**BRIEF REPORT**

**Associations Between Radiographic and Ultrasound-Detected Features in Hand Osteoarthritis and Local Pressure Pain Thresholds**

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**Objective.** Pain sensitization contributes to the complex osteoarthritis (OA) pain experience. The relationship between imaging features of hand OA and clinically assessed pain sensitization is largely unexplored. This study was undertaken to examine the association of structural and inflammatory features of hand OA with local pressure pain thresholds (PPTs) in the Nor-Hand study.

**Methods.** The cross-sectional relationship of severity of structural radiographic features of hand OA (measured according to the Kellgren/Lawrence scale [grade 0–4] and the absence or presence of erosive joint disease) as well as ultrasound-detected hand joint inflammation (assessed by gray-scale synovitis [grade 0–3] and the absence or presence of power Doppler activity) to the PPTs of 2 finger joints was examined by multilevel regression analyses adjusted for age, sex, and body mass index, using beta values with 95% confidence intervals (95% CIs).

**Results.** A total of 570 joints in 285 participants included in the Nor-Hand study were assessed. Greater structural and inflammatory severity was associated with lower PPTs, with adjusted beta values of −0.5 (95% CI −0.6, −0.4) per Kellgren/Lawrence grade increase, −1.4 (95% CI −1.8, −0.9) for erosive versus non-erosive joints, −0.7 (95% CI −0.9, −0.6) per gray-scale synovitis grade increase, and −1.5 (95% CI −1.8, −1.1) for joints with power Doppler activity on ultrasound versus those without.

**Conclusion.** Greater severity of structural pathologic features and hand joint inflammation was associated with lower PPTs in the finger joints of patients with hand OA, indicating pain sensitization. Our results indicate that pain sensitization might be driven by structural and inflammatory pathology in hand OA.

**INTRODUCTION**

Pain is the main symptom experienced by patients with hand osteoarthritis (OA) and represents a major health care challenge (1). About 14% of women and 7% of men between the ages of 40 and 84 years are estimated to have symptomatic hand OA (2). Although OA is one of the most prevalent chronic pain conditions worldwide, treatment options remain focused on symptom relief, and both traditional analgesics and nonpharmacologic strategies have limited effect on pain or problematic side effects. The lack of effective analgesics may be due to our poor understanding of the determinants of OA-related pain. Increased knowledge of the mechanisms causing OA pain is therefore needed to develop new and better strategies for pain management and prevention.

A peripheral nociceptive input is traditionally believed to cause OA pain, and both structural and inflammatory changes in finger
joints are associated with pain (3–5). However, by which mechanisms joint pathologies mediate pain is unclear. Alterations in the peripheral and central sensory nervous systems, called peripheral and central sensitization, allow pain signaling to be facilitated and cause an increased pain experience. These mechanisms may be induced by injury from, for example, mechanical pressure or inflammatory cytokines, and have been proposed as an explanation as to why OA pain becomes chronic and persistent for a subgroup of patients. Clinically assessed signs of pain sensitization, using quantitative sensory testing methods, have been found to be related to the presence and severity of pain in knee and hand OA (6,7). Pain sensitization is acknowledged as a clinically important treatment target. Yet, whether there are certain pathologic features that cause sensitization, and whether these are potential targets for the prevention or treatment of OA pain, is largely unknown.

OA-related tissue damage and inflammation has been associated with peripheral sensitization to mechanical stimuli in animal studies (8). The excitation threshold for local nociceptors and the transmission of pain signals is lowered and causes increased sensitivity to painful stimuli (hyperlgesia) and painful sensation from normally nonpainful stimuli (allodynia), consequently aggravating OA pain. Pain sensitization is difficult to investigate in humans because of the complexity of the many factors that influence pain perception. Sensory testing of the mechanical pressure pain threshold (PPT) on skin in close proximity to an affected joint is considered to reflect mechanisms of peripheral and/or central sensitization (9). Magnetic resonance imaging (MRI)–detected inflammation in knee OA, but not severity of radiographic features, is associated with the development and worsening of local pressure pain sensitivity in the knee (10). In contrast, a study on hand OA found that greater structural damage was associated with greater local sensitivity to mechanical pressure pain stimuli (11). However, the study sample was small (n = 13), and no data on inflammation were reported. Inflammation in hand OA is an important symptom and might precede damage of cartilage and bone as an inducer of sensitization.

