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## ORIGINAL ARTICLE

# Neuropathic-like pain symptoms in inflammatory hand osteoarthritis lower quality of life and may not decrease under prednisolone treatment

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## Abstract

**Background:** Pain is common in hand osteoarthritis (OA) and multiple types 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 OA. Neuropathic-like pain was measured with the painDETECT questionnaire. Associations between baseline characteristics and baseline neuropathic-like pain were analysed with ordinal logistic regression, association of baseline neuropathic-like pain symptoms with baseline HR-QoL with linear regression, painDETECT and visual analogue scale (VAS) change from baseline to week 6 and interaction of painDETECT with prednisolone efficacy on VAS pain change from baseline 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 prednisolone efficacy on VAS pain.

**Conclusions:** In this study, 16% of inflammatory hand OA patients had neuropathic-like pain. They were more often female, had more comorbidities and had lower QoL.

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

## 1 | INTRODUCTION

Hand osteoarthritis (OA) is a common disease accompanied by pain and disability, with prevalences of between 3% and 16% (Kloppenburg & Kwok, 2011; Marshall et al., 2018). 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, by inflammatory, mechanical or other stimuli, causing nociceptive pain (Kloppenburg & Kwok, 2011; O'Neill & Felson, 2018). 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 (Bannuru et al., 2019; Kolasinski et al., 2020). Oral corticosteroids have shown beneficial effects on pain in inflammatory hand OA in the Hand Osteoarthritis Prednisolone Efficacy (HOPE) trial. However, not all patients responded and some pain persisted (Kroon et al., 2019).

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. The term neuropathic-like pain is often used in the OA field to describe non-nociceptive pain. Studies in hip and knee OA described the presence of neuropathic-like pain (Freynhagen et al., 2006, 2016; Gwilym et al., 2009). 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 (Pedersini et al., 2020; Steen Pettersen et al., 2019, 2020; Wajed et al., 2012; Westermann et al., 2011). Another tool is the painDETECT questionnaire, a standardized 9-item questionnaire developed for neuropathic pain in the lower back pain and validated against diagnosis by expert pain physicians. It measures various symptoms associated with neuropathic-like pain, such as burning, tingling and allodynia and showed good sensitivity (84%) and specificity (84%). In patients with hip and knee OA, the painDETECT was successfully used to identify neuropathic-like pain (Hochman et al., 2011; Rienstra et al., 2015) and was shown to be valid for identifying central sensitization compared to the QST as a gold standard (Hochman et al., 2013).

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 patients with inflammatory hand OA. Furthermore, the effect of prednisolone on neuropathic-like pain symptoms was investigated.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design

A post hoc analysis was performed on data collected during the HOPE study (Kroon et al., 2019), a double-blind, randomized, placebo-controlled trial. The full protocol was published previously (Kroon et al., 2019). The study was approved by medical ethics committees at the Leiden University Medical Center (LUMC) and Zuyderland medical centre 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.

## 2.2 | Patient and public involvement

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

## 2.3 | Study population

The study population consisted of adults with symptomatic hand OA according to the ACR criteria, showing signs of inflammation ( $\geq 1$  distal interphalangeal joint (DIP)/proximal interphalangeal joint (PIP) with soft swelling or erythema,  $\geq 1$  PIP/DIP with a positive power Doppler signal or  $\geq 1$  PIP/DIP with synovial thickening of grade  $\geq 2$  on ultrasound investigation of digits 2–5) and finger pain of  $\geq 30$  mm on a 100 mm visual analogue scale (VAS) with a flare-up after washout of non-steroidal anti-inflammatory drugs (NSAIDs) (Altman et al., 1990). 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  $\geq 2$  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 ischaemic 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 the start of the trial.

## 2.4 | Randomization, blinding and intervention

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

Patients took 10 mg placebo or prednisolone daily for 6 weeks, after which medication was tapered to cessation in 2 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.

