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

Meulen, C. van der

CHAPTER 5

NEUROPATHIC-LIKE PAIN SYMPTOMS IN INFLAMMATORY HAND OSTEOARTHRITIS LOWER QUALITY OF LIFE AND MAY NOT DECREASE UNDER PREDNISOLONE TREATMENT

Coen van der Meulen, Lotte A. van de Stadt, Féline P.B. Kroon, Marion C. Kortekaas, Annelies E.R.C.H. Boonen, Stefan Böhringer, Marieke Niesters, Monique Reijnierse, Frits R. Rosendaal, Nagmeh Riyazi, Mirian Starmans-Kool, Franktien Turkstra, Jendé van Zeben, Cornelia F. Allaart, Margreet Kloppenburg

European Journal of Pain. 2022 September; 26(8): 1691-1701.

doi: 10.1002/ejp.1991.

ABSTRACT

Background

Pain is a common symptom in hand osteoarthritis (OA) and multiple types of pain may occur. We investigated the prevalence, associated patient characteristics, influence on health-related quality of life (HR- QoL) and response to anti-inflammatory treatment of neuropathic-like pain in inflammatory hand OA.

Methods

Data were analysed from a 6-week, randomized, double-blind, placebo-controlled trial investigating prednisolone treatment in 92 patients with painful inflammatory hand osteoarthritis. Neuropathic-like pain symptoms were measured with the painDETECT questionnaire. Associations between characteristics at week 0 and neuropathic-like pain at week 0 were analysed with ordinal logistic regression, association of neuropathic-like pain at week 0 symptoms with HR-QoL at week 0 with linear regression, painDETECT change and visual analog scale (VAS) change from week 0 to week 6 and interaction of painDETECT with effect of prednisolone on VAS pain change from week 0 to week 6 with generalized estimating equations (GEE).

Results

Of 91 patients (79% female, mean age 64) with complete painDETECT data at baseline, 53% were unlikely to have neuropathic-like pain, 31% were indeterminate and 16% were likely to have neuropathic-like pain. Neuropathic-like pain was associated with female sex, less radiographic damage and more comorbidities. Patients with neuropathic-like pain had lower HR-QoL (PCS -6.5 (95%CI -10.4 to -2.6) than those without. Neuropathic-like pain symptoms remained under prednisolone treatment and no interaction was seen between painDETECT and efficacy of prednisolone on VAS pain.

Conclusion

In this study, 16% of patients with inflammatory hand osteoarthritis had neuropathic-like pain. These patients were more often female, had more comorbidities and a lower QoL than those without. Neuropathic-like pain symptoms remained despite prednisolone treatment and did not seem to affect the outcome of prednisolone treatment.

Significance

Pain is the dominant symptom in hand osteoarthritis, with an unclear aetiology. In this study we found that neuropathic-like pain may play a role in hand osteoarthritis, that it showed associations with female sex, younger age, and more comorbidities, and that it lowered health-related quality of life in hand osteoarthritis. Neuropathic-like pain in hand osteoarthritis seems resistant to prednisolone therapy, but did not seem to interfere with treatment of inflammatory pain with prednisolone.

INTRODUCTION

Hand osteoarthritis (OA) is a common disease accompanied by pain and disability, with prevalences ranging from 3% to 16% (1, 2). The aetiology of pain in hand OA has not been fully elucidated yet, hampering treatment.

Part of the pain in OA is thought to originate from the activation of nociceptors in the joint, either by inflammatory, mechanical or other stimuli, leading to nociceptive pain (1, 3). Targetting nociceptive pain through inflammation with anti-inflammatory medication can alleviate pain in selected OA patients, for example intra-articular corticosteroids in knee OA as recommended by the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) guidelines (4, 5). Oral corticosteroids have also shown beneficial effects on pain in inflammatory hand OA in the Hand Osteoarthritis Prednisolone Efficacy (HOPE) trial. However, not all patients responded to prednisolone treatment and some pain persisted (6).

This incomplete response might be explained by the presence of non-nociceptive pain. Possible types of pain involved are neuropathic and nociplastic pain. Neuropathic pain originates from lesions of the nervous system, whereas nociplastic pain reflects alterations of the nervous system without evident tissue damage. As no lesions in the nervous systems are expected in hand OA, nociplastic pain is more likely to be present. The term neuropathic-like pain is often used in the OA field to describe non-nociceptive pain. Studies in hip and knee OA described presence of neuropathic-like pain (7-9). However, studies describing neuropathic-like pain symptoms in hand OA are few. Given that hand OA symptoms are thought to arise from different mechanics than knee OA, for example the difference in mechanical load on the joint and the polyarticular nature of hand OA, neuropathic-like pain in hand OA requires separate analysis.

Various tools are available to assess symptoms of neuropathic-like pain, for example quantitative sensory testing (QST), which was used previously in hand OA, with studies showing conflicting results regarding the presence of these symptoms (10-14). Another tool is the painDETECT questionnaire, a standardized 9-item questionnaire developed for neuropathic pain in lower back pain and validated against diagnosis by expert pain physicians. The painDETECT measures various symptoms associated with neuropathic-like pain, such as burning, tingling and allodynia. The questionnaire showed good sensitivity (84%) and specificity (84%). In patients with hip and knee OA, the painDETECT was succesfully used to identify neuropathic-like pain (15, 16), and was shown to be valid for identifying central sensitization compared to the QST as the gold standard (17).