More knowledge about the mechanisms by which pain sensitization occurs in OA is needed, especially for hand OA wherein the role of inflammation in the pathogenesis of pain sensitization is unknown. Hence, this study was undertaken to explore the cross-sectional association of structural radiographic features and ultrasound-detected inflammatory features with local PPTs in the finger joints of patients with hand OA in a large study from Norway and, additionally, to examine whether the observed associations were different between joints with pain and those without.

PATIENTS AND METHODS

Study design and population. We used baseline data from the Nor-Hand study, which included 300 individuals with hand OA. Detailed inclusion and exclusion criteria have been previously published (12). Participants received oral and written information and provided their written informed consent to participate. The Norwegian Regional Committee for Medical and Health Research Ethics approved the study (reference no. 2014/2057).

Pressure pain threshold of painful and nonpainful finger joints. We tested PPTs in each participant at the following sites in the hand: 2 joints among the distal interphalangeal (DIP) joints 2–5 and proximal interphalangeal (PIP) joints 1–5, the joint a patient reported to be “the most painful in daily life,” and a nonpainful joint. If none of the joints were reported to be painful, the joint with the most severe clinical OA (swelling and/or bony enlargements) was chosen for assessment. If none of the joints were pain free, the joint with the least pain and either no OA or the least clinically severe OA was chosen. A handheld algometer (FPX 25; 1 cm² flat rubber probe) was applied in a perpendicular direction on the dorsal aspect of the joint with increasing pressure (0.5 kg/second). The participants were instructed to say “stop” when the pressure first changed to slight pain. The average value (kg/cm²) from 3 tests on each joint was recorded.

Table 1. Demographic and clinical characteristics of the 285 study participants at the person level and joint level*

| Demographic variables | Age, median (IQR) years | 61 (57–66) |
|-----------------------|-------------------------|------------|
| Female sex            | 251 (88)                |            |
| Fulfillment of ACR hand OA criteria | 263 (94) | |
| Body mass index, mean ± SD kg/m² | 26 ± 5 | |
| Symptom duration, median (IQR) years | 6 (3–13) |
| Numeric rating scale of hand pain in the last 24 hours, mean ± SD (0–10) | 3.8 ± 2.3 |
| Regular use of analgesics | Acetaminophen | 11 (4) |
| Oral or topical nonsteroidal antiinflammatory drugs | 35 (12) |
| Opioids or opioid-like drugs | 5 (2) |
| Antiepileptics, TCAs, and/or SNRIs | 15 (5) |
| Kellgren/Lawrence sum score, median (IQR) (0–128)† | 28 (16–43) |
| Erosive OA‡ | 101 (35) |
| Ultrasound gray-scale synovitis sum score, median (IQR) (0–90)† | 3 (1–7) |
| Number of joints with power Doppler activity grades 1–3 on ultrasound, median (IQR) (0–30)† | 1 (0–3) |
| Finger joints assessed (n = 570)§ | 290 (51) |
| Joints with Kellgren/Lawrence grade ≥2 | 63 (11) |
| Joints with erosive joint disease | 147 (26) |
| Joints with gray-scale synovitis grades 1–3 on ultrasound | 98 (17) |

* Except where indicated otherwise, values are the number (%). IQR = interquartile range; ACR = American College of Rheumatology; OA = osteoarthritis; TCAs = tricyclic antidepressants; SNRIs = serotonin and norepinephrine reuptake inhibitors.
† Includes the bilateral distal and proximal interphalangeal, metacarpophalangeal, first carpometacarpal, and scaphotrapeziotrapezoidal joints.
‡ Defined as a participant having disease activity in the Vleburggen/Veys erosive or remodeling phases present in at least 1 interphalangeal joint.
§ Two joints (the joint reported to be most painful by a participant as well as a nonpainful joint among distal interphalangeal joints 2–5 and proximal interphalangeal joints 1–5) were assessed in each participant.
In a subset of 9 participants, test–retest reliability of PPT was found to be moderate to good (intraclass correlation coefficient 0.52–0.61).

