, ankles, toes and vertebrae according to the Doyle index. (33, 34) Additionally, the knees and hips are examined to enable classification of OA following the ACR criteria.

Questionnaires

After the first visit of the SensOA study, patients receive an automated email with a link to the electronic case report form (eCRF). When they prefer, patients can opt to receive a paper version of the questionnaires. The content of questionnaires is summarized in table 1.

Radiographs

At the first visit, radiographs of the hands will be collected from patient care when available from the last 6 months, or new ones will be made. These radiographs will be scored for OA severity with the Kellgren-Lawrence system, and for erosive disease following the Verbruggen-Veys system. (35, 36)

Laboratory investigations

At the first visit, serum glucose, total cholesterol, HDL cholesterol, HDL-cholesterol ratio and triglycerides will be measured to enable the assessment of the metabolic syndrome. In case these data are available from the last 6 months these will be used. Additionally, at baseline blood and urine samples will be collected, to be investigated for the presence of biomarkers when the study is concluded.

Ultrasonography

At the second visit ultrasonography of the hands will be performed. Synovial thickening, Doppler signal, effusion and presence of osteophytes will be scored semi-quantitatively (0-3 per joint, for the scaphotrapeziotrapezoidal, first carpometacarpal, metacarpophalangeal, interphalangeal, proximal interphalangeal and distal interphalangeal joints for each feature). Additionally, collateral ligaments are assessed for structural damage (scored as 0, no abnormalities, 1, abnormalities, or 2, total destruction of the ligament, and presence or absence of Doppler signal). (37)

Table 1. Overview of questionnaires

Questionnaire	Content
Demographics	Marital status; Education level; Smoking and alcohol usage; Working status; Physical activity; Intensive hand usage
Disease characteristics	Symptom duration; Dominant hand; Most problematic hand; Chronicity of hand pain; Other hand symptoms; Morning stiffness hand; Previous injections in the hand joints; Previous physical therapy for hands; Use of assistive devices for hand OA symptoms; Previous operation on the hands; Previous fractures in the hands
Joint symptoms	0-10 NRS pain for past 48 hours; Patient reported painful and stiff joints; Other painful joints; Other stiff joints
Medication usage	Use of painkillers; Use of dietary supplements; Calcium intake; Vitamin D intake; Use of other medication
SCQ	Presence of, impairment due to and treatment for various comorbidities
Family history	Presence of signs of OA and other diseases in the first degree family members
AUSCAN	Pain, function and stiffness of the hands
MHOQ	Total function, general daily functioning, labor performance, pain, esthetics and general satisfaction about the hands
PainDETECT	Signs of neuropathic pain. Additionally, a PainDETECT adjusted to specifically report for the left and right hands separately is collected at baseline
SF-36	Mental and physical health-related quality of life, divided into domains physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.
IPQ	Illness perceptions, consisting of symptoms associated with disease, expectation regarding duration and constancy of disease, control over disease from personal and treatment influence, understanding of disease and emotions and consequences attributed to disease
HADS	Signs of anxiety and depression
CORS	Coping styles employed, divided into comforting cognitions, limiting activities, seeking distractions, optimism, adjusting activities, using creative solutions, accepting dependency and taking others into consideration
CSI	Signs of and diagnoses associated with central sensitization
PCS	Signs of pain catastrophizing

NRS= Numeric Rating Scale. SCQ = Self-administered comorbidity questionnaire. AUSCAN = Australian/Canadian Hand Osteoarthritis Index. MHOQ = Michigan Hand Outcome Questionnaire. SF-36 = Short Form-36. IPQ = Illness Perception Questionnaire. HADS = Hospital Anxiety and Depression Scale. CORS = Coping with Rheumatic Stressors. CSI = Central Sensitization Inventory. PCS = Pain Catastrophizing Scale.

Ultrasonography will be performed with a GE Logiq E9 (GE Healthcare, Chicago, Illinois, United States) with a 6-15 MHz linear array transducer (GE ML6-15) and a 5-15 MHz linear array transducer (GE L8-18i).

Quantitative Sensory Testing

QST tests are performed twice, once in a short set at the rheumatology outpatient clinic by a trained researcher at the first visit, and once following the extensive protocol of the second visit at the anesthesiology outpatient clinic by trained research nurses or researcher.