This study aimed to investigate the presence of neuropathic-like pain symptoms using the painDETECT questionnaire and associations of patient characteristics and physical health-related quality of life (HR-QoL) with these symptoms in patient with inflammatory hand OA. Furthermore, the effect of prednisolone on neuropathic-like pain symptoms was investigated.

PATIENTS AND METHODS

Study design

A post-hoc analysis was performed on data collected during the HOPE study (6), a double-blind, randomized, placebo-controlled trial. The full protocol was published previously (6). The study was approved by medical ethics committees at the Leiden University Medical Center (LUMC) and Zuyderland medical center and was in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the revised Helsinki Declaration. All patients provided written informed consent.

Patient and public involvement

Patient partners were involved in development and execution of the study and written information towards patients.

Study population

The study population consisted of adults with symptomatic hand OA according to the ACR criteria, showing signs of inflammation (≥1 distal interphalangeal joint (DIP)/proximal interphalangeal joint (PIP) with soft swelling or erythema, ≥1 PIP/DIP with a positive power Doppler signal or ≥1 PIP/DIP with synovial thickening of grade ≥2 on ultrasound investigation of digits 2-5) and finger pain of ≥30mm on a 100mm visual analog scale (VAS) with a flare-up after washout of non-steroidal anti-inflammatory drugs (NSAIDs) (18). Patients were excluded if their pain was located predominantly in the thumb base instead of the fingers, they were pregnant or breast-feeding during the trial, they had liver enzyme levels ≥2 times above normal, they had an eGFR <60; they were seropositive for rheumatoid factor or anti-cyclic citrullinated protein antibodies or if they suffered from one of the following comorbidities: fibromyalgia, chronic inflammatory rheumatic disease, psoriasis, blood dyscrasias, coagulation disorders, malignancies (except successfully treated squamous or basal cell skin carcinoma), uncontrolled diabetes mellitus, uncontrolled hypertension, unstable ischemic heart disease, heart failure, severe pulmonary disease, severe and/or opportunistic infections, chronic infections, recent stroke or bone marrow hypoplasia. Finally, patients were also excluded if they

used systemic or local immunomodulating drugs including corticosteroid injections or received hyaluronic acid injections in the thumb base up to 90 days before start of the trial.

Randomization, blinding and intervention

Patients were randomly assigned to receive either placebo or prednisolone. Patients and assessors of treatment outcome were blinded for treatment allocation.

Patients took 10 mg placebo or prednisolone daily for six weeks, after which medication was tapered to cessation in two weeks. Paracetamol as rescue medication and a stable dosage of chondroitin sulphate/glucosamine/bisphosphonate/tetracycline/estrogens were allowed. NSAIDs and intramuscular or intra-articular injections of glucocorticoids or hyaluronic acid at any location were not. Patients were advised against starting non-pharmacological interventions during the trial.

Clinical outcomes

The primary outcome of the current analysis, the presence of neuropathic-like pain symptoms, was measured at weeks 0 and 6 with the painDETECT, a standardized 9-item questionnaire consisting of seven questions on the quality of pain, scored 0-5, a descriptive question on the pattern of pain over time, scored -1/0/1, and a question assessing radiating pain, scored 0/2. Total scores are calculated by summing the individual questions, with the final score ranging from -1 to 38. Total scores <13 indicate unlikely presence of neuropathic pain, scores ranging from 13-18 indicate indeterminate presence of neuropathic pain, and scores >18 indicate likely presence of neuropathic pain (7).

Questionnaires collected during the RCT further included: VAS fingers and thumb pain (0-100), the Australian-Canadian Hand Osteoarthritis Index (AUSCAN), patient global assessment on VAS (0-100) and the SF-36 at weeks 0, 2, 4, 6, 8 and 14. The short form (SF-) 36 questionnaire consists of 36 questions divided over 8 domains. The questions were summed per domain, transformed to a 0-100 range and afterwards standardized to age- and sex-specific Dutch-population based norms. Finally, physical and mental component scales were calculated by calculating a weighted sum score of the standardized eight domains, with higher scores indicating better outcomes (19). At weeks 0 and 6, a 0-100 VAS for overall fatigue was collected. The self-administered comorbidity questionnaire (SCQ) and the Hospital Anxiety and Depression scale (HADS) were collected at week 0 (20, 21). For an overview of the collected variables and the time of collection, see figure 1.

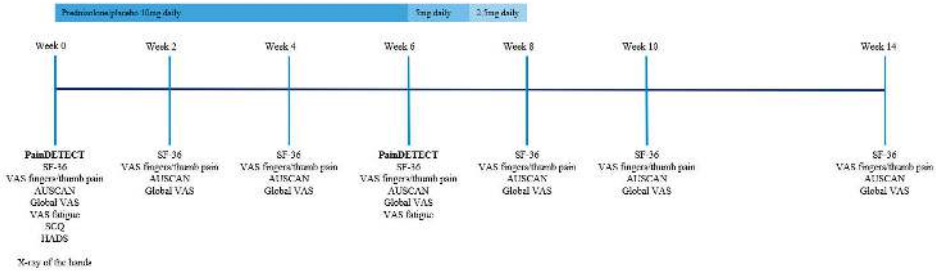

Figure 1
Timeline of data collection.

