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 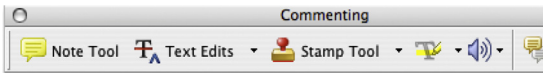

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 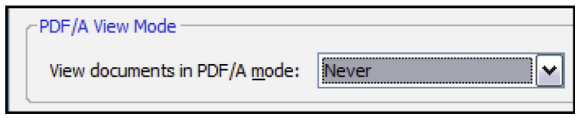

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 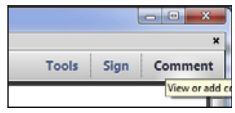

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 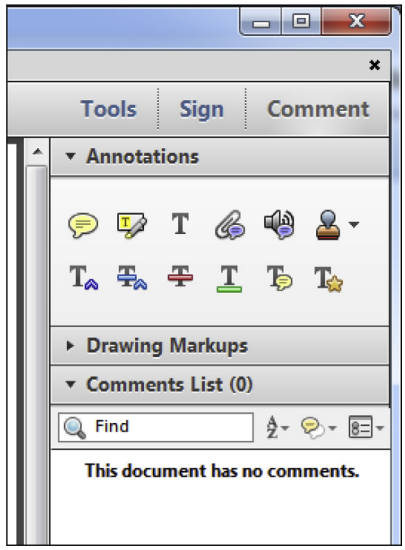
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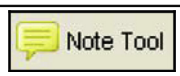
Leave a note/ comment	Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

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Highlights

- Preoperative neuropathic pain like symptoms in knee osteoarthritis (OA) can predict pain after total knee replacement (TKR).
- PainDETECT can identify neuropathic pain like symptoms in patients with OA in the knee.
- Central sensitization is present in patients with OA with a neuropathic pain phenotype.
- Subgrouping patients based on pain phenotype may explain chronic pain after TKR.
- An individualized medical approach to patients with OA may improve outcomes after TKR.

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Original Reports

Preoperative Neuropathic Pain-like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery

Q1 Thomas Kurien,*,†,‡ Lars Arendt-Nielsen,§ Kristian K. Petersen,§ Thomas Graven-Nielsen,¶ and Brigitte E. Scammell*,†,‡

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Abstract: **Preoperative pain characteristics in patients with osteoarthritis may explain persistent pain after total knee replacement. Fifty patients awaiting total knee replacement and 22 asymptomatic controls were recruited to evaluate the degree of neuropathic pain symptoms and pain sensitization. Patients with OA were pain phenotyped into 2 groups based on the PainDETECT questionnaire: high PainDETECT group (scores ≥19) indicating neuropathic pain-like symptoms and low PainDETECT group (scores <19) indicating nociceptive or mixed pain. Cuff algometry assessing pain detection thresholds and pain tolerance thresholds was conducted on the lower legs. Temporal summation of pain was assessed using 10 sequential cuff stimulations and a von Frey stimulator. Conditioning pain modulation was assessed by cuff pain conditioning on 1 leg and parallel assessment of pain detection thresholds on the contralateral leg. Pressure pain thresholds were recorded by pressure handheld algometry local and distant to the knee. Knee pain intensity (visual analogue scale) and pain assessments were collected before and 6 months after total knee replacement. Thirty percent of patients demonstrated neuropathic pain-like symptoms (high PainDETECT group). Facilitated temporal summation of pain and reduced pressure pain thresholds distant to the knee were found in the high PainDETECT group compared with the low PainDETECT group and healthy controls ($P < .001$). Patients with OA with high PainDETECT scores had higher postoperative visual analogue scale pain scores than the low PainDETECT patients ($P < .0001$) and facilitated temporal summation of pain ($P = .022$) compared with healthy control subjects.**

Perspective: **This study has found that preoperative PainDETECT scores independently predict postoperative pain. Patients with knee OA with neuropathic pain-like symptoms identified using the PainDETECT questionnaire are most at risk of developing chronic postoperative pain after TKR surgery.**

Key words: *Neuropathic pain, osteoarthritis, total knee replacement, postoperative pain, sensitization.*

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Knee osteoarthritis (OA) pain has been traditionally attributed to the activation of peripheral nociceptors within the joint or periarticular structures.[49] Significant discordance between radiographic features and knee pain severity[31] has led to researchers investigating the central pain mechanisms with the identification of OA subgroups with different pain phenotypes.[2,4–7,39,40] Up to 34% of patients with OA exhibit neuropathic pain-like symptoms[25,26,42,53] (electric shock sensations,[25,26] burning pain,[14] and allodynia[48]), which have been associated with symptoms of central pain facilitation.[24,35] In the United States, 3.5 million total knee replacements (TKRs) are expected to be performed by 2030[33]; however, it is worrying that ≤20% of patients will develop chronic postoperative pain despite objective measures of operative success,[57] which will be a major challenge for health care systems in the future.[9] A definition of chronic postoperative pain has been proposed by Werner et al[55] and has been adopted by the International Association for the Study of Pain as "pain persisting at least 3 months following surgery that localized to the surgical site or a referred area, that is not be present before surgery or has different characteristics or increased intensity from the preoperative pain." Preoperative screening and identification as to which patients are at greater at risk of developing postoperative knee pain remains an elusive goal for orthopedic surgeons and researchers. Recent work subgrouping patients with knee OA based on different pain phenotypes has identified subgroups of patients with evidence of central pain facilitation that are at more at risk of developing postoperative pain after TKR surgery.[39,40] Whether the presence of neuropathic pain-like symptoms before surgery is predictive for chronic postoperative pain after TKR is unknown and requires investigation.

Animal models of OA have demonstrated injury to sensory nerves within subchondral bone,[15,28,50] increased expression of immunoreactivity markers (activating transcription factor-3) within the dorsal root ganglia, and spinal microglial activation, all suggestive of a neuropathic component.[28] In human OA, increased sensory nerve fiber densities have been seen in the meniscus,[8] and meniscal extrusion has been reported in patients with neuropathic pain-like symptoms,[45] indicating an association between the structural pathology of OA and the development of neuropathic pain.