The short QST set performed at the rheumatology outpatient clinic consist of four elements:

1) Temporal summation, by application of a single pinprick with a 256 mN punctate probe, followed by 10 repetitive pinpricks at the same location. Intensity of the first and last pinprick will be asked of the patient, using a 11-point NRS. The process will be performed 5 times, after which the difference of NRS between mean initial stimulus and mean last stimulus will be calculated. An increase >2 is considered wind-up (an increase in pain intensity over time in response to repeated stimuli).
2) Numbness, tested by applying a pinprick with a 256 mN punctate probe on the patient's skin with patient's eyes closed. Patient will be asked to rate the pinprick as sharp or numb. Test will be performed on 5 areas of the hand. Any of the pinpricks rated as numb is considered abnormal.
3) Dynamic mechanical allodynia, tested by applying a stroke with a standardized brush of approximately 2 cm over the skin, with patient's eyes closed. This will be repeated five times with an approximately 10s inter-stimulus interval to account for potential wind-up. Patient will be asked to score a pain rating on a 0-10 NRS. Ratings above 0 are considered allodynia.
4) Pressure pain threshold, tested by a handheld Wagner algometer 100N. The algometer is used to apply pressure, perpendicular to the surface to be tested. Pressure through the probe will be increased until the participants indicate the test becomes painful, at which point the measurement is written down and stopped. The test is repeated three times per location, with 30 seconds between each measurement, and a slightly different location each time. The PPT is computed as the average of the three measurements. The locations are as follows:
   - The left distal radioulnar joint
   - The middle portion of trapezius muscle
   - The middle portion of tibialis anterior muscle

Another set of PPT measurements is made in 20 patients. A single PPT measurement will be made at the dorsal side of all interphalangeal and metacarpophalangeal joints, as well as the CMC-I joints, of both hands, with the hands of the patient resting on the table.

Reliability of short QST test set

At the time of writing, inclusion of participants has started and reliability of the short QSTS test set has been investigated. In 25 patients, the first three elements of this set were repeated twice with 60-75 minutes in between. Reliability was assessed separately for each test and for each hand. Percentage exact agreement (PEA) and Cohen's kappa were calculated to assess reliability. To assess the effect of the skewed prevalence of test

outcomes on the kappa values, the prevalence-adjusted bias-adjusted kappa (PABAK) was additionally determined. (38)

All tests showed a high degree of agreement between the measurements (80-100%). Temporal summation of the right hand and numbness testing of both hands showed moderate reliability based on both Cohen's kappa and the PABAK, all other tests showed almost perfect reliability on both indices. For details, see table 2.

Table 2. Measures of reliability of short QST test set for right and left hand

		Percentage agreement	Kappa	PABAK
Temporal summation	Left	0.92	0.83	0.94
	Right	0.80	0.60	0.60
Numbness	Left	0.80	0.48	0.60
	Right	0.80	0.53	0.60
Dynamic Mechanical allodynia	Left	1	1	1
	Right	1	1	1

PABAK = Prevalence-adjusted Bias-adjusted Kappa.

Extensive QST protocol

The extensive QST protocol consists of 13 tests, measured at the most painful hand and least painful foot. The following tests are applied:

Cold detection threshold

The temperature at which a cold sensation is experienced is determined. For this a 3 x 3 thermode is placed on the skin of the patient. Baseline temperature is set at 32°C and slowly (1°C/s) declines to 0°C. When a cold sensation is experienced, the patient presses a response button.

Warmth detection threshold

The temperature at which a warm sensation is experienced is determined. For this a 3 x 3 thermode is placed on the skin of the patient. Baseline temperature is set at 32°C and slowly (1°C/s) increases to 50°C. When a warm sensation is experienced, the patient presses a response button.

Cold pain threshold

The temperature at which cold pain is experienced is determined. For this a 3 x 3 thermode is placed on the skin of the patient. Baseline temperature is set at 32°C and slowly

(1°C/s) declines to 0°C. When the cold sensation transfers to a painful sensation the patient presses a response button.

Heat pain threshold

The temperature at which heat pain is experienced is determined. For this a 3 x 3 thermode is placed on the skin of the patient. Baseline temperature is set at 32°C and slowly (1°C/s) increases to 50°C. When the warm sensation transfers to a painful heat sensation the patient presses a response button.