Radiography

Anterior-posterior hand radiographs were obtained at baseline or within 6 months before start of the study. Radiographic damage was scored using the Kellgren-Lawrence (KL) system (0-4 score per joint, for a total score of 0-120). Erosive OA was defined as having ≥1 PIP/DIP joint of digits 2-5 in the Verbruggen-Veys erosive or remodeling phase. Reliability of scoring was excellent (6).

Statistical analysis

Variables previously shown to be associated with neuropathic-like pain symptoms were selected for analysis based on literature research to explore whether these same associations were found in hand OA patients. Percentage of missing data was <5%. Variables were described using descriptive statistics. Possible statistical differences between painDETECT category groups were investigated using oneway ANOVA for normally distributed continuous variables, Kruskal-Wallis tests for not normally distributed continuous variables and chi^2 tests for categorical variables.

For the cross-sectional analysis of associations with neuropathic-like pain symptoms, baseline variables of interest were investigated using univariate ordinal logistic regression analysis with painDETECT score as dependent variables and the painDETECT <13 (unlikely neuropathic-like pain) group as the index group, compared to the indeterminate and likely neuropathic-like pain groups. Following that, a multivariate ordinal logistic regression model with painDETECT categories as the dependent variable was used to further assess the relations between painDETECT categories and variables of interest. Variables were selected based on description of associations with neuropathic-like pain in literature. The variables included in the final model were age, sex, BMI, comorbidity score, HADS depression score, KL sum score and baseline VAS pain of the fingers.

A series of multivariate linear regression models was used to further analyse the association between painDETECT score at baseline (independent) and HR-QoL at baseline (dependent). First, the unadjusted effect was investigated. Then the model was adjusted for age, BMI and sex, after which other potential confounders selected based on previous studies of neuropathic-like pain, being comorbidities and VAS pain, were included in the final model as covariates.

To assess whether the presence of neuropathic-like pain at baseline influenced changes in VAS score after 6 weeks of prednisolone treatment, separate linear generalized estimated equations (GEE) were used with robust standard errors and the correlation structure specified as exchangeable. First, a model was run with VAS pain as the outcome, dependent on treatment and time in weeks. This model was repeated after addition of an interaction term for painDETECT score categories and treatment. Afterwards, the basic model without the interaction term was repeated, stratified on painDETECT categories as a sensitivity analysis.

Changes in painDETECT were first described categorically, divided into unchanged, increased and decreased. To assess changes in continuous painDETECT scores as a measure of the number of symptoms indicative of neuropathic-like pain, linear generalized estimated equations (GEE) were used with robust standard errors and the correlation structure specified as exchangeable, with painDETECT dependent on time and treatment group.

Sensitivity analyses were performed for using only the patients that had indicated the hand as the most painful area, and had subsequently filled in the painDETECT for the hands.

Given the amount of analyses performed, the Bonferroni correction was applied. A P-value of 0.05 was regarded as statistically signficant prior to the correction. After the correction, this was adjusted to 0.001, allowing for up to 50 tests.

All statistical analyses were performed using STATA version 16.

RESULTS

Patient characteristics and distribution of painDETECT categories

Patient characteristics are summarized in table 1. Of 92 patients included in the HOPE trial, 91 completed the painDETECT at baseline; 45 used placeboes and 46 used prednisolone. PainDETECT scores >18 (likely neuropathic pain) were seen in a considerable

Table 1: Patient characteristics

	All (n=91)	PainDETECT < 13 (N=48)	PainDETECT 13-18 (N=28)	PainDETECT > 18 (N=15)	P-value
Treatment arm; no.(%)					
Placebo	45 (49)	26 (54)	13 (46)	6 (40)	0.587
Prednisolone	46 (51)	22 (46)	15 (54)	9 (60)	0.587
PainDETECT score; median (IQR)	12 (8-17)	8 (6.5-10)	15 (14.5-17)	23 (20-25)	0.000
Female; no.(%)	72 (79)	35 (73)	23 (82)	14 (93)	0.211
Age; years	64 (9)	66 (9)	60 (8)	63 (8)	0.012
BMI, kg/m^2; median (IQR)	27 (24-29)	27 (23-29)	27 (24-32)	27 (24-28)	0.592
SCQ score 0 – 45; median (IQR)	2 (1-5)	2 (0-5)	3 (0-6)	5 (3-7)	0.047
VAS pain score, 0-100					
Fingers	54 (20)	50 (22)	56 (19)	61 (15)	0.204
Thumb base; median (IQR)	30 (9-52)	30 (0-51)	27 (10-51)	45 (20-75)	0.168
VAS fatigue score, 0-100; median (IQR)	39 (11-60)	35 (15-60)	47 (2-68)	50 (20-85)	0.268
VAS global score					
Patient assessment	56 (22)	52 (25)	56 (19)	64 (15)	0.071
AUSCAN					
Pain score, 0-20	10 (3)	10 (4)	11 (3)	12 (3)	0.204
Function score, 0-36	19 (7)	18 (8)	20 (7)	21 (6)	0.323
Erosive OA*; no. (%)	66 (73)	36 (75)	19 (68)	11 (73)	0.795
KL sumscore, 0-120	37 (16)	42 (16)	34 (14)	29 (15)	0.666
SF36†					
PCS;	45 (7)	48 (6)	44 (7)	39 (7)	0.527
MCS; median (IQR)	55 (50-59)	56 (52-59)	54 (46-59)	54 (45-59)	0.529

