Neuropathic pain symptoms in a community knee OA cohort

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Objective: A neuropathic pain (NP) questionnaire may facilitate the identification of a neuropathic component to osteoarthritis (OA) pain. An existing questionnaire, the painDETECT, was modified for use in knee OA and administered to measure the prevalence and correlates of NP symptoms among adults with this condition.

Method: Sensibility of the modified painDETECT (mPD-Q) was assessed in 20 OA subjects followed by mail administration in an established knee OA cohort. NP symptoms were defined using a previously established, painDETECT cut-point. Correlates of NP symptoms, including OA severity (Western Ontario and McMaster Universities Osteoarthritis Index, Von Korff Chronic Pain Grade pain subscale score), psychological factors (Centre for Epidemiological Studies Depression Scale, Pain Catastrophizing Scale), and concomitant medical conditions, were evaluated using logistic regression. Construct validity of the mPD-Q was evaluated through co-administration with another NP questionnaire (S-LANSS).

Results: The mPD-Q had face and content validity. Of 259 eligible cohort members, 171 (66%) completed the questionnaire; 28% had NP symptoms on the mPD-Q (19% among those without neurological conditions). Independent correlates of NP symptoms were: pain intensity (adjusted odds ratio [OR] = 2.1 per 10 unit increase, \( P < 0.0001 \)), the presence of referred back/hip pain (adjusted OR = 2.9, \( P = 0.024 \)), number of painful joints (OR = 1.2, \( P = 0.20 \)) and one or more self-reported neurological condition (OR = 3.0, \( P = 0.026 \)).

Conclusions: Among older adults with chronic symptomatic knee OA, one-quarter had NP symptoms localized to their knees using the mPD-Q. The mPD-Q may facilitate the identification of a neuropathic component to pain in adults with knee OA who may benefit from further evaluation and/or treatment for NP.

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Introduction

Osteoarthritis (OA)-related pain has been attributed to local tissue injury causing “nociceptive” pain⁴. However, cumulative data suggest both neuropathic and nociceptive mechanisms may contribute to the OA pain experience⁵–⁷. Therefore, there may be a subset of people with OA who could benefit from an alternative treatment strategy, employing medications that target neuropathic pain (NP)⁵. The first step towards individualized treatment, however, is the development of clinically feasible tools to identify NP among people with symptomatic OA.

This study was based on the 1994 definition of NP as “pain initiated or caused by a primary lesion or dysfunction of the nervous system”⁶. Though a new definition has since been proposed, it awaits validation and was not accepted when this study was conducted⁷. The diagnosis of NP remains clinical, based on a characteristic symptom profile (e.g., pins and needles, electric-shock like sensations), somatosensory abnormalities (e.g., hyperalgesia, hypoesthesia, allodynia) and, sometimes, ancillary tests⁷⁸. Like other chronic pain conditions, central sensitization may contribute to OA pain arising from chronic nociceptor stimulation and subsequent modification of central pain transmitting neurons⁸⁹. Using the 1994 definition, central sensitization could be considered a neuropathic mechanism, causing an uncoupling of...
pain sensations and localization from peripheral nociceptive activity. However, injury to nerves innervating affected joints has not been ruled out. Indeed, some animal OA models have shown that nerves re-innervating damaged tissues had profiles similar to that in nerve-injury models, including abnormal morphology and an excess of neuropeptides involved in pain transmission. Comorbid pain conditions, psychological factors and/or subclinical neuropathies may further alter central pain processing and influence the OA pain experience. These factors may, however, go unrecognized in musculoskeletal clinics where evaluation for NP is not part of the standard OA assessment.

Evidence for a neuropathic component to pain in OA arises predominately from quantitative sensory testing studies that assess responses to experimental pain induction. However, quantitative sensory testing is impractical for widespread use. Thus, capitalizing on the characteristic NP symptom profile, NP questionnaires have been developed to help distinguish neuropathic from nociceptive pain. However, little is known about the performance of these measures in OA. From focus groups on the pain experience in knee OA, we found that 1/3 of participants described their OA pain using characteristic NP descriptors, suggesting that NP questionnaires may facilitate the identification of a neuropathic component to OA pain.