Quantitative sensory testing (QST) aims at profiling the sensitivity of the pain system.[2] Lower pressure pain thresholds (PPTs) assessed distant to the knee, facilitated temporal summation of pain (TSP), and impaired conditioned pain modulation (CPM) have been found as signs of increased pain sensitization in patients with OA compared with control subjects.[7,38] Preoperative facilitated TSP has been associated with chronic postoperative pain after TKR[39] and total hip replacement,[29] indicating the importance of facilitated central pain mechanisms in OA pain.[3]

PainDETECT, like the Doleur Neuropathic 4 and the Leeds Assessment of Neuropathic Symptoms and Signs questionnaires, is a validated self-report questionnaire that can be used in patients with OA to evaluate of the likelihood of neuropathic pain.[24,26,35,36,45] Scores range from 0 to 38 with scores of ≥19 indicating likely neuropathic pain. Recently, Moss et al HYPERLINK \l "bib36" [36] found that patients with OA classified into the likely neuropathic pain group displayed lower PPTs around the knee, the lower leg, and the arm, indicating that the PainDETECT is associated with pain sensitization.

In this study, it was hypothesized that knee patients with OA with neuropathic pain-like symptoms before TKR surgery would report higher preoperative knee pain intensity with augmented central pain processing, assessed by widespread pain sensitization, CPM, and TSP, than those patients with OA with less neuropathic pain-like symptoms. It was further hypothesized that those patients with neuropathic pain-like symptoms and augmented pain processing before TKR are more likely to develop chronic postoperative pain 6 months after TKR surgery.

Methods

Study Participants

Fifty patients (mean age 66.4 years, standard deviation [SD] = 8.3, 60% women) with chronic knee OA awaiting TKR surgery were recruited from orthopedic clinics in Nottingham, United Kingdom. These participants were compared with 22 healthy control subjects (mean age 56.7 years, SD = 9.0, 59.1% women) with no symptomatic OA or a chronic pain condition who were recruited via local advertisement using posters at the University of Nottingham. The study was approved by the local ethics committee (REC reference: 10/H0408/115), all participants gave informed consent, and the procedures were performed according to the Declaration of Helsinki. Knee radiographs were obtained for the patients with OA (anterior-posterior, lateral, and skyline views) as part of their routine preoperative care and were graded using the Kellgren-Lawrence system for OA.[30] Patients with knee OA with associated symptomatic hip OA, psychiatric illness, active cancer, sensory dysfunction, contraindication to magnetic resonance imaging, or other chronic pain condition, such as fibromyalgia or rheumatoid arthritis, were excluded at the time of recruitment. All patients were asked not take any analgesic medication for 24 hours before the assessment. Healthy control subjects were free of any major medical, neurologic, or pain-related conditions.

Protocol

All participants completed the self-reported questionnaire PainDETECT to assess for neuropathic pain-like symptoms in OA pain. Participants were asked to record their responses with respect to their pain in the last 4 weeks and to answer each question specifically related to the osteoarthritic knee that was to be operated on. The total score can range from 0 to 38 with a higher score (≥19) indicative of neuropathic pain-like symptoms, a score of ≤12 representing a nociceptive pain phenotype, and a score of ≥13 but ≤18 indicative of a mixed pain phenotype.[17] The questionnaire has high

sensitivity and specificity, and good internal consistency.[18] Subjective knee pain intensity scores were recorded using the visual analogue scale (VAS, 0-10 cm) on the day of assessment. After completion of the PainDETECT questionnaire, QST was performed with the participants lying on a couch in the supine position in a quiet room. QST data were collected blinded with the examiner unaware of the PainDETECT questionnaire scores of all the participants. PPTs were recorded local and distant to the knee. Cuff algometry assessing pain thresholds and tolerance was done on the lower legs.[20] TSP assessment was based on VAS scores after 10 sequential cuff stimulations. CPM was assessed by cuff pain conditioning on 1 leg and assessment on the contralateral leg. Finally, the degree of temporal summation to cutaneous von Frey stimulation was assessed.

On average 57 (range 12.8-116) days elapsed between the assessment procedures and TKR. All patients were invited to return for a follow-up assessment at 6 months after TKR surgery to reassess their pain and repeat their QST assessments to determine which patients had developed chronic postoperative pain after TKR surgery. The postoperative QST assessment scores for the high PainDETECT and low PainDETECT groups were compared with the pain-free healthy control subjects' scores 6 months after TKR surgery to assess whether there had been any normalization of the sensitization profiles in those individuals or if some degree of pain sensitization remained after the surgery. Patients reporting significant postoperative knee pain with a VAS score of $\geq$4 assessed at the 6-month follow-up visit with a definitive change in pain quality after TKR assessed using the PainDETECT questionnaire were defined as having chronic postoperative pain, similar to previous studies.[1,10,43,46,54]

Pressure Algometry

Using a handheld pressure algometer (Somedic AB, Sösdala, Sweden), PPTs were assessed using a 1-cm^2 probe. A pressure was applied at 30 kPa/s until the subject first perceived a change in the pressure stimulus and it no longer felt like pressure but started to feel painful. At this point, the subject pressed a button and the pressure stimulus was removed, and the PPT value was recorded. For the patients with OA, PPTs were recorded on the side of the affected knee scheduled to be replaced; the left side was chosen for the healthy control subjects. Five sites were assessed. Site 1 was 3 cm medial to mid-point of the medial edge of patella. Site 2 was 2 cm proximal to superior lateral edge of patella. Site 3 was 2 cm proximal to superior medial edge of patella. Site 4 was the tibialis anterior muscle (5 cm distal to the tibial tuberosity) was chosen as a distant site to assess for spreading sensitization. Site 5, the extensor carpi radialis longus (ECRL) muscle (5 cm distal to the lateral epicondyle of the humerus), was selected as the remote site (arm) to assess for widespread hyperalgesia.[6] A 30-second interval between trials at assessment sites was kept. The PPTs were recorded in triplicates and averaged for each site for further analysis. Lower PPT values indicate increased pain sensitivity.

Cuff Pressure Algometry

A cuff algometer (NociTech and Aalborg University, Aalborg, Denmark) connected to a 13-cm-wide single chamber tourniquet cuff (VBM Medizinetechnik GmbH, Sulz, Germany) was used alongside a computer-controlled air compressor and an electronic 10-cm VAS rating system (Aalborg University) for cuff algometry assessment. The cuff was applied to the lower leg at the level of the gastrocnemius muscle ipsilateral to the affected knee in the patients with knee OA and the left side in the controls. The cuff was positioned with a 5-cm distance between the upper border of the cuff and the tibial tuberosity. The cuff was inflated automatically by a computer at the rate of 1 kPa/s until a maximum pressure limit of 100 kPa was reached. The participants used an electronic VAS to rate their pressure-induced pain intensity and were instructed to press a button to release the pressure. The VAS signal was sampled at 10 Hz and 0 and 10 cm on the scale were defined as no pain and maximum pain, respectively. The participants were all asked to rate the pressure-pain intensity continuously using the electronic VAS with the cuff pain detection threshold (PDT) being defined as the pressure value when the subject rated pain as 1 cm on the electronic VAS.[44,52] The cuff pain tolerance threshold (PTT) was defined as the maximum pressure at the point the subject had to press the release button as a result of the pain intensity being intolerable.