Thermal sensory limen and paradoxal heat sensations

Warm and cold stimuli are alternated and the patient reports whether a cold or a warm sensation is felt. For this a 3 x 3 thermode is placed on the skin of the patient. The temperatures at which a sensation is experienced are recorded as well as the number of times the warm or cold sensations are felt correctly as warm or cold.

Mechanical detection and mechanical pain thresholds

The mechanical detection threshold is determined using von Frey filaments ranging from 0.25 to 512 mN. For the mechanical pain threshold, a set of seven weighted pinprick stimulators exerting a force of 8-512 mN are used. The patient reports the moment at which touch (for the detection threshold) or a prick (for the pain threshold) is experienced.

Mechanical pain sensitivity

The patient is touched with seven weighted pinprick stimulators ranging from 8-512 mN. Five stimulations with each pinprick stimulator are performed on the skin of the patients after which the patient scores the amount of pain felt on the tested area on a scale from 0 to 10, where 0 is no pain and 10 the most pain imaginable.

Dynamic mechanical allodynia

The skin of the patient is stimulated with a brush, a cotton wisp and a cotton wool tip on elastic strip. The patient scores the amount of pain felt on the tested area on a scale from 0 to 10, where 0 is no pain and 10 the most pain imaginable.

Wind-up ratio

In this test the perceived magnitude of a single pinprick stimulus is compared with that of a train of 10 pinprick stimuli of the same force repeated at a 1/s rate (256 mN). The patient is asked to rate the pain on a scale from 0 to 10 (where 0 is no pain and 10 the most pain imaginable) after the single stimulus and after the train of stimuli.

Vibration detection threshold

A Rydel–Seiffer tuning fork (64 Hz, 8/8 scale) is placed over a bony prominence near the test area. The time the patient feels the vibration is recorded.

Pressure pain threshold

The pressure pain threshold (PPT) is determined using the algometer pressure device of Medoc ltd. Pressure is applied on the test area with increasing pressure (50 kPa/s). The patient presses a response button when pain is felt.

Cornea confocal microscopy

Corneal confocal microscopy will be performed with the Rostock Corneal Module of the Heidelberg Retinal Tomograph III. The subject's eyes are anesthetized with a drop of 0.4% Benoxinate Hydrochloride, and Viscotears is used on the front of the eye for lubrication. The subject is seated comfortably, with the chin on the chin rest and asked to press their forehead firmly against the forehead bar. The patient is asked to open his/her eye as wide as possible and the laser-scanning camera is advanced slowly forward towards the patient until the TomoCap contacts the patient's cornea. A series of microphotographs corresponding to a variety of corneal depths is then automatically obtained. The entire procedure takes less than ten minutes. There is no disturbance of accommodation, so vision will be normal and the patient will be allowed to drive immediately following testing.

Timeline

Inclusion of participants was started in April 2022 and finished December 2024. Data analysis will be performed during the rest of 2024, after which results will be reported.

Handling of variables

The QST outcomes from the extensive QST test set will be expressed as z-scores for each of the 13 domains, with a z-score >2 indicating gain of function and a z-score <2 indicating loss of function. These scores will be used to make descriptive somatosensory phenotypes, including sensitization and neuropathic pain symptoms, for patients with hand OA, giving an overview of the pain phenotype of patients with hand OA compared to the general population. Z-scores will be based on the German general population. (19)

For the short QST test set, the PPT measurements will be analyzed as continuous variables. The other tests will be dichotomized as normal or abnormal, as outlined above.