Among existing measures, the painDETECT questionnaire appears most appropriate for use in OA; it was developed and validated in adults with chronic low back pain (CLBP), a condition with potentially mixed neuropathic and nociceptive pain mechanisms, and it does not include a physical examination component. However, in its original form, the painDETECT does not meet some basic principles of scale development for the intended population. The questions are not site-specific, but rather ask respondents to report on their “main area of pain”; the format (e.g., crowded layout, small font) makes self-completion difficult, particularly by older adults with visual or dexterity limitations; and the time frame for symptom reporting is not explicit. To date, only one study has evaluated the relationship between painDETECT scores and signs of central sensitization in OA. Gwilym et al. self-administered the painDETECT to 20 adults with hip OA. Though scores above the sample median were associated with findings suggestive of central sensitization on quantitative sensory testing and functional magnetic resonance imaging, the study was limited by lack of control for confounders, in particular, concomitant back pain.

The purpose of this study was to modify the painDETECT for use in knee OA and to administer the modified questionnaire, the mPD-Q, to an established knee OA cohort to evaluate: (1) the prevalence of NP symptoms; (2) convergent construct validity of the mPD-Q through co-administration with another NP questionnaire, the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS); and, (3) potential correlates of NP symptom scores in OA.

Methods

Development and pilot testing of the modified painDETECT (mPD-Q)

The painDETECT was developed as a self-administered psychometric questionnaire to distinguish NP from non-NP among people with CLBP. It is comprised of 7 items evaluating pain quality, one evaluating pain pattern, and one evaluating pain radiation, which all contribute to an aggregate score (range: 0 to 38). The painDETECT has been validated against expert physician diagnosis of NP in people with a range of chronic pain conditions including “typical” NP (i.e., diabetic neuropathy) or “typical” non-NP entities (i.e., repetitive strain injury). Overall sensitivity, specificity, and positive predictive values using the cut-off score of 19 (NP symptoms ≥ 19) were 85%, 80%, and 83%, respectively.

Careful evaluation of the painDETECT identified that it failed to meet some basic principles of scale development for the intended population. To address these issues, the mPD-Q was developed with the following modifications: enlargement of font, numbering of questions, addition of an introductory ‘framing’ paragraph, and framing of questions to ask about symptoms ‘in or around’ the worst knee, over a specific time frame. For example, the question:

“Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?” was changed to:

“Please select the response that best describes the quality of your RIGHT knee pain over the PAST MONTH. Remember that we are using the word ‘pain’ to refer to any uncomfortable sensation that you may or may not describe as ‘pain’.

3a. Do you suffer from a burning sensation (e.g., stinging nettles) in or around your RIGHT knee?” Questions on pain intensity that were not included in the overall score were removed.

The mPD-Q was pilot tested in 20 individuals with OA in self-administered form along with a questionnaire designed to assess respondents’ opinions regarding the measure’s understandability and ease of use. Additional changes were made as a result of this feedback prior to administration to the OA cohort. For example, the question on radiation of pain was misunderstood by some who responded by marking non-contiguous joint regions. The original question was therefore changed from:

“How does your pain radiate to other regions of your body?”

To:

“How has your right knee pain run up or down your RIGHT leg over the past month?”

As well, questions were separated for right and left knees. This pilot study confirmed that the mPD-Q had improved face validity and ease of use compared to the original painDETECT in older adults with knee OA.

mPD-Q validation

Participants were recruited from an established community-based hip/knee arthritis cohort, recruited between 1995 and 1997 from a survey of 100% of the population, aged 55+ years, in two regions, one urban and one rural. Respondents with moderate to severe hip or knee arthritis symptoms were selected for subsequent follow-up (n = 2,411). Details regarding the recruitment have been published elsewhere. A validation study was performed on a subsample of survey respondents who did and did not meet screening criteria for hip/knee arthritis; self-reported arthritis was validated against joint examination and radiographs. Ninety-six percent of participants who met screening criteria for arthritis had clinical exam signs of hip and/or knee arthritis. The arthritis diagnosis was OA in 86%.