**Hand radiographs.** Radiographs of the bilateral posteranterior hand joints were obtained for all participants. One experienced reader (IKH) scored all hand joints for OA severity on a 0–4 scale using a modified Kellgren/Lawrence (K/L) scale (2) and scored the DIP/PIP joints using the Verbruggen/Veys (V/V) anatomical phase scoring system (13). Joints in the erosive or remodeling phases were defined as erosive (14). DIP/PIP joints on 20 radiographs were reassessed for intrareader reliability, which was excellent ($\kappa$ with linear weighting = 0.92 for K/L grades 0–4; $\kappa$ = 0.98 for the absence/presence of erosions in a yes/no format).

**Ultrasound.** On the same day as PPT testing, a trained medical student (Nicolai Ravn Aarskog, Diakonhjemmet Hospital, Oslo, Norway) performed the ultrasound examinations using a Logic S8 ultrasound machine with a linear 6–15 MHz probe and a preset for optimal imaging of gray-scale synovitis and power Doppler (PD) activity (pulse repetition frequency 0.6 kHz, frequency 7.7 MHz) (General Electric). Initial scorings were done in consensus with an experienced ultrasonographer (Alexander Mathiessen, MD, PhD, Diakonhjemmet Hospital, Oslo, Norway).

The hand examination was performed with the participant’s hands resting in a flat position. All hand joints were scanned dorsally with longitudinal projection from the radial to the ulnar side of each joint. An additional transverse scan was performed when the presence of pathologic features of OA was uncertain. Gray-scale synovitis and PD activity were scored on 0–3 scales (15). Due to the low frequency of grade 2–3 PD activity, we dichotomized this variable (grade 0 versus grades 1–3). Interreader reliability of the assessments of the DIP/PIP joints in 10 participants between the medical student (Nicolai Ravn Aarskog) and the ultrasonographer (Alexander Mathiessen) was good, determined by prevalence and bias–adjusted kappa values for categorical variables with linear weighting ($\kappa = 0.80$ for gray-scale synovitis grades 0–3 and $\kappa = 0.79$ for the absence/presence of PD activity).

### Statistical analysis

Our study sample includes the assessment of 2 joints per participant. The PPTs of 2 joints in 1 person are likely to correlate. To account for this within-person effect, mixed model regression analyses were performed. The association between each structural and inflammatory imaging feature (independent variables) and PPT (dependent variable) was examined with adjustment for age, sex, and body mass index, using beta values with 95% confidence intervals (95% CIs). To explore whether inflammation is a confounder in the associations between radiographic OA and PPTs and whether radiographic severity is a confounder in the associations between inflammatory features and PPTs, we repeated the analyses, with adjustment for gray-scale synovitis and K/L grade, respectively. We also explored whether additional adjustment for nonsteroidal antiinflammatory drugs (NSAIDs) altered the associations between inflammation and PPT. Finally, to explore how pain influences these associations, we performed separate analyses for the painful joints and painful joints.