Table 3. Overview of examinations during in-person visit

Investigations	Content
General physical examination	Height, weight, middle circumference, blood pressure
Doyle Index	Standardized examination of pain evoked through application of pressure (elbow, shoulder, acromioclavicular, sternoclavicular, MTP-I and MTP II-V joints) or movement (cervical spine, lumbar spine, ankle, talocalcaneal and midtarsal joints), scored 0-3.
Standardized examination of hands	Assessment of pain, bony enlargement, soft swelling and deformity of the CMC-I, IP, PIP, DIP, MCP joints and the wrist.
Grip strength	Assessment of grip strength, as the average of 3 measurements per hand, with VAS pain scores collected before and after the 6 measurements.
Knee examination	Standardized knee examination, consisting of palpation, investigation of range of motion for extension and flexion, crepitation, soft swelling, bony swelling, warmth, morning stiffness and knee pain.
Hip examination	Standardized hip examination, consisting of range of motion of flexion and endorotation, pain on movement and endorotation, crepitation, flexion contractures, morning stiffness and hip pain.
Short QST	Wind-up ratio, numbness and dynamic mechanical allodynia on the backs of both hands, including feasibility questions. Pressure pain threshold collect for left distal radio-ulnar joint, trapezius muscle, tibialis anterior muscle and CMC-I, IP, PIP, DIP and MCP joints.
Extensive QST	Standardized collection of the cold and warm detection thresholds, cold and heat pain thresholds, thermal sensory limen, paradoxical heat sensations, mechanical detection and pain thresholds, mechanical pain sensitivity, dynamic mechanical allodynia, wind-up ratio, vibration detection threshold and pressure pain threshold. Tested at the most painful hand and least painful foot.
Ultrasonography	Assessment of STT, CMC-I, IP, MCP, PIP and DIP joints for grey scale synovitis, osteophytes, effusion and doppler signal (all scored 0-3 according to the OARSI system). Additional assessment of collateral ligaments of IP, PIP and DIP joints for structural damage (scored as normal, damaged, or absent) and doppler signal (scored as absent or present).
WPI/SSS	Verbally collected questionnaire regarding areas with pain in the past week, as well as questions regarding fatigue, waking refreshed, cognitive symptoms and various somatic symptoms, used to establish the ACR criteria for fibromyalgia.
Signs of nociplastic pain	Questions regarding pain on movement, hypersensitivity to light, scents or sounds, and frequent waking during sleep.
CCM	Confocal Cornea Microscopy, collecting images of both eyes.
Laboratory investigations	Serum glucose, cholesterol, HDL-cholesterol, HDL-cholesterol ratio and triglycerides collected from patient care if available from the past six months, otherwise collected at baseline.
Biomarker material collection	Blood and urine samples collected and stored at -80C for determination of biomarkers at a later point in time.
X-ray of the hands	Collected from patient care or previous research if available from the past six months, otherwise collected at baseline.
VAS pain hands	Hand pain over the past 48 hours.

Table 3. Overview of examinations during in-person visit (continued)

Investigations	Content
Adverse event recording	Information on adverse events (any undesirable experience occurring to a subject during the study) and serious adverse events (untoward medical occurrence or effect that results in death, is life threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or any other important event that did not results in any of the previous but could have based on appropriate judgement by the investigator. Elective hospitalisation is not considered a serious adverse event.

MTP = Metatarsophalangeal. CMC-I = first carpometacarpal. IP = Interphalangeal. PIP = Proximal interphalangeal. DIP = Distal interphalangeal. MCP = Metacarpophalangeal. VAS = Visual analog scale. STT = Scaphotrapeziotrapezoidal. OARSI = Osteoarthritis Research Society International. ACR = American College of Rheumatology. HDL = High density lipoprotein.

Two computer programs will be used to calculate the thickness, length and number of nerve fibers from the CCM pictures: Heidelberg Eye Explorer Heyex 2 for the acquisition of data, and ACCmetrics, University of Manchester for analysis. These measures will then be used to describe the status of the small fibers. Abnormal cornea nerve fiber morphology will be classified as below the 5th percentile of the reference category. (39) Prevalence of small fiber pathology will be described based on these calculations.

Ultrasound scores will be summed over all joints, using the sum of all bilateral joints in analyses.

Metabolic syndrome will be determined based on a modified version of the International Diabetes Federation Metabolic Syndrome World-wide Definition, substituting raised plasma glucose for raised fasting plasma glucose.

Surgically modified joints at baseline will be considered missing for joint specific measures (joint tenderness, swelling, radiographic scores). For radiographic scores, the surgically modified joints will be given the highest score possible

Statistical analysis

Continuous outcomes will be summarized using mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate, based on whether data are distributed normally. Categorical outcomes will be summarized using frequency counts and percentages.