Temporal Pain Summation by Cuff Algometry

Ten repeated cuff pressure stimulations (1-second duration, 1-second interval) with an intensity equal to the PTT were delivered to the lower leg below the affected knee scheduled to be replaced in patients with OA and the left side in controls. participants were asked to rate the pain intensity continuously throughout the 10 pressure cuff stimulations using the electronic VAS and were informed not to return the VAS to zero between cuff stimulations. A constant pressure of 5 kPa was kept between each cuff stimulation to ensure the position of the cuff on the leg did move during the assessment. The VAS score immediately after the individual cuff stimuli was extracted. For the analysis of TSP the mean VAS score of the first to fourth cuff stimulations (VAS-I) was subtracted from the mean VAS score of the 8th to 10th cuff stimulations (VAS II), as used in similar studies.[38,52]

Conditioning Pain Modulation by Cuff Algometry

Two 13-cm-wide cuffs were used to conduct CPM assessment with 1 cuff on each leg over the gastrocnemius muscles. The painful conditioning cuff stimulus was inflated on the contralateral side, with the inflation pressure set equivalent to the subject's cuff PTT. Simultaneous reassessment of the subject's cuff PDT was performed with a second cuff on the ipsilateral lower leg (test stimulus). The CPM was defined as the difference

between the cuff PDT during the conditioning stimulus and the initial trial without it.

Von Frey–Induced TSP

A weighted 25.6-g von Frey stimulator (Aalborg University) was used to assess and induce cutaneous TSP. The monofilament was applied directly to the affected knee (5 cm proximal to the center of patella) in the patients with OA or the left knee in the healthy control subjects. All participants rated the pain intensity on a VAS. Consecutively, 10 monofilament stimulations were applied repeatedly to the same site on the subject's knee by the assessor, with a 1-second interstimulus interval. Participants were asked to rate the pain intensity of the first stimulation and the tenth stimulation. Temporal summation was calculated by assessing the difference in the VAS score of the tenth stimulation to the first stimulation.[6]

Statistical Analysis

The patients with OA were grouped based on the preoperative PainDETECT score. Patients with OA with a score of ≥19 indicating neuropathic pain-like symptoms were assigned to the high PainDETECT group and those with nociceptive or mixed pain based on PainDETECT score of <19 were assigned to the low PainDETECT group.[17] Healthy control subjects with no chronic pain condition or OA were recruited for comparison.

The data were analyzed using Prism 7.0 (GraphPad, La Jolla, CA). Parametric data were presented as the mean and SD with median and interquartile ranges being expressed for data that was nonparametric. In figures, data are presented as mean and standard error of the mean (SEM). Data were evaluated to determine whether they met the assumption of normality using the D'Agostino-Pearson omnibus normality test. An analysis of variance (ANOVA) with Tukey post hoc tests for normally distributed data, or Kruskal-Wallis ANOVA with Dunn's post hoc tests for the analysis of nonparametric data, was conducted for comparisons of age, body mass index, PPTs, TSP, and CPM among the 3 groups.

A mixed-model ANOVA was used to assess PPTs, cuff PDTs cuff PTT, cuff TSP, and von Frey induced TSP with group factors (high PainDETECT and low PainDETECT) as well as repeated factor time (before and after TKR) for data that were normally distributed. The Wilcoxon matched paired rank tests for nonparametric data was used to assess pre-TKR and post-TKR changes for the cuff CPM. Differences in gender distribution were assessed using a χ^2 test. Pain duration and VAS pain scores of the patients with OA were assessed between the high PainDETECT and low PainDETECT groups using the Mann-Whitney U test and unpaired t-tests, respectively.

Changes in pain quality were assessed by comparing the preoperative PainDETECT questionnaire scores with the 6-month post-TKR PainDETECT scores in the 2 pain subgroups (high PainDETECT and low PainDETECT). The paired t-tests were used to assess changes in PainDETECT scores for each group after TKR. In those patients who reported a post TKR VAS score of ≥4 at 6 months after surgery, the PainDETECT scores before and after TKR were assessed using a paired t-test to identify whether there had been a change in pain quality after surgery to confirm the diagnosis of chronic postoperative pain. An association between parameters was assessed by Pearson's correlation for parametric data and Spearman's correlation for nonparametric data. A P value <.05 was considered significant. Pre-TKR correlations between pain characteristics and QST measures were assessed using pooled data from all 3 groups and adjusted for multiple comparisons (Bonferroni). The associations between pre-TKR and post-TKR pain characteristics were by correlation analysis and significant preoperative factors were used in a linear stepwise regression to identify independent variables.

Results

Demographic Data and Pain Profiles

Analysis of the demographic data showed no differences in age (ANOVA, $F = 9.9$, $P = .0002$) between the high PainDETECT and low PainDETECT patients with OA (Tukey, $P = .78$), but significant differences between the high PainDETECT patients and healthy control subjects (Tukey, $P = .01$) and the low PainDETECT patients and healthy control subjects (Tukey, $P = .0001$) were seen (Table 1). There were no differences in body mass index (Kruskal-Wallis test, $H = 10.73$, $P = .005$) between the high PainDETECT and low PainDETECT patients with OA

Table 1. Patient and Healthy Control Subject Demographics

	High PainDETECT Knee OA (N = 15)	*Low PainDETECT Knee OA (N = 35)*	*Healthy Control Subjects (N = 22)*
PainDetect score (0-38)	23 (21-27)	10 (6-13)	0 (0-.25)*
Age, y	65.1 [8.9]	66.9 [8.0]	56.7 [9.0]*
Male:female	5:10	15:20	9:13
Female, %	66.6	57.1	59.1
Body mass index	30 (27-33.4)	30 (27-39)	26 (24-28.3)*
Kellgren and Lawrence Radiological Grade Knee OA	4 (3-4)	4 (3-4)	N/A
Pain duration, mo	61.4 (54.5-86.4)	54.5 (36.4-61.4)**	N/A
Peak pain VAS score in previous 24 h, cm	6.5 [2.1]	4.7 [2.3]**	N/A

Values are mean [SD] or median and (interquartile range) unless otherwise indicated.
* $P < .05$, significantly different from high the PainDETECT and the low PainDETECT groups.
** $P < .05$, significant differences between the high PainDETECT and the low PainDETECT groups.