Of the 2411 original cohort members, 757 continued to participate in 2007. For the current study, eligible participants were those with discomfort in at least one non-replaced knee on most days (≥15) over the past month. Those with self-reported physician-diagnosed inflammatory arthritis, bilateral knee surgery, or factors that interfered with questionnaire self-completion, e.g., reduced cognition, were excluded. Ethics approval to administer a supplemental study questionnaire by mail was obtained from the institutional Research Ethics Board.

Standardized annual telephone interviews have been conducted since 1999. Data were obtained from the most recent interviews (within 12 months of the current study) on sociodemographic
factors (age, sex, race [Caucasian, non-Caucasian]), education (≤ high school, > high school), OA severity, and psychological factors (depressed mood and pain catastrophizing). A supplemental questionnaire was mailed to eligible cohort participants to measure NP symptoms and collect additional information on OA symptom severity, symptomatic joints using a joint homunculus, and specific comorbid conditions including chronic back pain or hip pain, referred pain to upper leg from hip or back ('referred back or hip pain'), fibromyalgia, any other chronic pain disorders, and diabetes (DM), neurological conditions (sciatrica, shingles, post-herpetic neuralgia, leg neuropathy, multiple sclerosis, Parkinsons disease, stroke), and medication use (acetaminophen, nonsteroidal antiinflammatory drugs [NSAIDs], opioids, NP treatments). NP treatments included anti-depressants [e.g., tricyclic anti-depressants [TCAs], selective serotonin, and norepinephrine reuptake inhibitors [SSRIs and SNRIs, respectively]] and anti-convulsants [e.g., calcium channel a2-3 ligand anti-convulsants]31. Medications containing opioids were grouped with the non-NP analgesics - acetaminophen and NSAIDs.

Participants self-completed the mPD-Q for each eligible (symptomatic, non-replaced) knee. OA symptom severity was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total and pain subscale scores25 and the Von Korff Chronic Pain Grade (CPG) pain intensity subscale28. The WOMAC32 and CPG33 have demonstrated reliability and validity in adults with chronic pain from the community. Higher scores on both of these instruments indicate greater symptom severity.

Depressive symptoms were measured using the Centre for Epidemiologic Studies Depression Scale (CES-D)34, a valid and reliable measure of depressive symptoms in community dwelling elderly. A score ≥ 16 is considered indicative of depression. The Pain Catastrophizing Scale (PCS), valid and reliable in older adults with OA, was used to measure pain catastrophizing. Higher scores indicate more pain catastrophizing.

In the absence of a gold standard test for NP, the S-LANSS has been validated to identify pain of predominately neuropathic origin in patients with chronic pain of any cause. The S-LANSS was selected over other NP questionnaires because it has been validated in people with 'mixed' neuropathic and nociceptive pain, does not have a physical exam component, and is the most widely used measure37–40. The painDETECT was, however, considered more suitable for the OA population as it was developed in adults with CLBP. Some pathophysiologic mechanisms of pain may be shared between peripheral OA and CLBP on the basis of facet joint OA. In addition, the 0–5 ordinal scale for measuring severity of NP symptoms was preferred to the weighted binary response options on the S-LANSS.

Statistical analysis

Responders were compared to non-responders for factors that may be associated with NP, including sociodemographic factors, OA severity, comorbid conditions, and psychological factors to assess for potential responder bias. An mPD-Q score was tallied for each eligible knee (s) of each participant. When the participant had two eligible knees, the participant mPD-Q score was calculated from the mean score for the 2 knees. In absence of a known appropriate cut-point score for NP in OA, the previously published painDETECT cut-point was chosen: participants with an mPD-Q score ≥ 19 in either knee were categorized as having a ‘NP range’ score. The proportion of knee OA cohort participants with mPD-Q scores ≥ 19 was calculated, with a 95% confidence interval (CI).