Main study outcome

Pain phenotypes will be derived based on the Z-scores of the QST tests. The phenotypes will be described, and used to divide the patient population into subgroups. These

subgroups will be characterized by logistic models (either binary or multinomial) to estimate associations with determinants. Determinants will consist of patient and disease characteristics, pain characteristics, and outcomes of the questionnaires described earlier. All analyses will be run crude and adjusted for age, sex and BMI, and adjusted further as needed. Similar analyses will be done to investigate the association of ultrasonography outcomes and biomarkers with pain phenotypes.

Secondary study outcomes

Prevalence of fibromyalgia and small fiber pathology (as measured by CCM) in the hand OA population will be described. Determinants of these conditions will be investigated with binary logistic regression models, first crude, then adjusted for age, sex and BMI, then adjusted further as needed.

The associations of central sensitization and small fiber pathology with inflammatory signs on ultrasound will be analyzed by two separate logistic regression models, with central sensitization and small fiber pathology as dependent variables. These models will be run first without adjustment, then adjusted for age sex and BMI, then adjusted further as needed.

The associations of serum and urine biomarkers will similarly be analyzed with two separate logistic regression models, with central sensitization and small fiber pathology as dependent variables. These models will first be run without adjustment, then adjusted for age sex and BMI, then adjusted further as needed.

The validity of the simplified QST and painDETECT questionnaire as screening tools for specific pain features aor phenotypes will be assessed by correlating the outcomes of these tools with the QST outcomes, using the extended QST as a "gold standard". Agreement between the short test set or painDETECT and the extensive QST will be assessed with Cohen's kappa. The feasibility of the short QST will be assessed through exploration of the questions regarding its duration and tolerability for patients.

Ethics and dissemination

The project received approval by the Leiden-Delft-Den Haag Medical Ethics Committee (registration number P21.094).

Patients are invited to participate by their rheumatologist at the outpatient clinic. When they are interested to participate, they receive the patient information folder. One week later the study-physician contacts them to discuss the folder and any potential questions, after which patients can decide to participate or not. It is made clear that study

participation is voluntary and refusal does not have negative impact on the patient. Patients sign informed consent forms prior to participation. All data is pseudonymized and stored safely at Leiden University Medical Center.

Study findings will be analyzed and submitted to peer-reviewed international journals and congresses. Data analysis will begin when all data have been collected and the database has been locked.

CONCLUSION

This protocol describes an observational study to gather information on the mechanistic types of pain involved in hand OA. It employs high quality techniques and measurements, including QST, physical examination and ultrasonography. This can be a first step for further research and the development of new treatment options for hand OA.

The data will also allow us to compare the extensive QST with the shortened QST set and various questionnaires on pain. In doing so we can investigate which are valid for clinical use, such as in investigating pain features and subtypes in patients in the clinic.

Finally, this study collects data on which conditions interfere with hand OA pain. This allows us to inform clinicians of specific comorbidities to watch out for in this patient population.

We hope that these data will further the hand OA research field and help us and others improve healthcare for patients with this condition.