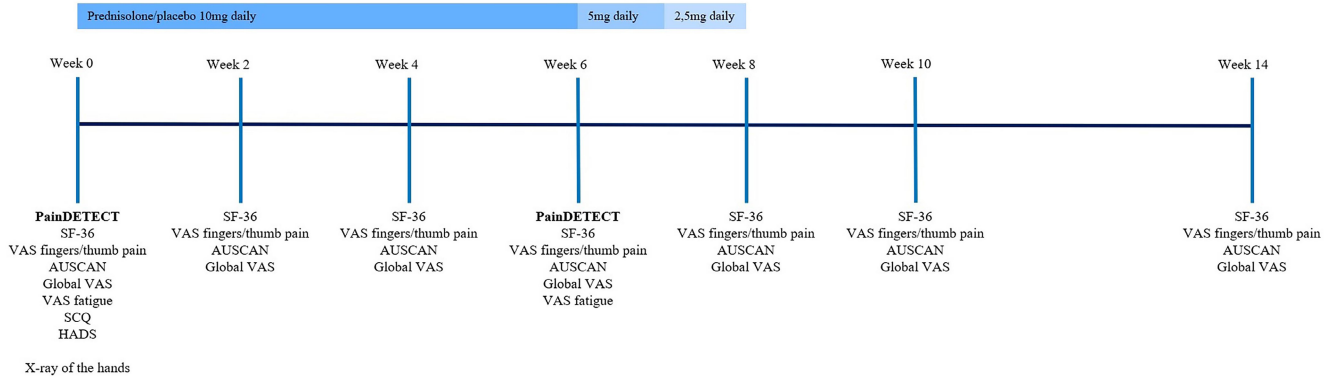
## 2.5 | Clinical outcomes

The primary outcome of the current analysis, the presence of neuropathic-like pain symptoms, was measured at weeks 0 (baseline) 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 to 18 indicate indeterminate presence of neuropathic pain and scores  $> 18$  indicate likely presence of neuropathic pain (Freynhagen et al., 2006).

Questionnaires collected during the RCT further included: VAS fingers and thumb pain (0–100), the Australian-Canadian Hand Osteoarthritis Index (AUSCAN), the 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 (Aaronson et al., 1998). 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 (Sangha et al., 2003; Zigmond & Snaith, 1983). For an overview of the collected variables and the time of collection, see Figure 1.

## 2.6 | Radiography

Anterior–posterior hand radiographs were obtained at baseline or within 6 months before the 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  $\geq 1$  PIP/DIP joint of digits 2–5 in the Verbruggen–Veys erosive or remodelling phase. The reliability of the scoring was excellent (Kroon et al., 2019).



**FIGURE 1** Timeline of data collection.

## 2.7 | 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. The percentage of missing data was <5%. Variables were described using descriptive statistics. Possible statistical differences between painDETECT category groups were explored using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis tests for not normally distributed continuous variables and chi-squared 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 variable and the painDETECT <13 (unlikely neuropathic-like pain) group as the index group, compared to the indeterminate (13–18) and likely (>18) 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 relationship between painDETECT categories and variables of interest. Variables were selected based on the 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 (GEEs) were used with robust standard errors and the correlation structure was 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 the 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 (GEEs) 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 using only the patients that indicated the hand as the most painful area and subsequently filled in the painDETECT for the hands.

Given the number of analyses performed, the Bonferroni correction was applied. A P value of 0.05 was regarded as statistically significant 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.

## 3 | RESULTS

### 3.1 | 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 placebos and 46 used prednisolone. PainDETECT scores >18 (likely neuropathic pain) were seen in a considerable number of patients ( $N = 15$ , 16%). Scores <13 (unlikely) and 13–18



**TABLE 1** Patient characteristics

	All (n = 91)	PainDETECT <13 (N = 48)	PainDETECT 13-18 (N = 28)	PainDETECT > 18 (N = 15)	p-value
Treatment arm, n (%)					
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, n (%)	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 <sup>2</sup> ); 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; n (%) <sup>a</sup>	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 <sup>b</sup>					
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.

Abbreviations: AUSCAN, Australian-Canadian Hand Osteoarthritis Index; BMI, body mass index; IQR, interquartile range; KL, Kellgren–Lawrence SF36, Short form 36; MCS, mental component scale; No., number; OA, osteoarthritis; PCS, physical component scale; SCQ, self-administered comorbidities questionnaire; VAS, visual analog scale.

<sup>a</sup>Defined as a joint in Verbruggen-Veys erosive or remodeling phase.

<sup>b</sup>Norm based scores of Short Form-36 scale with a standardized mean of 50 and SD of 10 using age-specific and sex-specific Dutch population-based norms.

(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 groups. 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). The presence of symptoms, defined as moderate or higher, ranged from 25% (numbness) to 63% (pain under slight pressure). Sudden pain attacks (51%) and pain in 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 summarized in Table S1.

### 3.2 | 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 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)

Note: Data presented as *n* (%). *N* = 91 patients.

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

Note: 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.

Abbreviations: AUSCAN, Australian-Canadian Hand Osteoarthritis Index; BMI, Body mass index; CI, Confidence interval; HADS, Hospital Anxiety and Depression scale; KL, Kellgren–Lawrence; OA, osteoarthritis.; OR, Odds ratio; SCQ, Self-administered comorbidities questionnaire; VAS, Visual analogue scale.

### 3.3 | Association of painDETECT categories with health-related quality of life

A painDETECT score of >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).