(Dunn's, $P > .99$), but significant differences were seen between high PainDETECT patients and healthy control subjects (Dunn's, $P = .02$) and low PainDETECT patients and healthy controls (Dunn's, $P = .01$). In addition, no differences in gender distribution were seen between groups (χ^2 test, $P = .818$). Comparing the 2 OA groups, the high PainDETECT group had a longer duration of pain symptoms (Mann Whitney U-test, $P < .02$) and higher peak pain VAS scores (Unpaired t-test, $P < .02$) compared with low PainDETECT group. The structural radiologic assessment of the knee showed no difference between the OA groups, with both groups having a median Kellgren-Lawrence score of 4 (Table 1).

Forty-six patients returned for the reassessment at 6 months after the TKR surgery (92% follow-up). Regarding the 4 patients who failed to return, 1 was excluded from the study owing to a fracture that required revision surgery, and the other 3 patients were unable to be contacted after surgery. PainDETECT assessment based on their preoperative pain phenotype showed that 13 of the 15 high PainDETECT patients and 33 of the 35 low PainDETECT patients returned for follow-up. High PainDETECT patients reported higher postoperative VAS pain scores at 6 months after TKR surgery (4 cm, range .75-7 cm), compared with low PainDETECT patients (0 cm, range 0-1 cm, Mann Whitney U-test, $P = .0003$).

Pressure Algometry

Pre-TKR Assessments

Lower average PPTs around the knee PPT (Fig. 1; ANOVA, $F = 27.1$, $P < .0001$) were found in the high PainDETECT (Tukey, $P < .0001$) and low PainDETECT (Tukey, $P < .0001$) groups compared with the healthy controls. Further, lower PPTs (ANOVA, $F = 15.0$, $P < .001$) were found at the tibialis anterior muscle for the high PainDETECT group compared with the low PainDETECT group (Tukey, $P < .02$) and healthy controls (Tukey, $P < .001$) and for the low PainDETECT group compared with the healthy controls (Tukey, $P < .03$). Assessment of the ECRL muscle showed lower PPTs (ANOVA, $F = 13.8$, $P < .0001$) in the high PainDETECT (Tukey, $P < .0001$) and the low PainDETECT groups (Tukey, $P < .008$) compared with healthy control subjects.

Post-TKR Assessments

Six months after TKR, lower PPTs values were seen over the knee (Fig. 1; ANOVA, $F = 16.0$, $P < .0001$) when comparing the high PainDETECT group and healthy control subjects (Tukey, $P < .0001$) and the low PainDETECT group with the healthy control subjects (Tukey, $P = .001$). Lower PPTs after surgery were found over the tibialis anterior muscle (ANOVA, $F = 14.5$, $P < .0001$) in the high PainDETECT (Tukey, $P < .0001$) and the low PainDETECT groups (Tukey, $P = .02$) compared with the healthy control subjects. Significantly lower PPTs were seen over the ECRL muscle (ANOVA, $F = 11.2$, $P < .0001$) in the high PainDETECT patients compared with the healthy control subjects (Tukey, $P < .0001$). However, no differences were seen between the low PainDETECT patients with OA and healthy controls, indicating a normalization of widespread hyperalgesia after TKR surgery in those patients with OA with preoperative nociceptive or mixed OA pain.

Comparing Assessments Before and After TKR

A 2-way ANOVA (group, high PainDETECT vs low PainDETECT groups) × (time, before TKR vs after TKR) was

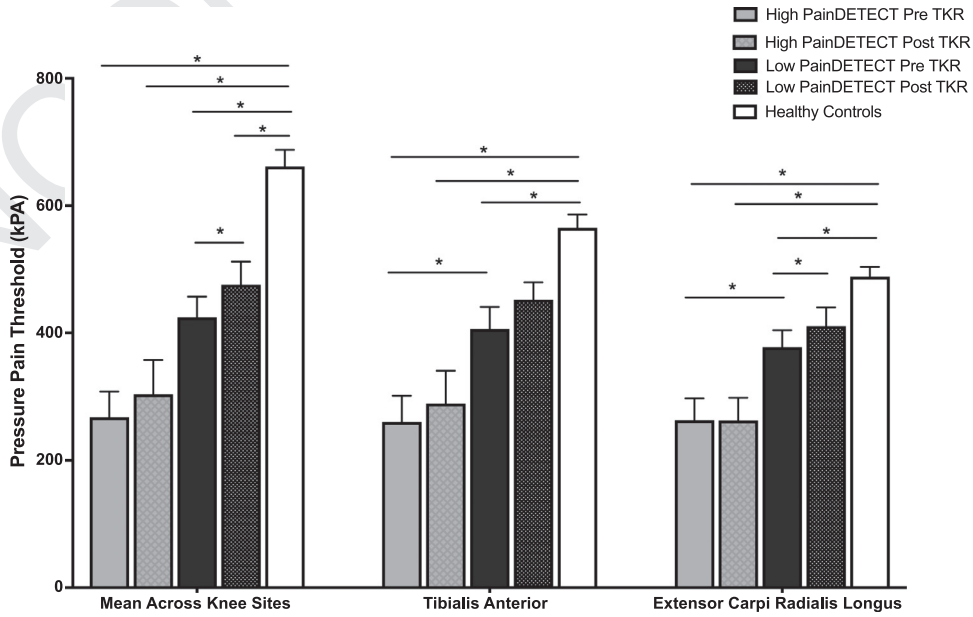

Fig. 1. Mean ± SEM PPTs assessed using pressure algometry patients with OA (high PainDETECT group, low PainDETECT group) and healthy controls. PPTs were assessed on the knee (mean of 3 sites), the tibialis anterior muscle, and the arm. Pre-TKR and 6-month post-TKR PPTs are shown. *$P < .05$.

conducted to assess how the mean knee, TA, and ECRL PPT scores differed between the 2 OA groups as a function of the TKR surgery. For the mean knee PPTs scores, there was a significant main effect of time (pre–post TKR surgery), $F(1,96) = 5.32$, $P = .02$, such that the mean knee PPTs were significantly higher after TKR surgery ($M = 437.1$, $SD = 211.9$) compared with pre TKR surgery ($M = 330.3$, $SD = 174.1$). There was no effect of group, $F(1,96) = 1.53$, $P > .05$, suggesting the mean knee PPTs scores in both OA groups were similar. There was also no significant interaction effect, $F(1,96) = .219$, $P > .05$.