Data are mean (SD), unless otherwise stated. For VAS thumb base and fatigue, N=90. PainDETECT < 13 indicates unlikely presence of neuropathic pain, painDETECT 13-18 indicates presence of neuropathic pain is undetermined, painDETECT > 18 indicates likely presence of neuropathic pain. P-values for comparisons between painDETECT groups. No. = Number. BMI = Body mass index. IQR = Interquartile range. SCQ = Self-administered comorbidities questionnaire. VAS = Visual analog scale. AUSCAN = Australian-Canadian Hand Osteoarthritis Index. OA = Osteoarthritis. *Defined as a joint in Verbruggen-Veys erosive or remodeling phase. KL = Kellgren-Lawrence SF36 = Short form 36. †Norm-based scores of Short Form-36 with a standardized mean of 50 and SD of 10 using age-specific and sex-specific Dutch population-based norms. PCS = Physical component scale. MCS = Mental component scale.

number of patients (N=15, 16%). Scores < 13 (unlikely) and 13-18 (undetermined) were seen in 48 (53%) and 28 (31%) patients, respectively. Mean VAS finger pain was 54 (standard deviation (SD) 20). VAS finger pain at baseline was somewhat higher in the painDETECT 13-18 group compared to <13, and even higher in the >18 group. The mean SF-36 PCS score was 45 (SD 7), and was lower in the groups with higher painDETECT categories (table 1). All neuropathic-like pain symptoms were frequently present in the study population (table 2). Presence of symptoms, defined as moderately or higher, ranged from 25% (numbness) to 63% (pain on slight pressure). Sudden pain attacks (51%) and pain on cold or heat (40%) were also reported frequently. Radiating pain was reported by 22 (24%) of participants. The median SCQ score was 2, with back pain as the most prevalent comorbidity. The presence of comorbidities is summerized in supplementary table S1.

Table 2: Distribution of scores on individual painDETECT items

Pain sensation	Never	Barely	Slightly	Moderately	Strongly	Very strongly
Burning	38 (42)	15 (16)	8 (9)	21 (23)	8 (9)	1 (1)
Tingling	38 (42)	22 (24)	6 (7)	22 (24)	3 (3)	0 (0)
Pain on light touch	22 (24)	27 (30)	16 (18)	22 (24)	4 (4)	0 (0)
Sudden pain attacks	17 (19)	12 (13)	15 (16)	34 (37)	12 (13)	1 (1)
Cold/heat painful	26 (29)	16 (18)	12 (13)	23 (25)	12 (13)	2 (2)
Numbness	36 (40)	22 (24)	10 (11)	15 (16)	7 (8)	1 (1)
Pain on slight pressure	4 (4)	16 (18)	13 (14)	33 (36)	23 (25)	2 (2)

Data presented as N (%). N=91 patients.

Patient characteristics associated with neuropathic-like pain symptoms

In univariate analysis, age and KL sumscore were negatively associated with higher painDETECT categories. Younger patients had more neuropathic-like pain. Less radiographic damage was associated with higher odds of higher painDETECT categories. VAS finger pain, female sex and SCQ score were positively associated with higher painDETECT categories in univariate analysis. In multivariate ordinal logistic regression KL sumscore remained negatively associated with higher painDETECT categories. SCQ score, VAS pain and female sex were positively associated with higher painDETECT categories in multivariate analysis (table 3).

Table 3: Univariate and multivariate associations between painDETECT categories and variables of interest

Independent variable	OR (95% CI)			
	Univariate analysis	P-value	Multivariate analysis	P-value
Age	0.95 (0.90 to 0.99)	0.018	0.96 (0.90 to 1.02)	0.202
Female sex	2.46 (0.86 to 7.00)	0.092	3.80 (1.18 to 12.23)	0.025
BMI	1.02 (0.94 to 1.11)	0.626	0.97 (0.89 to 1.07)	0.583
SCQ score	1.14 (1.02 to 1.28)	0.026	1.18 (1.02 to 1.35)	0.021
VAS pain score				
Fingers	1.02 (1.00 to 1.04)	0.079	1.02 (1.00 to 1.05)	0.052
Thumb base	1.01 (1.00 to 1.02)	0.189	-	
VAS fatigue score	1.01 (1.00 to 1.02)	0.119	-	
VAS patient global assessment	1.02 (1.00 to 1.04)	0.093	-	
HADS depression score	1.10 (0.95 to 1.28)	0.211	1.03 (0.86 to 1.23)	0.750
AUSCAN				
Pain score	1.15 (1.01 to 1.32)	0.031	-	
Function score	1.05 (0.99 to 1.11)	0.112	-	
KL sum score	0.96 (0.93 to 0.99)	0.003	0.96 (0.93 to 1.00)	0.043
Previous hand surgery	0.91 (0.32 to 2.63)	0.866	-	
Erosive OA	0.83 (0.35 to 1.98)	0.677	-	

Ordinal logistic regression with painDETECT categories as dependent, with painDETECT <13 as the index group. Outcomes given as the OR for being in a higher painDETECT category compared to a lower category, per point increase in the investigated variable. N=91. PainDETECT < 13 indicates unlikely presence of neuropathic pain, painDETECT 13-18 indicates presence of neuropathic pain is undetermined, painDETECT > 18 indicates likely presence of neuropathic pain. OR = Odds ratio. CI = Confidence interval. BMI = Body mass index. SCQ = Self-administered comorbidities questionnaire. VAS = Visual analog scale. HADS = Hospital Anxiety and Depression scale. AUSCAN = Australian-Canadian Hand Osteoarthritis Index. KL = Kellgren-Lawrence. OA = osteoarthritis.