For convergent construct validity testing, the Spearman’s correlation coefficient was used to compare continuous mPD-Q scores to continuous S-LANSS scores; we hypothesized a moderate high correlation (≈ 0.7). Correlates of mPD-Q scores ≥ 19 were first assessed using bivariate analyses. Continuous variables were compared amongst ‘NP’ and ‘non-NP’ participants using the Student’s t-test or Wilcoxon Rank Sum Test where appropriate. Categorical variables were assessed using the Chi-square test or Fisher’s exact test where the cell value was < 5. Significance was based on two-tailed tests with a 5% level of significance. Variables that differed significantly among the two groups were assessed for collinearity. Non-collinear significant variables were considered for multivariable logistic regression modeling.

Groups of conceptually similar variables were first entered in the following blocks: arthritis severity; concomitant medical/pain/ neurological conditions; and psychological factors. Within these blocks, logistic regression was used to model the relationships of these variables with the dichotomized mPD-Q score (≥ 19 vs ≥ 19). Interactions were assessed between use of NP medications and independent factors, including each of diabetes an fibromyalgia, any neurological conditions, and scores on the CES-D and PCS. The variable(s) contributing to the best model fit were selected from each variable block to be included in the final multivariable logistic regression model. Manual backwards selection was used to remove independent variables with insignificant maximum likelihood estimates (P > 0.05). A sensitivity analysis was conducted excluding participants with self-reported neurological conditions. All statistical analyses were done using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). Significance was based on two-tailed tests with a 5% level of significance.
Table I
Characteristics of study participants (N = 171)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n/N (%)</th>
<th>Median (min–max)</th>
</tr>
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<tbody>
<tr>
<td><strong>Sociodemographic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>76.0 (67.0–99.0)/171</td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>132/171 (77.2)</td>
<td></td>
</tr>
<tr>
<td>Race (% caucasian)</td>
<td>154/161 (95.7)</td>
<td></td>
</tr>
<tr>
<td>Education (% ≤ high school)</td>
<td>131/165 (79.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoarthritis severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC – total score (/96)</td>
<td>53.0 (8.0–85.0)/167</td>
<td></td>
</tr>
<tr>
<td>WOMAC – pain score (/20)</td>
<td>10.1 (3.7) /168</td>
<td></td>
</tr>
<tr>
<td># Painful joints (/18)</td>
<td>8.0 (1.0–18.0)/167</td>
<td></td>
</tr>
<tr>
<td>CPG pain intensity score (/100)</td>
<td>53.3 (6.7–100.0)/171</td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic back or hip pain</td>
<td>129/165 (78.2)</td>
<td></td>
</tr>
<tr>
<td>Referred back/hip pain to upper leg</td>
<td>73/158 (46.2)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>43/166 (26.9)</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>20/165 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Other pain conditions†</td>
<td>47/151 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Neurological condition†</td>
<td>73/167 (43.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological factors</strong></td>
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<td></td>
</tr>
<tr>
<td>CES-Depression (/160)</td>
<td>9.0 (0–41.0)/164</td>
<td></td>
</tr>
<tr>
<td>PCS score (/52)</td>
<td>5.0 (0–41.0)/165</td>
<td></td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any NP treatment</td>
<td>37/163 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Non-NP analgesics</td>
<td>128/163 (78.5)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy use</td>
<td>5/160 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Mean and standard deviation is reported for the WOMAC pain subscale (normally distributed).
† Any other pain condition (yes/no).
‡ Neurological conditions included stroke, leg neuropathy, sciatica, shingles, post-herpetic neuralgia, multiple sclerosis, and Parkinson’s disease.

Results

Study sample

Compared with the original cohort, participants with knee OA in 2007 (n = 516) were older, better educated, had higher income, and were more likely to be women and residing in the rural region. Among these knee OA cohort members, 426 were potentially eligible to participate and were mailed study questionnaires; 259 met eligibility criteria for the current study and 171 (66% of 259) were more likely to be women and residing in the rural region. Among these knee OA cohort members, 426 were potentially eligible non-responders, responders had lower scores for depressive symptoms and pain catastrophizing.