For the tibialis anterior PPTs, no significant effect of group were seen, $F(1,96) = .5$, $P > .05$, with similar PPT scores in the high PainDETECT group ($M = 386.4$, $SD = 212.3$) and low PainDETECT groups ($M = 356.3$, $SD = 175.6$). There was also no significant effect of time (before vs after TKR) $F(1,96) = 3.148$ $P > .05$, or interaction $F(1,96) = .116$, $P > .05$.

Assessment of the ECRL PPTs showed a significant main effect of group, $F(1,96) = 14.77$, $P < .001$, such that the high PainDETECT patients ($M = 261.4$, $SD = 124$) had significantly lower ECRL PPTs than the low PainDETECT patients ($M = 393.9$, $SD = 162.7$). The main effect of time (pre–post TKR surgery) was not significant, $F(1,96) = .264$, $P > .05$. The interaction effect was also not significant, $F(1.96) = .203$, $P > .05$.

Cuff Pressure Algometry

Pre-TKR Compared With Controls

No significant differences in cuff PDTs (Kruskal-Wallis test, $H = .72$, $P > .05$) were seen when comparing the high PainDETECT group (Dunn's, $P > .05$) and low PainDETECT group (Dunn's, $P > .05$) with healthy controls. The PPTs results also were not significantly different (Kruskal-Wallis test, $H = .44$ $P > .05$) comparing high PainDETECT group (Dunn's, $P > .05$) and low PainDETECT group (Dunn's, $P > .05$) with healthy controls.

Post-TKR Compared With Controls

At 6 months after TKR, surgery both the high PainDETECT and low PainDETECT patients with OA showed no significant differences in postoperative cuff PDT and PTT thresholds to cuff stimulation when compared with the healthy control subjects (cuff PDT $P = .23$, cuff PTT $P = .50$, Kruskal-Wallis test).

Pre-TKR and Post-TKR in Patients With OA

No differences were seen in the preoperative cuff PDT scores, ANOVA, $F(1,42) = 2.463$, $P = .124$, and PTT scores, ANOVA, $F(1,42) = 1.61$, $P = .212$, between the high PainDETECT and low PainDETECT groups.

TSP by Cuff Algometry

Pre-TKR Compared With Control Subjects

Higher cuff TSP scores (Kruskal-Wallis test, $H = 10.64$ $P < .005$) were found in the high PainDETECT groups (Dunn's, $P < .01$) and low PainDETECT groups (Dunn's, $P < .04$) compared with healthy controls (Fig. 2).

Post-TKR Compared With Control Subjects

No significant differences were found comparing the post TKR cuff TSP scores of high PainDETECT groups (Dunn's, $P > .999$) or low PainDETECT groups (Dunn's, $P = .784$) with healthy control subjects (Fig. 2; Kruskal-Wallis test, $H = 3.26$ $P = .197$).

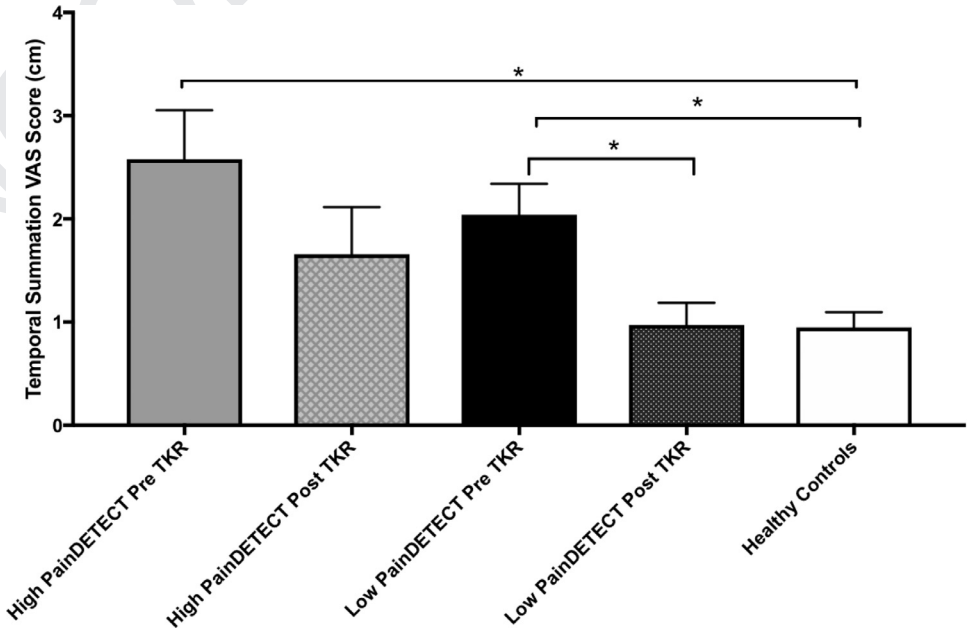

Fig. 2. Mean ± SEM cuff TSP scores for both OA groups (high PainDETECT and low PainDETECT) and healthy control subjects before and after TKR. *$P < .05$.

Pre-TKR and Post-TKR in Patients With OA

A 2-way ANOVA (group, high PainDETECT vs low PainDETECT) × (time, before TKR vs after TKR) was conducted to assess how the cuff TSP scores differs between the high PainDETECT and low PainDETECT groups as a function of TKR surgery. There was a significant main effect of time (pre–post TKR surgery), $F(1,96) = 8.69$, $P = .004$, such that the cuff TSP were significantly lower after TKR surgery (M = 1.11, SD = 1.39) compared with before TKR surgery (M = 2.13, SD = 1.75). There was no significant effect of group, F (1,96) = .75, $P > .05$, suggesting that the cuff TSP scores in both the high PainDETECT and low PainDETECT groups were similar were similar. There was also no significant interaction effect, $F(1,96) = 0$, $P > .05$.

Von Frey–Induced TSP

Pre-TKR Compared With Control Subjects

Higher preoperative von Frey–induced TSP VAS scores (Fig. 3, ANOVA, F = 35.7, $P < .0001$) were seen in high PainDETECT patients compared with healthy control subjects (Tukey, $P < .0001$) and low PainDETECT patients and healthy control subjects (Tukey, $P = .0006$).

Post-TKR Compared With Control Subjects

Increased (ANOVA, F = 8.3, $P = .0006$) von Frey–induced VAS scores were seen in high PainDETECT patients post-TKR surgery compared with healthy control subjects (Tukey, $P = .02$) but no difference was seen comparing low PainDETECT with healthy control subjects (Tukey, $P = .36$).