### Table 2

|                      | No. (% ) | PPT, mean ± SD kg/cm² | Adjusted β (95% CI) | Adjust for Kellgren/Lawrence OA grade or synovitis grade, β (95% CI)† |
|----------------------|----------|------------------------|----------------------|---------------------------------------------------------------------|
| **Kellgren/Lawrence** |          |                        |                      |                                                                     |
| Grade 0              | 187 (33 )| 4.9 ± 2.1              | Referent             | Referent                                                            |
| Grade 1              | 93 (16)  | 4.7 ± 2.0              | −0.3 (−0.6, 0.1)     | −0.1 (−0.5, 0.2)                                                   |
| Grade 2              | 137 (24)| 4.7 ± 2.1              | −0.5 (−0.9, −0.2)    | −0.4 (−0.7, 0.0)                                                   |
| Grade 3              | 79 (14)  | 3.5 ± 1.6              | −1.6 (−2.0, −1.1)    | −1.2 (−1.7, −0.7)                                                  |
| Grade 4              | 74 (13)  | 2.9 ± 1.3              | −2.0 (−2.4, −1.6)    | −1.4 (−1.9, −0.9)                                                  |
| **Erosive OA disease** |         |                        |                      |                                                                     |
| No                   | 507 (89 )| 4.6 ± 2.1              | Referent             | Referent                                                            |
| Yes                  | 63 (11)  | 2.9 ± 1.2              | −1.4 (−1.8, −0.9)    | −0.7 (−1.1, −0.2)                                                  |
| **Gray-scale synovitis on ultrasound** | |                       |                      |                                                                     |
| Grade 0              | 423 (74 )| 4.7 ± 2.1              | Referent             | Referent                                                            |
| Grade 1              | 72 (13)  | 3.9 ± 1.9              | −0.9 (−1.3, −0.5)    | −0.3 (−0.7, 0.1)                                                   |
| Grade 2              | 48 (8)   | 3.3 ± 1.2              | −1.4 (−1.9, −1.0)    | −0.9 (−1.4, −0.4)                                                  |
| Grade 3              | 27 (5)   | 2.5 ± 1.5              | −2.0 (−2.6, −1.4)    | −1.2 (−1.8, −0.6)                                                  |
| **Power Doppler activity grades 1–3 on ultrasound** | |                       |                      |                                                                     |
| No                   | 472 (82 )| 4.7 ± 2.1              | Referent             | Referent                                                            |
| Yes                  | 98 (17)  | 3.1 ± 1.4              | −1.5 (−1.8, −1.1)    | −0.9 (−1.2, −0.5)                                                  |

* Mixed-effects multilevel regression analysis of 2 joints (units) per person (cluster). All analyses were adjusted for age, sex, and body mass index. PPT = pressure pain threshold; 95% CI = 95% confidence interval.
† Analyses of Kellgren/Lawrence grade of radiographic osteoarthritis (OA) severity and erosive OA were adjusted for gray-scale synovitis. Analyses of gray-scale synovitis and power Doppler activity were adjusted for Kellgren/Lawrence OA grade.
the nonpainful joints. Analyses were performed using Stata software version 15.

RESULTS

Quantitative sensory testing data were missing for 15 of the 300 individuals in the cohort due to equipment error (n = 9), incomplete examination (n = 1), and incomplete information on assessed joints (n = 5). Hence, 570 joints from 285 participants were examined in analyses (Table 1).

Radiographic OA features and PPT. As a continuous variable, a higher grade on the K/L scale was statistically significantly associated with lower PPT values (β = −0.5 [95% CI −0.6, −0.4]). Joints with possible, definite, or severe OA observed on radiographs (K/L grades 2, 3, or 4, respectively), but not joints with doubtful radiographic OA (K/L grade 1), had significantly lower PPTs than joints with no radiographic OA (K/L grade 0) (Table 2). Similarly, the PPT values were significantly lower in erosive versus non-erosive joints (Table 2). Additional adjustment for gray-scale synovitis grade as a continuous variable (adjusted β = −1.0 [95% CI −2.1, 0.2]) did not alter the results (data not shown).

Ultrasound-detected inflammation and PPT. Greater severity of gray-scale synovitis (indicated by higher synovitis grades) was associated with lower PPT values (β = −0.7 [95% CI −0.9, −0.6]). Joints assessed as having synovitis grade 1, 2, and 3 had statistically significantly lower PPTs than joints without synovitis (gray-scale synovitis grade 0), even after additional adjustment for K/L grade (Table 2). Similar associations were found for PD activity (Table 2). Additional adjustment for regular use of NSAIDs did not alter the results (data not shown).