Association of painDETECT categories with health-related quality of life

A painDETECT score >18 was associated with a lower SF-36 PCS at baseline. This association remained after adjusting for age, sex, BMI, VAS finger pain and SCQ score (table 4).

Effect of prednisolone on neuropathic-like pain symptoms

During follow-up, 6 patients withdrew from the trial and 3 did not complete the painDETECT at week 6. Thus, 82 patients were included in analyses at week 6 (painDETECT < 13 n=45 [55%], 13-18 n=22 [27%], >18 n=15 [18%]. Placebo n=39, prednisolone n=43). The distribution of the three painDETECT categories was comparable between the treatment groups at baseline and at week 6 (supplementary tables S2 and S3). There was no between-group difference in continuous painDETECT score change between treatment groups (mean between-group difference -1.8 [95%CI -4.0 to 0.4])(figure 1, table

Table 4: Multivariate Association between painDETECT categories and health-related quality of life

Independent	Mean Δ (95% CI) in SF-36 PCS					
	Crude	P-value	Model 1	P-value	Model 2	P-value
PainDETECT						
<13	1		1		1	
13-18	-3.9 (-7.0 to -0.7)	0.016	-3.6 (-7.0 to -0.3)	0.032	-2.2 (-5.2 to 0.8)	0.140
>18	-9.6 (-14 to -5.7)	0.000	-10 (-14 to -6.2)	0.000	-6.9 (-11 to -3.1)	0.000
Age			-0.0 (-0.2 to 0.1)	0.711	0.0 (-0.1 to 0.2)	0.573
Female sex			1.3 (-2.2 to 4.7)	0.469	0.5 (-2.6 to 3.6)	0.753
BMI			-0.3 (-0.6 to -0.0)	0.044	-0.2 (-0.5 to 0.0)	0.106
VAS finger pain					-0.1 (-0.2 to -0.0)	0.001
SCQ score					-0.7 (-1.1 to -0.3)	0.001

Multivariate linear regression with SF-36 PCS as the dependent variable. N=91. PainDETECT score <13 group as index for painDETECT categories. PainDETECT < 13 indicates unlikely presence of neuropathic pain, painDETECT 13-18 indicates presence of neuropathic pain is undetermined, painDETECT > 18 indicates likely presence of neuropathic pain. CI= Confidence interval. PCS = Physical component scale. BMI = Body mass index. VAS = Visual analog scale. SCQ = Self-administered comorbidity questionnaire.

5). In contrast, a substantial difference for VAS finger pain was seen between treatment groups when analysing the subset of patients with complete painDETECT outcomes, comparable to the original analysis (mean between-group difference -17.4 [(-26.9 to -7.9]) (figure 1, table 5) (6).

Table 5: Mean between-group difference in changes in painDETECT score and VAS pain over 6 weeks of treatment with prednisolone vs placebo

	Mean between group difference (95% CI)	P-value
PainDETECT score	-1.7 (-3.9 to 0.4)	0.114
VAS finger pain		
Crude	-17.4 (-26.9 to -7.9)	0.000
Adjusted model[a]	-17.3 (-26.8 to -7.8)	0.000

Mean between group difference of change in painDETECT score and VAS pain for prednisolone vs placebo, with negative scores indicating more effect in the prednisolone group. [a]Adjusted for painDETECT score and interaction between painDETECT score and treatment

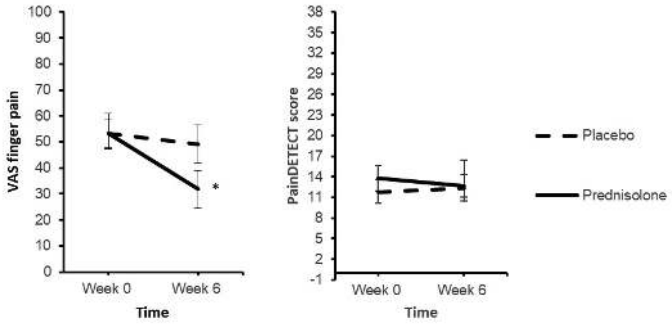

Figure 2: Change of VAS and painDETECT during treatment with prednisolone vs placebo
Mean score at week 0 and week 6, per treatment arm, for VAS finger pain and PainDETECT scores. Placebo shown in dashed line, prednisolone 10 mg daily in solid line. * Indicates a significant change over time. Whiskers indicate 95% CI. N=82. The VAS pain score shows a decrease to the prednisolone treatment over the course of six weeks, which is not mirrored by the painDETECT score over six weeks.

Effect of neuropathic-like pain symptoms at baseline on prednisolone treatment effect

The GEE for VAS finger pain for the whole cohort was adjusted for the interaction of painDETECT categories with treatment group. No difference in effect size of prednisolone treatment effect was seen compared to the model without the interaction term (table 5). GEE models were run for the effect of treatment on VAS finger pain, stratified by painDETECT category as a sensitivity analysis. The mean (95% CI) between group differences between prednisolone and placebo groups were -11.3 (-24.2 to 1.5), -23.9

(-40.3 to -7.4) and -21.9 (-47.0 to 3.3) for the painDETECT <13, 13-18 and >18 groups, respectively (supplementary table S4).