Pre-TKR and Post-TKR in Patients With OA

A 2-way ANOVA (group, high PainDETECT vs low PainDETECT) × (time, before TKR vs after TKR) was conducted to assess how the von Frey–induced TSP scores differ between the high PainDETECT and low PainDETECT groups as a function of TKR surgery. There was a significant main effect of time (pre–post TKR surgery), $F(1,96) = 8.82$, $P = .004$, such that the von Frey–induced TSP scores were significantly lower after TKR surgery (M = 2.13, SD = 2.22) compared with before TKR surgery (M = 3.54, SD = 2.29). There was no significant effect of group, F (1,96) = .75, $P > .05$, with similar von Frey–induced TSP scores in both high PainDETECT (mean = 3.17, SD = 2.31) and B (mean = 2.73, SD = 2.31). There was also no significant interaction (group × time) effect, $F(1,96) = 0$, $P > .05$.

Conditioning Pain Modulation

Before TKR Compared With Control Subjects

Preoperative assessment of conditioning pain modulation showed impaired CPM in high PainDETECT patients compared with healthy control subjects (Dunn's, $P = .012$, Fig. 4, Kruskal-Wallis test, H = 8.68, $P = .013$), but not the low PainDETECT compared with healthy control subjects.

Before TKR Compared With Control Subjects

After TKR surgery, no significant differences in CPM scores were found between high PainDETECT patients and healthy control subjects (Dunn's, $P = .1687$) or low PainDETECT patients and healthy controls (Dunn's, $P = .434$; Kruskal-Wallis test, H = 4.09, $P = .129$).

Before TKR and After TKR in Patients With OA

No significant differences were found between the pre-TKR CPM results between the high PainDETECT and low PainDETECT patients with OA (Dunn's, $P = .5198$, Fig. 4, Kruskal-Wallis test, H = 8.68, $P = .013$). At 6

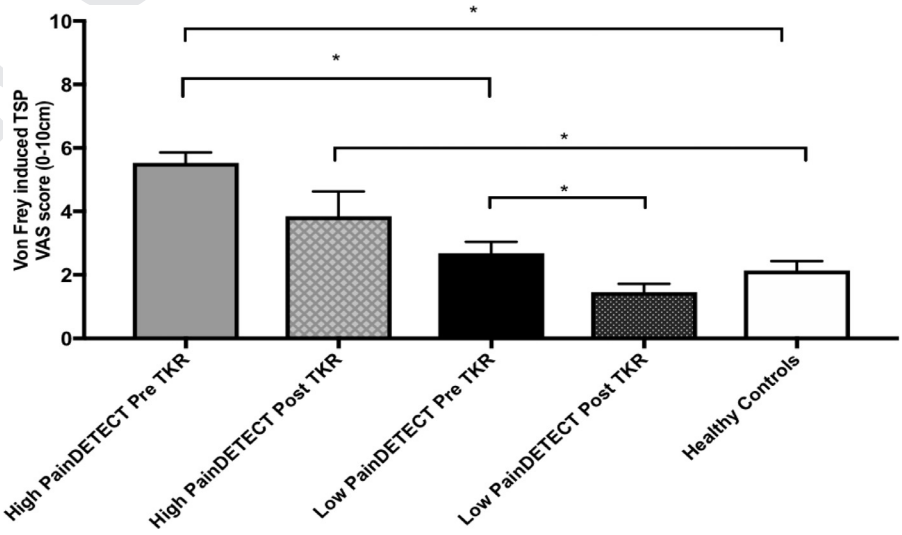

Fig. 3. Mean ± SEM Von Frey–induced TSP for both OA groups (high PainDETECT and low PainDETECT). Pre-TKR and post-TKR compared with healthy control subjects. *$P < .05$.

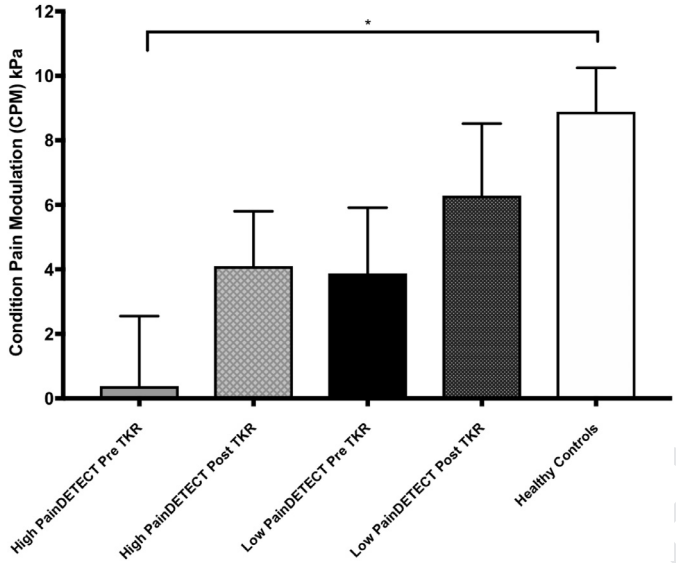

Fig. 4. Mean ± SEM CPM before and after TKR for patients with OA (high PainDETECT and low PainDETECT groups) and healthy control subjects (Kruskal-Wallis ANOVA by ranks test). *$P < .05$.

months after TKR surgery, no significant differences were seen when comparing the pre-TKR and post-TKR CPM scores of high PainDETECT patients (Wilcoxon, $P = .3804$) and low PainDETECT patients (Wilcoxon, $P = .4992$).

Incidence of Chronic Postoperative Pain After TKR Surgery in All Patients With OA

Fourteen patients (30.4%) were defined as having chronic postoperative pain at 6 months after TKR surgery with a VAS knee pain score of ≥4, with 8 patients originating from high PainDETECT group (53.3%) and 6 from the low PainDETECT group (17.1%) before surgery. A change in pain quality was identified in these patients with OA with chronic postoperative pain at 6 months after TKR surgery assessed using the PainDETECT questionnaire. These 14 patients preoperatively had a mean and SD PainDETECT score of 19.1 ± 7.8 and at 6 months post TKR their PainDETECT scores were 12.1 ± 8.5 (paired t-test, $P = .005$). Based on the thresholds used in the PainDETECT scoring those patients who continue to report severe postoperative pain after TKR had an altered pain quality after surgery with a change from neuropathic symptoms to more nociceptive pain after TKR surgery in keeping with the International Association for the Study of Pain definition of chronic postoperative pain defined by Werner et al.[55]

From the 32 responders to TKR surgery (VAS ≤ 3), 27 (84.4%) originated from low PainDETECT group and only 5 (15.6%) from high PainDETECT group. At 6 months after TKR, the PainDETECT questionnaire was repeated for all 46 patients who returned for follow-up. The patients with OA with high PainDETECT score before surgery showed a significant change in their pain quality after surgery with post-TKR PainDETECT scores of 13.7 ± 8.6, which was a -9.85-point improvement (SD = 8.7) in their score, (paired t-test, $P = .002$).