Sensitivity analyses. In separate analyses of the painful finger joints (n = 285), the strength of the associations remained similar to the main analyses (Table 3).

In the nonpainful joints (n = 285), similar trends were observed between lower PPTs and increasing K/L grade as a continuous variable (adjusted β = −0.3 [95% CI −0.5, −0.1]), presence of erosions (adjusted β = −1.2 [95% CI −2.6, 0.2]), increasing gray-scale synovitis grade as a continuous variable (adjusted β = −0.6 [95% CI −1.3, 0.0]), and presence of PD activity grades 1–3 (adjusted β = −1.0 [95% CI −2.1, 0.2]). Pathologic features were less frequently present in these nonpainful joints (Table 3), and fewer associations reached statistical significance.

DISCUSSION

In our study, both structural and inflammatory hand OA features, independent of each other, were associated with lower PPT at finger joints and may represent possible drivers of pain sensitization. We also demonstrated that the relationship between more severe joint disease and greater local pain sensitivity was similar in joints with pain and those without.

Previous hand OA studies have shown that structural features and inflammatory severity observed on radiographs, MRI, and ultrasound are strongly associated with joint tenderness on palpation (3–5). Our results are the first to support these findings with a semiquantitative measure of pain sensitization. While the Doyle Index evaluates the presence of pain elicited by pressure or passive joint movement on a 0–3 scale (16), PPT determines the exact threshold at which increasing pressure first feels slightly painful. PPT testing, a recognized measure of pain sensitivity in pain research, is more standardized and nuanced with a scale value and could be more sensitive to change than joint tenderness, though we acknowledge that the potential added clinical value of PPT needs further exploration.

Our results are consistent with a small study of 13 patients with hand OA, in whom significant correlations between K/L grade and PPT at the same IP joint were found (11). Other studies have explored the associations between knee OA pathology and local pain sensitivity. MRI-detected synovitis was associated with lower PPT at the patella and predicted a significant reduction in PPT after 2 years (10). In contrast to the strong association we observed between radiographic features of OA and PPT values, several studies on knee OA have not been able to demonstrate such an association between radiographic knee OA and PPT after adjustment for potential confounders and pain severity (10). While the differences in our results between the painful and nonpainful joints should be interpreted with caution due to potential issues of precision, the stronger associations observed with painful joints may indicate an important role for pain symptoms themselves beyond radiographic abnormalities, similar to prior findings observed at the knee.

By using the PPT testing method, we demonstrated for the first time that even in joints without self-reported pain, radiographic structural severity and ultrasound-detected inflammatory severity were associated with local pain sensitivity. These new and important findings may indicate that pain sensitization is an early feature in the pathogenesis of pain. Future longitudinal studies are needed to explore whether a low PPT in pain-free joints predicts the development of self-reported pain.

A limitation of our study is its cross-sectional design. However, the observed dose-dependent associations and the likeness that pain sensitivity causes joint disease supports a true relationship. Further, the study population assessed in this study has a wide range of disease severity, which makes it possible to present dose-response data that otherwise could have been difficult to uncover. This study was confined to explore primarily peripheral sensitization via joint level associations. Local PPT was only tested in 2 finger joints per participant, which was a pragmatic choice. DIP/PIP joints are the joints with the highest prevalence of OA, and we considered the selection of the most
symptomatic joint and an asymptomatic joint to be sufficient to represent the local mechanisms we examined. Still, it is important to acknowledge that a PPT assessed adjacent to a site of pathologic changes in an individual could also be considered a component of the individual’s overall central pain sensitization. Although the results of our study imply that preventing structural changes and treating inflammation might have clinical consequences, the relationship between structural changes/inflammation and central sensitization is still unknown. A study investigating the relationship between OA joint pathologic changes in the hand and PPTs at distant sites with no evident disease, or utilizing other quantitative sensory testing modalities of central sensitization (e.g., temporal summation), might help in making a clear distinction between peripheral sensitization and central sensitization.