**TABLE 3** Univariate and multivariate associations between painDETECT categories and variables of interest

### 3.4 | Effect of prednisolone on neuropathic-like pain symptoms

During the follow-up, six patients withdrew from the trial and 3 did not complete the painDETECT at week 6. Thus, 82 patients were included in the 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 (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 2, Table 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  $-17.4$  [( $-16.9$  to  $-7.9$ )] (Figure 2, Table 5) (Kroon et al., 2019).

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

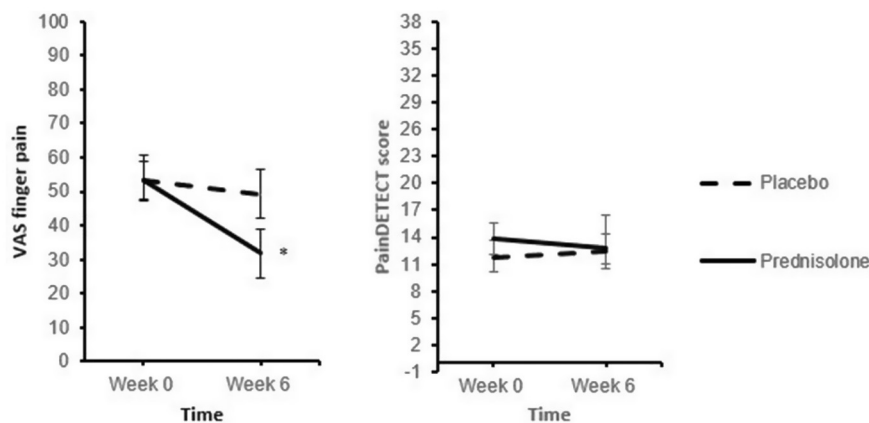
The GEE for VAS finger pain for the whole cohort was adjusted for the interaction of painDETECT categories with the treatment group. No difference in effect size of prednisolone treatment effect was seen compared to the model without the interaction term (Table 5). GEE models were run for the effect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

**TABLE 4** Multivariate Association between painDETECT categories and health-related quality of life

Independent	Mean $\Delta$ (95% CI) in SF-36 PCS					
	Crude	<i>p</i> -value	Model 1	<i>p</i> -value	Model 2	<i>p</i> -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

Note: 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.

Abbreviations: BMI, Body mass index; CI, Confidence interval; PCS, Physical component scale; SCQ, Self-administered comorbidity questionnaire; VAS, Visual analog scale.



**FIGURE 2** 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 under the prednisolone treatment over the course of 6 weeks, which is not mirrored by the painDETECT score over 6 weeks.



**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 <sup>a</sup>	-17.3 (-26.8 to -7.8)	0.000

Note: Mean between-group difference of change in painDETECT score and VAS pain for prednisolone versus placebo, with negative scores indicating more effect in the prednisolone group.

<sup>a</sup>Adjusted for painDETECT score and interaction between painDETECT score and treatment.

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 (Table S4).

### 3.6 | Sensitivity analyses

Sensitivity analyses using only patients that 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).

## 4 | 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 (Koop et al., 2015), with a prevalence of up to 20% in outpatient clinics (Rifbjerg-Madsen et al., 2017). 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 hand OA itself play a role, for example through sensitization.

In this study, 16% of patients had neuropathic-like pain symptoms 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 (Pedersini et al., 2020; Wajed et al., 2012; Westermann et al., 2011). One study reported a prevalence of 42% for central sensitization in participants, examined with temporal summation tests (Steen Pettersen et al., 2019). 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 (Hochman et al., 2013). 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 (Gudala et al., 2017). 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 on 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 the female sex has previously been described in the literature (Colloca et al., 2017). Associations between pain and neuropathic-like pain symptoms have also been described previously (Steen Pettersen et al., 2019). 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 (Colloca et al., 2017). The association found here may be an underrepresentation, given the stringent exclusion criteria regarding comorbidities (Kroon et al., 2019). 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 (Marshall et al., 2018). Our finding contrasts with a recent study showing a positive association between sensitization and KL score, the presence of erosions and inflammatory signs on ultrasound (Steen Pettersen et al., 2020). This may be in part not only due to patient selection (general hand OA versus hand OA with signs of inflammation) but also due to different methods used to assess the presence of neuropathic-like pain symptoms (pressure 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 the literature describing a similar negative association of neuropathic-like pain symptoms with HR-QoL (Colloca et al., 2017). The clinically important effect on HR-QoL (a change of  $\frac{1}{2}$  SD [5 in this study]) as described by Norman et al. Norman et al., 2003) stresses the importance of targeting 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, as shown by the lack of decrease in painDETECT scores (Gierthmühlen & Baron, 2016). It contributes to 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, targeting 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 pregabalin (Sofat et al., 2017).

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 by 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 (Rayahin et al., 2014; Tanaka & Hirohama, 2018) 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.

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## CONFLICT OF INTEREST

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