The low PainDETECT group patients also showed a significant decrease in their PainDETECT scores post TKR (preoperative PainDETECT score, mean = 9.3, SD = 4.4 vs postoperative PainDETECT, mean = 3.9 SD = 4.3, $P < .0001$, paired t-test).

Pre-TKR Correlations Between Pain Characteristics and QST

The preoperative PainDETECT score correlated with OA pain duration (Spearman's R = .6519, $P < .0001$) and preoperative pain VAS score (Spearman's R = .7836, $P < .001$). Table 2 outlines the correlations between preoperative pain VAS scores and each of the pre-TKR QST assessments.

Correlations Between Pre-TKR and Post-TKR Pain Characteristics and the QST

Correlation analysis revealed that preoperative PainDETECT (R = .397, $P = .003$), VAS (R = .413, $P = .004$), mean knee PPT (R = -.262, $P = .039$), and von

Table 2. Correlation of Preoperative QST Assessments to Preoperative Pain VAS Scores

Preoperative Assessment	Pearson's/Spearman's Correlation (r)	P Value
Mean knee PPT	Pearson	-.6792	<.0001
Tibialis anterior PPT	Pearson	-.5251	<.0001
ECRL PPT	Pearson	-.5115	<.0001
von Frey–induced TSP	Spearman	.5746	<.0001
Cuff TSP	Spearman	.4968	<.0001
Cuff CPM	Spearman	-.3403	NS
Cuff PDT	Spearman	-.02078	NS
Cuff PTT	Spearman	.04225	NS

NS, not significant.
Based on pooled data from groups all 3 groups. Pearson's correlation for parametric data and Spearman's correlation for nonparametric data.

Frey–induced TSP (R = .343, P = .010) were significantly associated with postoperative pain. A linear stepwise regression, including preoperative significant associated parameters, found that preoperative PainDETECT was the only independent factor associated with postoperative pain (crude coefficient .132, standard error .46, adjusted coefficient .397, t = 2.873, P = .006).

Discussion

This exploratory study found that patients with knee OA and preoperative neuropathic pain-like symptoms displayed greater knee pain intensity and duration, widespread hyperalgesia, facilitated TSP, and impaired CPM before surgery. This group of patients also demonstrated greater postoperative pain intensities after TKR compared with patients with knee OA with facilitated von Frey–induced TSP at 6 months after surgery compared with healthy control subjects. Finally, this study found that preoperative PainDETECT scores independently predicted postoperative pain.

Pre-TKR Neuropathic Pain-Like Symptoms in Knee OA and PainDETECT Questionnaire

Neuropathic pain-like symptoms (eg, burning, shooting, electric shock-like pain, and allodynia) have been reported in patients with knee OA.[26,47] Participants with knee OA awaiting TKR surgery in this study demonstrated a range of PainDETECT scores preoperatively; however, 30% of patients with OA had a PainDETECT score of ≥19, suggesting that they had features of neuropathic pain. Previous studies assessing pre-TKR patients with OA has demonstrated that the percentage of patients with high PainDETECT scores of ≥19 (range 5%–34%), indicating that our study findings are consistent with previously published data. Patients with OA with neuropathic pain-like symptoms reported longer knee OA pain duration and greater subjective knee pain intensity scores before TKR surgery, which may have contributed to the observed group differences seen postoperatively. It has been reported that greater knee pain intensity scores before surgery are predictive of chronic pain after TKR surgery[34,37] and that the longer duration of OA pain symptoms are associated with the development of central sensitization.[6] It is therefore possible that these 2 confounding factors seen in knee patients with OA with neuropathic pain-like symptoms may influence their outcomes at 6 months after TKR, but, from our regression model, neither factor was independently predictive, unlike the PainDETECT questionnaire, which demonstrated an association with the development of chronic postoperative pain after TKR surgery.

A high PainDETECT of ≥19 is, however, not diagnostic of neuropathic pain and the questionnaire can only be used as an assessment tool to identify the symptoms in patients with OA that are neuropathic pain-like. Treede et al[51] proposed an initial grading system for neuropathic pain, which has recently been updated[16] and identified 3 categories of possible, probable, and definite neuropathic pain. Possible neuropathic pain is based on the anatomic distribution of the pain, as well as the history from the patient. Probable neuropathic pain is present when there is the presence of measurable sensory deficit in the region that is anatomically neuropathic. A definite grade of neuropathic pain requires the use of diagnostic imaging tests confirming a lesion or disease explaining the neuropathic pain.

Post-TKR Neuropathic Pain-Like Symptoms

Neuropathic pain-like symptoms have been reported previously in patients with OA after TKR surgery; however, the reported estimates vary, ranging from 1% to 63%.[13,23,57] Buvanendran et al[13] showed that, at 6 months after TKR surgery, the rate of neuropathic pain characteristics was 5% in a prospective series of 120 patients; Wylde et al HYPERLINK \l "bib57" [57] reported the incidence of neuropathic pain characteristics to be 6% at 3 to 4 years after TKR in a retrospective study of 632 patients.

Reversal of Widespread Hyperalgesia after TKR Surgery

Increasing evidence suggests that preoperative widespread deep tissue hyperalgesia in patients with knee OA normalizes in pain-free patients who respond well to TKR surgery compared with healthy control subjects.[21,32] A recent study has shown that patients with OA with neuropathic pain-like symptoms based on the PainDETECT showed widespread hyperalgesia with lower PPTs and cold detection thresholds compared with patients with OA who have nociceptive pain-like symptoms.[36] In the present study, patients with OA who have neuropathic pain-like symptoms exhibited preoperative widespread hyperalgesia and increased pain sensitivity than those patients with OA with a more nociceptive or mixed pain phenotype. Furthermore, no significant postoperative improvement was seen in widespread hyperalgesia in the neuropathic pain-like group, which was in contrast with the nociceptive/mixed pain-like group, which demonstrated postoperative improvements in PPTs scores at the knee and the arm.

Finally, the current study demonstrated that preoperative PPTs assessed at the knee was associated with chronic postoperative pain. Previous reports in this field are mixed; most studies do not find this association, but recent evidence has found similar findings in both patients undergoing total hip replacements and TKRs.[40,58,59]

TSP

Facilitated preoperative TSP has been shown to be associated with chronic pain after TKR surgery[39,41] and for total hip replacement surgery.[29] This study is the first

study to evaluate TSP using cuff algometry in OA subgroups based on neuropathic pain-like symptoms. From the present study, normalization of TSP occurs in those patients who have nociceptive or mixed type pain preoperatively and this normalization does not occur in the neuropathic pain-like group. Significant correlations were also seen between preoperative cuff TSP score and the self-report PainDETECT questionnaire, indicating an association between the questionnaire and the central pain mechanisms in OA.