Our results have potential implications for future research and therapeutic approaches. Pain sensitization is a potential treatment target both indirectly and directly. Indirectly, disease-modifying drugs that target structural and inflammatory disease activity could alter

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Table 3. Association between PPT values and severity levels of structural radiographic features/inflammatory characteristics of OA in 285 painful finger joints and 285 nonpainful finger joints*

|                         | No. of patients | PPT, mean ± SD kg/cm² | Adjusted β (95% CI) | Adjustment for Kellgren/Lawrence OA grade or synovitis grade, β (95% CI)† |
|-------------------------|----------------|-----------------------|---------------------|-------------------------------------------------------------------------|
| **Painful finger joints** |                |                       |                     |                                                                         |
| Kellgren/Lawrence       |                |                       |                     |                                                                         |
| Grade 0                 | 63             | 4.5 ± 1.9             | Referent            | Referent                                                                |
| Grade 1                 | 41             | 4.3 ± 1.8             | −0.3 (−1.1, 0.4)    | −0.3 (−1.0, 0.4)                                                        |
| Grade 2                 | 62             | 4.6 ± 2.2             | 0.0 (−0.7, 0.7)     | 0.0 (−0.7, 0.7)                                                         |
| Grade 3                 | 55             | 3.2 ± 1.6             | −1.4 (−2.1, −0.7)   | −1.2 (−1.9, −0.5)                                                       |
| Grade 4                 | 64             | 2.8 ± 1.2             | −1.9 (−2.5, −1.2)   | −1.6 (−0.4, −0.9)                                                       |
| Continuous scales (grades 0–4) | 231     | 4.1 ± 2.0             | −0.5 (−0.6, −0.3)   | −0.4 (−0.6, −0.2)                                                       |
| Erosive OA disease      |                |                       |                     |                                                                         |
| No                      | 231            | 4.1 ± 2.0             | Referent            | Referent                                                                |
| Yes                     | 54             | 2.8 ± 1.2             | −1.3 (−1.9, −0.7)   | −1.0 (−0.6, −0.2)                                                       |
| Gray-scale synovitis on ultrasound |    |                       |                     |                                                                         |
| Grade 0                 | 159            | 4.3 ± 2.0             | Referent            | Referent                                                                |
| Grade 1                 | 57             | 3.8 ± 2.0             | −0.5 (−1.1, 0.1)    | 0.0 (−0.5, 0.6)                                                         |
| Grade 2                 | 43             | 3.3 ± 1.2             | −1.0 (−1.6, −0.3)   | −0.3 (−0.9, 0.4)                                                        |
| Grade 3                 | 26             | 2.5 ± 1.5             | −1.8 (−2.6, −1.0)   | −1.1 (−1.9, −0.3)                                                       |
| Continuous scales (grades 0–3) | 201     | 4.2 ± 2.0             | −0.6 (−0.8, −0.3)   | −0.3 (−0.5, −0.0)                                                       |
| Power Doppler activity grades 1–3 on ultrasound |    |                       |                     |                                                                         |
| No                      | 201            | 4.2 ± 2.0             | Referent            | Referent                                                                |
| Yes                     | 84             | 3.0 ± 1.3             | −1.3 (−1.8, −0.8)   | −0.8 (−1.3, −0.3)                                                       |
| **Nonpainful finger joints** |            |                       |                     |                                                                         |
| Kellgren/Lawrence       |                |                       |                     |                                                                         |
| Grade 0                 | 124            | 5.1 ± 2.3             | Referent            | Referent                                                                |
| Grade 1                 | 52             | 5.0 ± 2.1             | −0.1 (−0.7, 0.6)    | −0.0 (−0.7, 0.6)                                                        |
| Grade 2                 | 75             | 4.8 ± 2.0             | −0.3 (−0.9, 0.4)    | −1.2 (−0.8, 0.4)                                                        |
| Grade 3                 | 24             | 4.2 ± 1.6             | −1.0 (−1.9, −0.1)   | −0.9 (−1.9, 0.0)                                                        |
| Grade 4                 | 10             | 3.6 ± 1.3             | −1.4 (−2.7, −0.0)   | −1.3 (−2.8, 0.1)                                                        |
| Continuous scales (grades 0–4) | 271     | 5.0 ± 2.1             | −0.3 (−0.5, −0.1)   | −0.2 (−0.5, −0.0)                                                       |
| Erosive OA disease      |                |                       |                     |                                                                         |
| No                      | 271            | 5.0 ± 2.1             | Referent            | Referent                                                                |
| Yes                     | 9              | 3.6 ± 1.4             | −1.2 (−2.6, 0.2)    | −1.1 (−2.5, 0.3)                                                        |
| Gray-scale synovitis on ultrasound |    |                       |                     |                                                                         |
| Grade 0                 | 264            | 5.0 ± 2.1             | Referent            | Referent                                                                |
| Grade 1                 | 15             | 4.3 ± 1.4             | −0.7 (−1.8, 0.4)    | −0.1 (−1.3, 1.1)                                                        |
| Grade 2                 | 5              | 3.4 ± 1.2             | −1.4 (−3.3, 0.4)    | −1.3 (−3.2, 0.6)                                                        |
| Grade 3                 | 1              | 3.7 ± 0.0             | −1.1 (−5.2, 2.9)    | −1.1 (−5.2, 3.0)                                                        |
| Continuous scales (grades 0–3) | 271     | 5.0 ± 2.1             | −0.6 (−1.3, −0.0)   | −0.4 (−1.1, 0.2)                                                        |
| Power Doppler activity grades 1–3 on ultrasound |    |                       |                     |                                                                         |
| No                      | 271            | 5.0 ± 2.1             | Referent            | Referent                                                                |
| Yes                     | 14             | 3.9 ± 1.4             | −1.0 (−2.1, 0.2)    | −0.5 (−1.7, 0.7)                                                        |