Characteristics of the 171 study participants are summarized in Table I. The majority were elderly (median age 76), female (77.2%), Caucasian (95.7%), and had ≤ high school education (79.4%). WOMAC and CPG measures indicated moderate symptom severity. Knee symptom duration was longstanding by virtue of original cohort recruitment at least 10 years prior to study completion. Self-reported comorbid conditions are shown in Table I. Median scores on the CES-D were below the cut-point for depressive symptoms (22% had scores ≥ 16 indicating probable depression), and median pain catastrophizing scores were low. Almost one-quarter of study participants (23%) reported use of medications that may be used to treat NP and other indications, e.g., depression; of these participants (n = 31), the majority (84%) were using an anti-depressant (TCA, SSRI or SNRI) that is recommended as a first line NP treatment.

NP questionnaire results

Frequencies of scores for individual items on the mPD-Q and S-LANSS are shown for each eligible knee in Table II. mPD-Q scores were right-skewed. Median (min–max) mPD-Q score for participants was 12.0 (0–38.0). Scores were similar for right and left knees, and for participants with bilateral versus unilateral eligible knees. Therefore, the remainder of the analysis was performed ‘by participant’. NP range scores on the mPD-Q (≥19/38) were found in 48/171 participants, with a corresponding proportion (95% CI) of 0.28 (0.21–0.35). Excluding those with self-reported neurological conditions, 19/98 participants, 0.19 (0.12–0.29), scored in the NP range. The correlation between continuous mPD-Q and S-LANSS scores was moderate (Spearman r = 0.73, P < 0.0001).

Correlates of NP symptoms

In bivariate analyses, NP range scores on the mPD-Q were significantly associated with greater OA severity, a greater number of self-reported painful joints, depressive symptoms and pain catastrophizing, the presence of referred back or hip pain, and self-reported neurological conditions attributable to stroke (P = 0.02) and leg neuropathy/nerve damage (P = 0.03) (Tables III and IV). No statistically significant differences between participants with vs without NP were found for DM, fibromyalgia or other pain conditions, other neurological conditions, use of medications to treat NP, use of standard treatments for OA, or history of cancer chemotherapy. Due to collinearity between WOMAC total and pain subscale scores, only the latter was retained in subsequent multivariable modeling (Table III and Table IV).
To our knowledge, this is the first study to utilize a NP question-naire items likely explain the observed correlation. The pain-scale validity and feasibility for knee OA. As hypothesized, a signi-
cificant association between other variables of interest and NP range scores were independently and significantly associ-
ated with greater pain intensity on the CPG pain intensity subscale (odds ratio OR 2.1 per 10 unit increase, P < 0.0001), a greater number of painful joints (OR = 1.2, P = 0.020), the presence of referred back/hip pain (OR 2.9, P = 0.024), and the presence of one or more self-reported neurological condition (OR 3.0, P = 0.026) (Table V). Excluding participants with neurological conditions, model fit remained stable (Table VI), NP medication use did not modify the relationship between other variables of interest and NP range scores.

**Discussion**

In a community cohort of older individuals with chronic, symptomatic knee OA, over one-quarter had NP symptoms, localized to their knees, as measured by a NP questionnaire modified for use in knee OA. Excluding participants with self-reported neurological conditions, 19% had knee symptom scores in the NP range. To our knowledge, this is the first study to utilize a NP question-naire to identify the prevalence of NP symptoms localized to knee OA. These findings support the growing evidence that neuropathic mechanisms may contribute to the pain experience in OA.