Conditioning Pain Modulation

Cuff algometry assessment is a valid and user-independent method of CPM with several studies showing good to excellent reliability in both healthy controls and patients with chronic pain.[19,20,27,52] The present study found impaired CPM in those patients with neuropathic pain-like symptoms preoperatively when compared with healthy controls. Studies have shown that an impaired CPM before surgery is associated for the development of chronic postoperative pain.[56,60] The current data demonstrate that patients who exhibit neuropathic pain-like symptoms before surgery are a subgroup characterized by impaired CPM and are at risk of developing chronic postoperative pain after TKR surgery.

PainDETECT and Central Pain Mechanisms

This study has shown that PainDETECT classifications are associated with central pain mechanisms in OA pain. Patients with high PainDETECT scores before TKR demonstrated local and widespread hyperalgesia, facilitated TSP, and impaired CPM compared with healthy controls; these patients seemed to be more pain sensitive than patients with nociceptive or mixed pain phenotypes. The correlation of QST measures used to identify the central integrative mechanisms and the PainDETECT questionnaire were also highly significant. Neuropathic pain-like scores were associated with the development of chronic postoperative pain after TKR and this information is supplemented by the significant correlations seen between preoperative VAS pain scores, cuff TSP, mean knee PPTs ,values and postoperative VAS pain scores. The PainDETECT questionnaire may have an additional role as an added construct to QST measures alongside subjective VAS scores and in identifying a subgroup of patients that are more likely to develop chronic postoperative pain after TKR surgery.

Moreton et al[35] showed that patients with knee OA with high PainDETECT scores demonstrated widespread sensitivity to PPTs and this finding was complemented by work by Hochman et al,[24] who showed that 45.6% of eligible OA knee pain cases in their series had ≥1 sign of sensitized central pain mechanisms on QST assessment (widespread hyperalgesia, facilitated TSP, or allodynia). In 20 patients with hip OA awaiting total hip replacement surgery, Gwilym et al[22] used functional brain magnetic resonance imaging and a reduced version of the German Research Network on Neuropathic Pain QST protocol to identify the relationship between PainDETECT score and signs of central mechanisms, which were sensitized. Patients with hip OA with preoperative PainDETECT scores above the sample median score showed significantly greater periaqueductal gray activity and were more pain sensitive to punctate stimuli compared with those with low PainDETECT scores.[22] Brummett et al[11,12] also studied the central pain mechanisms in OA and found that patients with OA with higher fibromyalgia survey scores assessed using the American College of Rheumatology Fibromyalgia Survey Criteria, as well as a more preoperative neuropathic pain phenotype were associated with a much poorer long-term outcomes after TKR and total hip replacement surgery. The higher fibromyalgia survey score was the strongest predictor variable of poor outcome after TKR and total hip replacement surgery, but because we excluded all patients with fibromyalgia at entry in this study, a direct comparison cannot be made. Both studies, however, have identified that subgroups of patients with different pain phenotypes knee OA exist and that a neuropathic preoperative component to the knee OA pain is a prognostic indicator for a poor outcome after TKR surgery.

Facilitated TSP before TKR surgery has been shown to predict poor outcome and postoperative pain at 12 months after TKR surgery. The current study did find preoperative TSP to be associated with postoperative pain, but TSP was not an independent factor. The present study did find the preoperative PainDETECT scores to be an independent factor that predicts postoperative pain. This finding therefore suggests that the PainDETECT questionnaire may provide additional value at identifying patients with central changes of pain facilitation in knee OA and can be used as a tool to predict postoperative pain after TKR surgery.

Benefits of QST and Neuropathic Pain Detection in OA and Future Direction

With the increasing use of the QST as a quantitative mechanistic assessment tool, it is becoming apparent that different subgroups of pain exist in patients with knee OA. This ability to stratify patients based on the degree of sensitization using the QST or neuropathic pain questionnaires like the PainDETECT will allow the assessment of patients for inclusion in future clinical trials evaluating new pharmacological and behavioral therapies to treat OA pain and allow the mechanistic profiling of joint pain to be conducted. With this mechanistic approach, it is hoped that in the future we can offer patients awaiting TKR surgery an individualized medical treatment for their pain based on their OA pain subgroup during surgery, which will improve their pain and reduce their risk of developing chronic postoperative pain after knee replacement surgery.

Study Limitations

This exploratory study is limited by the small sample size of the patients with knee OA and it is important that the results of this study be interpreted with care. However, Petersen et al[39] reported that preoperative

TSP was significantly different between patients with OA with severe chronic postoperative pain (mean = 2.18, SEM = .66) compared with patients with OA with less chronic postoperative pain (mean = .85, SEM = .21) after TKR. A sample size calculation with a power of 95% and a significance level of .05 showed that 46 patients were needed for this study.[39] Longitudinal studies are at risk of patients being lost to follow-up period; thus, 50 patients were recruited in this prospective study to account for dropouts. After recruitment of all patients with OA and healthy controls, it was noted that there was a significant difference in age between the 2 groups. However, a recent study by Petersen et al[38] has shown that dynamic pain mechanisms such as TSP and CPM used in this study are unaffected by age and are robust for studies with large age ranges and reliable for pain studies with long- term follow-up.

In addition, this study did not assess for sensory deficits in knee OA, which are diagnostic for neuropathic pain. Further research is required to explore the relationship between pain, neuropathic pain-like symptoms identified using the PainDETECT questionnaire, and the neurologic assessment of sensory deficits in knee patients with OA.

Conclusions

Patients with OA with neuropathic pain-like symptoms demonstrated preoperative widespread hyperalgesia, facilitated temporal pain summation, and impaired condition pain modulation. This patient group reported higher postoperative pain intensities after TKR surgery. We have demonstrated that preoperative PainDETECT scores are an independent predictor of postoperative pain after TKR surgery. The preoperative assessment of neuropathic pain-like symptoms and central pain mechanisms in patients with knee OA may aid clinicians in the decision-making process as to whether to embark on TKR surgery for that individual patient based on the likelihood of a successful outcome in terms of pain relief and satisfaction from the procedure. This technique may lead to improved medical advice being given to patients with OA with a stratified treatment approach and ultimately personalized therapy.

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