* Data were examined by linear regression analysis. All analyses were adjusted for age, sex, and body mass index. See Table 2 for definitions.
† Analyses of Kellgren/Lawrence grade of radiographic OA severity and erosive OA were adjusted for gray-scale synovitis. Analyses of gray-scale synovitis and power Doppler activity were adjusted for Kellgren/Lawrence OA grade.
pain sensitization and consequently pain. Directly, mechanisms by which pain sensitization occurs are potential treatment targets themselves. Studies performed in recent years have revealed several promising targets that are mediators of pain sensitization (e.g., nerve growth factor, tropomyosin-related kinase receptor A, and ion channels [1]). So far, only one clinical trial of disease or symptom-modifying drugs in hand OA has included characterization of pain sensitization (17). Future clinical trials could benefit from including quantitative sensory testing of pain sensitization as a predictor of treatment efficacy, as a stratification tool to evaluate subgroup effects, or as an inclusion criterion to select the right pain phenotype for the intervention in question.

In summary, this is the first study to demonstrate an independent association of structural and inflammatory hand OA features with lower local PPTs, indicating pain sensitization. The associations were similar in joints with pain and those without. These results complement preclinical evidence that pain sensitization, especially peripheral, might be driven by structural and inflammatory features. Future research should investigate the role of pain sensitization as a potential target for hand OA pain management or prevention.

ACKNOWLEDGMENTS

We would like to thank the study participants in the Nor-Hand study. A thank you is also extended to the project coordinators, Elisabeth Mulrooney and Janicke Magnus, as well as Nicolai Ravn Aarskog for performing ultrasound examinations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Steen Pettersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy to be published. Dr. Steen Pettersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy to be published.

Study conception and design. Steen Pettersen, Neogi, Hammer, Uhlig Kven, Haugen.

Acquisition of data. Steen Pettersen, Hammer, Kven, Haugen.

Analysis and interpretation of data. Steen Pettersen, Neogi, Magnusson, Hammer, Uhlig, Kven, Haugen.

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