**Table IV**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NP symptoms (N = 48) n/N (%)</th>
<th>No NP symptoms (N = 123) n/N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic back or hip pain</td>
<td>41/46 (89.1)</td>
<td>88/119 (74.0)</td>
<td>0.034</td>
</tr>
<tr>
<td>Back/hip pain referred to upper leg</td>
<td>32/44 (72.7)</td>
<td>41/114 (36.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>15/46 (32.6)</td>
<td>28/120 (23.3)</td>
<td>NS*</td>
</tr>
<tr>
<td>Other pain</td>
<td>14/40 (35.0)</td>
<td>33/111 (29.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Neurological</td>
<td>29/47 (61.7)</td>
<td>44/120 (36.7)</td>
<td>0.003</td>
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<tr>
<td>Medication use</td>
<td></td>
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</tr>
<tr>
<td>Non-NP analgesics</td>
<td>38/45 (84.4)</td>
<td>90/118 (76.3)</td>
<td>NS</td>
</tr>
<tr>
<td>NP treatment</td>
<td>13/45 (28.9)</td>
<td>24/118 (20.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1/45 (2.2)</td>
<td>4/115 (3.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Not significant.

**Multivariable modeling**

NP range scores were independently and significantly associated with greater pain intensity on the CPG pain intensity subscale (odds ratio OR 2.1 per 10 unit increase, P < 0.0001), a greater number of painful joints (OR = 1.2, P = 0.020), the presence of referred back/hip pain (OR 2.9, P = 0.024), and the presence of one or more self-reported neurological condition (OR 3.0, P = 0.026) (Table V). Excluding participants with neurological conditions, model fit remained stable (Table VI), NP medication use did not modify the relationship between other variables of interest and NP range scores.

Our results are in keeping with our previous qualitative study, in which 34% of participants spontaneously used NP descriptors to characterize their pain;26 and with estimates in other chronic pain populations.27,38,43,44 From multiple questionnaire-based studies, the frequency of NP amongst people with CLBP has ranged from 10 to 54%25,43,45. Two recent, large studies of people with chronic pain from any cause found the prevalence of NP to be 17% among UK family practice patients (n = 6000)39 and 22% in a national population-based cohort in France (n = 7522).44 Potential explanations for the variability in NP prevalence estimates across studies include: (1) differential recruitment practices (estimates based on patients recruited from specialists’ offices have been consistently higher than those from community-based studies); (2) variable exclusion criteria or statistical control for other potential sources of NP (e.g., diabetic neuropathy); and (3) use of different NP measures. Though a core set of discriminatory symptoms are shared among NP questionnaires, these measures differ in inclusion of other symptom and/or physical examination items and by scoring systems, which may lead to differential classification of people with similar pain types22. Nonetheless, these cumulative data support the notion that neuropathic mechanisms may contribute to the pain experience for a subset of people with chronic pain (not limited to typical NP entities). The mPD-Q may serve as a clinically feasible tool to aid in the identification of NP among adults with knee OA. From pilot testing, the mPD-Q improved upon the painDETECT in content and face validity and feasibility for knee OA. As hypothesized, a significant, moderate to high, positive correlation was observed between the mPD-Q and the S-LANSS. Differences in scoring schemes and questionnaire items likely explain the observed correlation. The painDETECT and its modified version have the advantage of measuring the severity of NP qualities using a 0–5 ordinal scale vs the S-LANSS which has weighted binary response options. The S-LANSS also uniquely assesses autonomic skin changes, which is not character-
istic of OA, but likely represents complex regional pain syndrome among the questionnaire development population.46 The relationship of NP range scores to self-reported neurological conditions provides further evidence of construct validity for the mPD-Q. While this is encouraging, further construct validity testing of the mPD-Q is needed, in particular to evaluate the relationship between mPD-Q scores and signs of NP on quantitative sensory testing.

Controlling for other factors, the likelihood of NP symptoms was two-fold greater with every 10 point rise in CPG pain intensity subscale score. More intense pain in OA may be associated with a greater degree of nociceptive input to the central nociceptive...
Factors associated with NP symptoms in all participants using logistic regression modeling with mPD-Q score ≥ 19 vs <19 as dependent variable. Total sample (N = 199); scores in NP range (N = 43)*