Sensitivity analyses

Sensitivity analyses using only patients that had indicated the hand as the most painful area, and thus the area described with the painDETECT questionnaire, showed similar results to the main analyses (data not shown).

DISCUSSION

In this study, neuropathic-like pain symptoms measured by painDETECT were present in patients with inflammatory hand OA. Neuropathic-like pain symptoms were associated with female sex, more VAS pain, less radiographic damage, more comorbidities and lower HR-QoL in this study. We showed in our study for the first time, that neuropathic-like pain symptoms may not decrease under prednisolone treatment in patients with inflammatory hand OA.

Neuropathic-like pain symptoms have previously been described in various inflammatory diseases, including rheumatoid arthritis (22), with a prevalence of up to 20% in outpatient clinics (23). This study contributes new evidence that neuropathic-like pain symptoms (such as radiating pain, tingling, burning or electric shock-like sensations combined with sensory abnormalities such as hyper- or hyposensitivity) also occur in hand OA. These symptoms are not usually expected in patients with joint pain, and could indicate that other pain mechanisms than only the hand OA itself play a role, for example through sensitization.

In this study, 16% of patients had neuropathic-like pain sypmtoms as determined by the painDETECT questionnaire, which was used for the first time in hand OA. Other studies reported the presence of neuropathic-like pain symptoms as well, although no prevalences were given. Two studies reported lowered pressure-pain thresholds in patients with hand OA compared to healthy controls, whereas another reported no significant differences between hand OA and healthy controls in neuropathic-like pain (12-14). One study reported a prevalence of 42% for central sensitization in participants, examined with temporal summation tests (10). This discrepancy in prevalences with our study might be due to different measuring methods, since the painDETECT is thought to assess the probability of the presence of neuropathic pain, whereas temporal summation is thought to indicate central sensitization. The two need not necessarily coincide, although similar symptoms may occur, and the painDETECT outcomes have

previously been shown to correlate with the presence of central sensitization (17). The lower frequency might also be due to the indeterminate group from the painDETECT, which likely contains patients with and without neuropathic-like pain. Some patients with neuropathic-like pain may thus have gone undetected. The lower prevalence may also be due to the exclusion of fibromyalgia patients in our study. Finally, the accuracy of the painDETECT questionnaire for diagnosing neuropathic pain has been disputed. (24) However, given the correlation previously found between painDETECT outcomes and sensitization in knee OA, we believe it to be a useful tool for hand OA patients as well. All in all, the prevalence of neuropathic-like pain symptoms in hand OA requires further validation in larger studies. This may be aided by a validation of the painDETECT in hand OA.

Female patients with more pain, more comorbidities and less radiographic damage were more likely to have neuropathic-like pain symptoms in this study. These associations were statistically significant prior to, but not after adjustment for multiplicity. Some of these effect sizes were quite small, in part due to the range of the outcome measures. For example, the VAS pain was collected as a 0-100 scale and analysed as such. Transforming it into a scale with a smaller step size, such as 0-10, would yield larger effects (1.19 instead of 1.02 in this case). Therefore, such effects were still regarded as relevant. The association with female sex has previously been described in literature (25). Associations between pain and neuropathic-like pain symptoms have also been described previously (10). Regarding the association between comorbidities and neuropathic-like pain symptoms in hand OA patients found in this study, no previous studies were found that investigated this. However, neuropathic-like pain symptoms occur in various other chronic pain syndromes such as chronic lower back pain and fibromyalgia. An association between the number of comorbidities and neuropathic-like pain symptoms is thus not unexpected (25). The association found here may be an underrepresentation, given the stringent exclusion criteria regarding comorbidities (6). Also, due to low numbers of patients per comorbidity no associations with specific comorbidities could be investigated, only associations with the total number of comorbidities, which included comorbidities not associated with neuropathic-like pain. This is an avenue for future research. The association between neuropathic-like pain symptoms and less radiographic damage found in this study is in accordance with the weak correlation between structural damage and pain described previously (2). Our finding contrasts with a recent study showing a positive association between sensitization and KL score, presence of erosions and inflammatory signs on ultrasound (11). This may be in part due to patient selection (general hand OA versus hand OA with signs of inflammation), but also due to different methods used to assess presence of neuropathic-like pain symptoms (pres-

sure pain thresholds versus painDETECT). The association of radiographic damage with neuropathic-like pain symptoms in hand OA warrants further investigation.

As hypothesized, neuropathic-like pain symptoms were negatively associated with HR-QoL measured by the SF-36 PCS in this study, which remained after adjusting for age, sex, BMI, comorbidities and overall pain. This result is supported by literature describing a similar negative association of neuropathic-like pain symptoms with HR-QoL (25). The clinically important effect on HR-QoL (a change of ½ SD [5 in this study] as described by Norman et al (26)) stresses the importance of targetting neuropathic-like pain symptoms.