REFERENCES

1. Marshall M, Watt FE, Vincent TL, Dziedzic K. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. Nature reviews Rheumatology. 2018;14(11):641-56.
2. Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. Pain. 2021.
3. IASP. Terminology 2011 [Available from: https://www.iasp-pain.org/resources/terminology/?ItemNumber=1698.
4. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157(7):1382-6.
5. Serge P, Anne-Priscille T. Pain in osteoarthritis from a symptom to a disease. Best Pract Res Clin Rheumatol. 2023:101825.
6. Trouvin A-P, Perrot S. Pain in osteoarthritis. Implications for optimal management. Joint bone spine. 2018;85(4):429-34.
7. Trouvin AP, Perrot S. New concepts of pain. Best Pract Res Clin Rheumatol. 2019;33(3):101415.
8. Gwilym SE, Keltner JR, Warnaby CE, Carr AJ, Chizh B, Chessell I, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum. 2009;61(9):1226-34.
9. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum. 2013;65(2):363-72.
10. van der Meulen C, van de Stadt LA, Kroon FPB, Kortekaas MC, Boonen A, Böhringer S, et al. Neuropathic-like pain symptoms in inflammatory hand osteoarthritis lower quality of life and may not decrease under prednisolone treatment. Eur J Pain. 2022;26(8):1691-701.
11. Kroon FPB, Kortekaas MC, Boonen A, Böhringer S, Reijnierse M, Rosendaal FR, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. The Lancet. 2019;394(10213):1993-2001.
12. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Current medical research and opinion. 2006;22(10):1911-20.
13. Pedersini P, Negrini S, Cantero-Tellez R, Bishop MD, Villafañe JH. Pressure algometry and palpation of the upper limb peripheral nervous system in subjects with hand osteoarthritis are repeatable and suggest central changes. J Hand Ther. 2020;33(1):103-11.
14. Steen Pettersen P, Neogi T, Magnusson K, Berner Hammer H, Uhlig T, Kvien TK, et al. Peripheral and Central Sensitization of Pain in Individuals With Hand Osteoarthritis and Associations With Self-Reported Pain Severity. Arthritis & rheumatology (Hoboken, NJ). 2019;71(7):1070-7.
15. Steen Pettersen P, Neogi T, Magnusson K, Hammer HB, Uhlig T, Kvien TK, et al. Associations Between Radiographic and Ultrasound-Detected Features in Hand Osteoarthritis and Local Pressure Pain Thresholds. Arthritis Rheumatol. 2020;72(6):966-71.
16. Wajed J, Ejindu V, Heron C, Hermansson M, Kiely P, Sofat N. Quantitative sensory testing in painful hand osteoarthritis demonstrates features of peripheral sensitisation. Int J Rheumatol. 2012;2012:703138.
17. Westermann A, Rönnau AK, Krumova E, Regeniter S, Schwenkreis P, Rolke R, et al. Pain-associated mild sensory deficits without hyperalgesia in chronic non-neuropathic pain. Clin J Pain. 2011;27(9):782-9.
18. Malcangio M. Role of the immune system in neuropathic pain. Scand J Pain. 2019;20(1):33-7.

19. Rolke R, Baron R, Maier C, Tölle TR, Treede DR, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006;123(3):231-43.
20. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(7):1043-56.
21. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2012;20(10):1075-85.
22. Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgraduate medicine. 2019;131(3):185-98.
23. Oudejans L, He X, Niesters M, Dahan A, Brines M, van Velzen M. Cornea nerve fiber quantification and construction of phenotypes in patients with fibromyalgia. Sci Rep. 2016;6:23573.
24. Binvignat M, Sellam J, Berenbaum F, Felson DT. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. Nat Rev Rheumatol. 2024;20(9):565-84.
25. Kortekaas MC, Kwok WY, Reijnierse M, Watt I, Huizinga TW, Kloppenburg M. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. Ann Rheum Dis. 2010;69(7):1367-9.
26. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990;33(11):1601-10.
27. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62(5):600-10.
28. Oudejans LC, Niesters M, Brines M, Dahan A, van Velzen M. Quantification of small fiber pathology in patients with sarcoidosis and chronic pain using cornea confocal microscopy and skin biopsies. J Pain Res. 2017;10:2057-65.
29. Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. Best Pract Res Clin Rheumatol. 2019;33(3):101423.
30. Haliloglu S, Carlioglu A, Akdeniz D, Karaaslan Y, Kosar A. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int. 2014;34(9):1275-80.
31. Slatkowsky-Christensen B, Haugen IK, Kvien TK. Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures. Ann Rheum Dis. 2010;69(1):198-201.
32. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366(9491):1059-62.
33. Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. Ann Rheum Dis. 1981;40(1):75-8.
34. Bijsterbosch J, Wassenaar MJ, le Cessie S, Slagboom PE, Rosendaal FR, Huizinga TW, et al. Doyle Index is a valuable additional pain measure in osteoarthritis. Osteoarthritis Cartilage. 2010;18(8):1046-50.
35. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494-502.
36. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum. 1996;39(2):308-20.

37. Keen HI, Lavie F, Wakefield RJ, D'Agostino MA, Hammer HB, Hensor E, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. Ann Rheum Dis. 2008;67(5):651-5.
38. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol. 1993;46(5):423-9.
39. Tavakoli M, Ferdousi M, Petropoulos IN, Morris J, Pritchard N, Zhivov A, et al. Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. Diabetes Care. 2015;38(5):838-43.