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
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<td>OA Severity</td>
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<td></td>
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<tr>
<td>CPG – pain intensity</td>
<td>1.9 (1.5–2.3)</td>
<td>&lt;0.0001</td>
<td>1.8 (1.4–3.1)</td>
<td>0.0004</td>
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<tr>
<td>(per 10 unit increase)</td>
<td>(100)</td>
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<td></td>
<td>(95% CL)</td>
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<tr>
<td>Concomitant conditions</td>
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<tr>
<td>Referred back/hip pain</td>
<td>4.8 (2.2–10.2)</td>
<td>&lt;0.0001</td>
<td>2.6 (0.7–9.8)</td>
<td>0.16</td>
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<tr>
<td>Neurological condition</td>
<td>2.7 (1.4–5.4)</td>
<td>0.004</td>
<td>3.0 (1.1–7.7)</td>
<td>0.026</td>
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<tr>
<td># Painful joints</td>
<td>1.12 (1.0–1.2)</td>
<td>0.01</td>
<td>1.1 (0.9–1.3)</td>
<td>0.33</td>
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<td>Adjusted R²</td>
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<tr>
<td>C Statistic</td>
<td>0.90</td>
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</table>

* Complete-case analysis.
† Adjusted for: Von Korff Chronic Pain Grade pain intensity subscale, back/hip pain referred to upper leg, and number of painful joints.
‡ Max rescaled R².

Factors associated with NP symptoms among participants without neurological conditions using logistic regression modeling with mPD-Q score ≥ 19 vs <19 as dependent variable. Total sample (N = 58); scores in NP range (N = 16)*

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Severity</td>
<td></td>
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<tr>
<td>CPG – pain intensity</td>
<td>1.9 (1.5–2.3)</td>
<td>&lt;0.0001</td>
<td>1.8 (1.4–3.1)</td>
<td>0.0004</td>
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<td>(per 10 unit increase)</td>
<td>(100)</td>
<td></td>
<td></td>
<td>(95% CL)</td>
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<tr>
<td>Concomitant conditions</td>
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<tr>
<td>Referred back/hip pain</td>
<td>4.8 (2.2–10.2)</td>
<td>&lt;0.0001</td>
<td>2.6 (0.7–9.8)</td>
<td>0.16</td>
<td></td>
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<tr>
<td># Painful joints</td>
<td>1.12 (1.0–1.2)</td>
<td>0.01</td>
<td>1.1 (0.9–1.3)</td>
<td>0.33</td>
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<tr>
<td>Adjusted R²</td>
<td>0.39</td>
<td></td>
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<tr>
<td>C Statistic</td>
<td>0.89</td>
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</tbody>
</table>

* Complete-case analysis.
† Adjusted for: Von Korff Chronic Pain Grade pain intensity subscale, back/hip pain referred to upper leg, and number of painful joints.
‡ Max rescaled R².

System, leading to a greater degree of central sensitization and NP. Alternatively, NP mechanisms, such as central sensitization or disinhibition, may be synergistically or independently induced by other factors that amplify the perception of the nociceptive stimulus; these factors may be reflected in higher pain intensity scores.

Controlling for pain intensity, the likelihood of NP symptoms at the knee rose with each additional painful joint on the joint homunculus, with the presence of back or hip pain referred to the upper leg, and self-reported neurological conditions, and number of painful joints. From a practical clinical perspective, a history of sensitization may contribute to the sensation of pain at multiple body sites. Referred pain referred to upper leg, and number of painful joints is associated with the presence of NP symptoms. Referred pain may confound NP at the knee. Similarly, individuals with multiple painful joints may be at greater risk for central sensitization and a neuropathic component to knee OA pain. Alternatively, referred pain may confound NP at the knee. Similarly, individuals with multiple painful joints may be at greater risk for central sensitization owing to cumulative nociceptive input. Alternatively, central sensitization may contribute to the sensation of pain at multiple body sites. From a practical clinical perspective, a history of multiple painful joints and/or the presence of referred back or hip pain among patients assessed for knee OA should prompt clinicians to evaluate knee pain quality as these patients may be more likely to have a neuropathic component to their knee pain. Excluding participants with neurological conditions, 19% still had scores in the NP range, suggesting that NP range scores were not explained solely by co-existing neurological conditions.