Our study concurs with previous studies which suggest that anti-inflammatory therapy such as prednisolone is not a fitting treatment for neuropathic-like pain symptoms, shown by the lack of decrease in painDETECT scores (27). It contributes evidence that prednisolone treatment achieves its effect through influencing inflammation rather than central mechanisms. On the other hand, other types of pain medication, such as anti-epileptics, targetting other mechanisms, might be effective in some patient groups. This hypothesis is supported by a recent RCT which showed a reduction in pain in hand OA patients treated with pregabaline (28).

In our study, overall pain scores were ameliorated by prednisolone therapy. No interaction was seen with the presence of neuropathic-like pain at baseline. Although the study was not powered for this post-hoc analysis, this finding suggests that the presence of neuropathic-like pain symptoms may not influence the effect of prednisolone on nociceptive pain as measured with VAS pain. This contradicts our hypothesis that the presence of neuropathic-like pain symptoms decreases the efficacy of prednisolone treatment in inflammatory hand OA. The clinical implication of this finding is that the presence of neuropathic-like pain might not necessarily be a contra-indication in treating nociceptive pain with prednisolone in properly selected patients with inflammatory hand OA. Future research should focus on exploring different patient phenotypes within the patient population reporting neuropathic-like pain symptoms. This is important as different pain phenotypes are likely related to different pain-generating pathophysiological mechanisms and may need a different treatment approach.

Limitations of this study are the previously mentioned comorbidity selection criteria, the overall strict patient selection for inclusion and the small sample size. This last limitation precludes drawing definitive conclusions from these findings, although these data are indicative of the importance and challenges of neuropathic-like pain symptoms in hand OA. Thus, larger replication studies are required before definite conclusions on

the associations with neuropathic-like pain and its response to prednisolone can be drawn. Additionally, the painDETECT has not been validated for hand OA specifically, although validation studies in knee OA indicate its value to assess neuropathic-like pain. An additional limitation of this study is that the Pain Catastrophizing Scale (PCS), a self-administered questionnaire regarding the tendency to catastrophize the pain experience, was not collected. Pain catastrophizing is associated with both worse pain outcomes and neuropathic(-like) pain in OA, ((29, 30)) and would thus be a valuable measure for future studies.

In conclusion, in this study neuropathic-like pain symptoms measured with the painDETECT were present in hand OA and associated with female sex, less radiographic damage, more comorbidities and lower HR-QoL. Neuropathic-like pain symptoms did not decrease under treatment with prednisolone, a strong anti-inflammatory drug, in this study. They also did not seem to modulate the effect of anti-inflammatory treatment in hand OA, which might indicate that neuropathic-like pain symptoms are not necessarily a contra-indication to such treatment. Its presence has important implications for the development of adequate individualized pain therapy, which may require combining nociceptive and neuropathic pain treatment. This study indicates that neuropathic-like pain symptoms are prevalent and have a strong impact, stressing the need for new treatment options and setting a challenge for future research.

Author contributions

FPBK, MCK, CFA, and MK designed the trial. FPBK, MCK, NR, MS, FT, JvZ, CFA, and MK collected the data. CM, LAS, and MK analysed the data. CM, LAS, FPBK, MCK, AB, SB, MN, MR, FRR, NR, MS, FT, JvZ, CFA, and MK interpreted the data, discussed the results and wrote the report. MK was the principal investigator. All authors approved the final version of the manuscript.

Role of the funding source

The funder of the study (ReumaNederland) had no role in study design, data collection, data analysis, data interpretation or writing and deciding to submit the manuscript.

Competing interest statement

Prof. Dr. Boonen received research grants from Celgene and Abbvie en honoraria for lectures or advisory board meetings from Eli Lilly, UCB, Abbvie and Galapagos: all paid to her department. Prof. Dr. Kloppenburg reports grants from Dutch Arthritis Association, during the conduct of the study. Outside the submitted work, fees for consultancy (Abbvie, Pfizer, Levicept, GlaxoSmithKline, Merck-Serono, Kiniksa, Flexion, Galapagos, Jansen, CHDR, Novartis, UCB, all paid to her institution); Fee for local investigator of

industry-driven trial (Abbvie, paid to her institution); Royalties or licences from Wolters Kluwer (UptoDate, paid to her institution), Springer Verlag (Reumatologie en klinische immunologie, paid to her institution); grants from IMI-APPROACH, paid to her institution; Board membership OARSI, unpaid; Presidency of the Dutch Society of Rheumatology, paid to her institution; Membership of EULAR Council, unpaid. All other authors report no competing interests.

REFERENCES

1. Kloppenburg M, Kwok W-Y. Hand osteoarthritis--a heterogeneous disorder. Nature reviews Rheumatology. 2011;8(1):22-31.
2. 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.
3. O'Neill TW, Felson DT. Mechanisms of Osteoarthritis (OA) Pain. Current osteoporosis reports. 2018;16(5):611-6.
4. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-89.
5. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020;72(2):149-62.
6. 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.
7. 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.
8. Freynhagen R, Tölle TR, Gockel U, Baron R. The painDETECT project - far more than a screening tool on neuropathic pain. Current medical research and opinion. 2016;32(6):1033-57.
9. 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.
10. 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 Rheumatol. 2019;71(7):1070-7.
11. 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.
12. 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.
13. 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.
14. 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.
15. Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage. 2011;19(6):647-54.
16. Rienstra W, Blikman T, Mensink FB, van Raay JJ, Dijkstra B, Bulstra SK, et al. The Modified painDETECT Questionnaire for Patients with Hip or Knee Osteoarthritis: Translation into Dutch, Cross-Cultural Adaptation and Reliability Assessment. PLoS One. 2015;10(12):e0146117.

17. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1236-42.
18. 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.
19. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055-68.
20. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis and rheumatism. 2003;49(2):156-63.
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
22. Koop SM, ten Klooster PM, Vonkeman HE, Steunebrink LM, van de Laar MA. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. Arthritis Res Ther. 2015;17(1):237.
23. Rifbjerg-Madsen S, Christensen AW, Christensen R, Hetland ML, Bliddal H, Kristensen LE, et al. Pain and pain mechanisms in patients with inflammatory arthritis: A Danish nationwide cross-sectional DANBIO registry survey. PLoS One. 2017;12(7):e0180014.
24. Gudala K, Ghai B, Bansal D. Usefulness of four commonly used neuropathic pain screening questionnaires in patients with chronic low back pain: a cross-sectional study. Korean J Pain. 2017;30(1):51-8.
25. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017;3:17002.
26. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.
27. Gierthmühlen J, Baron R. Neuropathic Pain. Semin Neurol. 2016;36(5):462-8.
28. Sofat N, Harrison A, Russell MD, Ayis S, Kiely PD, Baker EH, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. J Pain Res. 2017;10:2437-49.
29. Rayahin JE, Chmiel Js Fau - Hayes KW, Hayes Kw Fau - Almagor O, Almagor O Fau - Belisle L, Belisle L Fau - Chang AH, Chang Ah Fau - Moisio K, et al. Factors associated with pain experience outcome in knee osteoarthritis. Arthritis care and research : the official journal of the Arthritis Health Professions Association. 2014(2151-4658 (Electronic)):1828-35.
30. Tanaka R, Hirohama K. Association of Pain Quality with Pain Catastrophizing and Self-efficacy in People with Knee Osteoarthritis. Progress in Rehabilitation Medicine. 2018(2432-1354 (Electronic)).

SUPPLEMENTARY FILES

Table S1: Incidences of comorbidities per painDETECT category

	PainDETECT score		
	<13	**13-18**	**>18**
No. of patients	48	28	15
SCQ score 0 – 45; median (IQR)	2 (0-5)	2.5 (0-5.5)	5 (3-7)
Back pain; no. (%)	14 (29)	10 (36)	7 (47)
Depression; no. (%)	1 (2)	2 (7)	2 (13)
Diabetes; no. (%)	4 (8)	4 (14)	3 (20)
Malignancy; no. (%)	1 (2)	0 (0)	1 (7)
Coronary disease; no. (%)	2 (4)	0 (0)	1 (7)
Hypertension; no. (%)	16 (33)	8 (29)	6 (40)
Pulmonary disease; no. (%)	3 (6)	2 (7)	5 (33)
Stomach condition; no. (%)	3 (6)	2 (7)	3 (20)
Renal disease	1 (2)	2 (7)	1 (7)
Liver disease	0 (0)	1 (4)	0 (0)
Anemia; no. (%)	0 (0)	1 (4)	1 (7)

N=91. PainDETECT < 13 indicates presence of neuropathic pain is unlikely, painDETECT 13-18 indicates presence of neuropathic pain is indeterminate, painDETECT > 18 indicates presence of neuropathic pain is likely. Outcomes are given in N (%). No. = number. SCQ = Self-administered comorbidities questionnaire.

Table S2: Neuropathic-like pain symptoms presence at baseline per treatment arm

	PainDETECT score			
	<13	**13-18**	**>18**	**Total**
Placebo	26 (57.8)	13 (28.9)	6 (13.3)	45 (100)
Prednisolone	22 (47.8)	15 (32.6)	9 (19.6)	46 (100)
Total	48 (52.7)	28 (30.8)	15 (16.5)	91 (100)

Values are given as no. (%). PainDETECT < 13 indicates presence of neuropathic pain is unlikely, painDETECT 13-18 indicates presence of neuropathic pain is indeterminate, painDETECT > 18 indicates presence of neuropathic pain is likely. Percentages are based on row totals, reflecting percentages per treatment arm.

Table S3: Neuropathic-like pain symptoms presence at week 6 per treatment arm

	PainDETECT score			
	<13	**13-18**	**>18**	**Total**
Placebo	20 (51.3)	12 (30.8)	7 (18.0)	39 (100)
Prednisolone	25 (58.1)	10 (23.3)	8 (18.6)	43 (100)
Total	45 (54.9)	22 (26.8)	15 (18.3)	82 (100)

Values are given as no.(%). PainDETECT < 13 indicates presence of neuropathic pain is unlikely, painDETECT 13-18 indicates presence of neuropathic pain is indeterminate, painDETECT > 18 indicates presence of neuropathic pain is likely. Percentages are based on row totals, reflecting percentages per treatment arm.

Table S4: Mean between-group difference in changes in VAS pain over 6 weeks per painDETECT stratum

	Mean between group difference (95% CI) in VAS finger pain
PainDETECT category	
<13	-11.3 (-24.2 to 1.5)
13-18	-23.9 (-40.3 to -7.4)
>18	-21.9 (-47.0 to 3.3)

Mean between group difference of change in VAS pain for prednisolone vs placebo, per painDETECT stratum, with negative scores indicating more effect in the prednisolone group.