Psychological factors may also contribute to central sensitization and NP in knee OA. According to Melzack’s neumatrix model, combined input from the neumatrix (thalamus, cortex, and limbic system) generates neuronal activity that affects pain transmission and/or pain modulation. Psychological factors may influence neumatrix activity through several pathways and thereby, influence pain perception in OA. For example, depression may contribute to central sensitization and NP in OA through reduced serotonin involved in descending inhibition of pain. To address these issues, we assessed these factors in our study. Consistent with prior studies, we found that higher scores for each of depressive symptoms and pain catastrophizing were associated with the presence of NP symptoms. However, when we controlled for pain intensity, these factors were no longer significant, suggesting that depressive symptoms and/or pain catastrophizing may exert an influence on NP symptoms through their effect on pain intensity. Further study is needed to assess the causal and temporal relationships of psychological factors to the development of NP in OA.

Strengths of our study include the focus on an unselected community-based sample of older adults with chronic symptomatic knee OA, and incorporation of psychological factors in our analyses. However, our study also has some limitations. First, although our sample size was large relative to previous studies examining features of NP in OA, we have insufficient power to evaluate, conclusively, the independent effects of postulated correlates of NP symptoms. Thus, we may have missed important relationships. However, the strong multivariable model fit implies that we identified a number of important correlates of NP symptoms in OA that should be considered in larger studies. Second, compared with non-participants, our participants had lower scores for psychological factors that have been associated with the presence and severity of NP. As a result, we may have underestimated the prevalence of NP symptoms in the cohort. Third, associations between responses on self-report measures may be due to the same method variance, e.g., participants who report greater pain intensity may be more likely to report stronger NP symptoms, in part, due to negative affect. However, the relationship between pain intensity and mPD-Q scores remained significant after adjusting for pain catastrophizing and depressive symptoms. Fourth, our study sample included only older adults with longstanding OA. Thus, our results may not be generalizable to adults who are younger/healthier or whose OA is of shorter duration. Further research is needed to determine if age and duration of symptoms contribute to the development of NP symptoms in OA. Finally, it remains unknown whether scores in the NP range on the mPD-Q reflect underlying mechanisms of NP. Validation of the mPD-Q against objective measures of NP including somatosensory testing in OA is needed, and is ongoing.

In summary, we have modified a NP questionnaire to identify a potential neuropathic component to pain in OA. Preliminary evaluation found the mPD-Q to be a feasible self-report tool with face and content validity for its intended purpose and moderately correlated to S-LANSS scores. Using the mPD-Q, we found a substantial proportion of older adults with chronic, symptomatic knee OA had symptoms of NP, localized to their knees. These findings suggest that neuropathic mechanisms may contribute to the OA pain experience. Excluding participants with self-reported neurological conditions, OA pain intensity, number of painful joints, and the presence of concomitant back or hip pain referred to the upper leg...
had high discriminative validity for distinguishing those with and without NP range symptoms. Though further validation work is needed, the mPD-Q appears to be a clinically feasible self-report tool for the screening of NP symptoms among adults with knee OA.

Author contributions

All authors have significantly contributed to (1) the conception and design of the study or acquisition of data or analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content and (3) final approval of the manuscript as follows: conception and design (JRH, GAH, AMD, LG), analysis and interpretation of data (JRH, GAH, AMD, LG), drafting of the article (JRH, GAH), critical revision of the article for important intellectual content (JRH, GAH, AMD, LG), final approval of the article (JRH, GAH, AMD, LG), provision of study material or patients (JRH, GAH), statistical expertise (JRH, GAH, AMD), obtaining funding (JRH, GAH), administrative, technical or logistic support (JRH, GAH), collection and assembly of data (JRH, GAH). On behalf of all authors, Dr Jacqueline R Hochman (j.hochman@utoronto.ca) takes public responsibility for the integrity of the work as a whole, from inception to finished article.

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Competing interests

None of the authors have any financial or personal relationships with other people or organizations that could potentially and inappropriately influence their work and conclusions.

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References


