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Highlight Points of Paper

- Preoperative neuropathic pain like symptoms in knee OA can predict pain after TKR
- PainDETECT can identify neuropathic pain like symptoms in knee OA patients
- Central sensitization is present in OA patients with a neuropathic pain phenotype
- Subgrouping patients based on pain phenotype may explain chronic pain after TKR
- An individualised medical approach to OA patients may improve outcomes post-TKR

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

Thomas Kurien[1,2,3], Lars Arendt-Nielsen[4], Kristian K Petersen[4], Thomas Graven-Nielsen[5] and Brigitte E. Scammell [1,2,3*]

(1) Academic Orthopaedics, Trauma and Sports Medicine, University of Nottingham.
(2) Nottingham Elective Orthopaedic Service (NEOS), Nottingham University Hospitals NHS Trust, Nottingham, UK
(3) Arthritis Research UK Pain Centre, The University of Nottingham, UK
(4) SMI, Aalborg University, Denmark
(5) Center for Neuroplasticity and Pain (CNAP), SMI, Aalborg University, Denmark

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*Corresponding Author
Professor Brigitte E. Scammell DM, FRCS (Orth)
Academic Orthopaedics, Trauma and Sports Medicine
Arthritis Research UK Pain Centre

The University of Nottingham

Queen's Medical Centre

Nottingham, UK

Phone: +44 1158231115, Fax +44115823118, Email: b.scammell@nottingham.ac.uk

ABSTRACT

Preoperative pain characteristics in osteoarthritis (OA) patients may explain persistent pain after total knee replacement (TKR). Fifty patients awaiting TKR and 22 asymptomatic controls were recruited to evaluate the degree of neuropathic pain symptoms and pain sensitisation. OA patients were pain phenotyped into two groups based on the PainDETECT questionnaire: High PainDETECT group (scores ≥19) indicating neuropathic pain-like symptoms, Low PainDETECT group (scores <19) indicating nociceptive or mixed pain. Cuff algometry assessing pain detection thresholds (PDT) and pain tolerance (PTT) was conducted on the lower legs. Temporal summation of pain (TSP) was assessed using ten sequential cuff stimulations and a von Frey stimulator. Conditioning pain modulation was assessed by cuff pain conditioning on one leg and parallel assessment of PDT on the contralateral leg. Pressure pain thresholds (PPTs) were recorded by pressure handheld algometry local and distant to the knee. Knee pain intensity (VAS) and pain assessment were collected before and 6 months post-TKR. 30% of patients demonstrated neuropathic pain-like symptoms (High PainDETECT group). Facilitated TSP and reduced PPTs distant to the knee were found in High PainDETECT group compared to Low PainDETECT group and healthy controls groups ($p<0.001$). OA patients with High PainDETECT scores had higher postoperative VAS pain scores than the Low PainDETECT patients ($p<0.0001$) and facilitated TSP ($p=0.022$) compared with healthy controls.

Perspective

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

Keywords: Neuropathic Pain; Osteoarthritis; Total Knee Replacement; Postoperative Pain; Sensitization.

1.INTRODUCTION

Knee osteoarthritis (OA) pain has been traditionally attributed to the activation of peripheral nociceptors within the joint or peri-articular 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 OA patients 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 US, 3.5 million TKR's are expected to be performed by 2030 [33], however it is worrying that up to 20% of patients will develop chronic postoperative pain in spite of 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 localised 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 more at risk of developing postoperative knee pain remains an elusive goal for orthopaedic surgeons and researchers. Recent work subgrouping knee OA patients 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 preoperatively 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 fibre 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 sensitisation in OA patients compared with controls [7, 38]. Preoperative facilitated TSP has been associated with chronic postoperative pain following 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 (DN4) and the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaires is a validated self-report questionnaire which can be used in OA patients to evaluate of the likelihood of neuropathic pain [24, 26, 35, 36, 45]. Scores range from 0-38 with scores ≥19 indicating 'likely neuropathic pain'. Recently, Moss *et al* found that OA patients 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 [36].

In this study, it was hypothesised that knee OA patients with neuropathic pain-like symptoms before TKR surgery would report higher preoperative knee pain intensity with augmented central pain processing, assessed by widespread pain sensitisation, CPM and TSP, than those OA patients with less neuropathic pain-like symptoms. It was further hypothesised 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.

2. METHODS

Study Participants

Fifty patients (mean age 66.4 years [8.3 SD], 60 % women) with chronic knee OA awaiting TKR surgery were recruited from orthopaedic clinics in Nottingham, United Kingdom. These were compared to twenty-two healthy controls (mean age 56.7 years [9.0 SD], 59.1% women) with no symptomatic OA or 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 Helsinki declaration. Knee radiographs were obtained for the OA patients (anterior-posterior, lateral and skyline views) as part of their routine preoperative care which were graded using the Kellgren-Lawrence (K-L) system for OA [30]. Knee OA patients with associated symptomatic hip OA, psychiatric

illness, active cancer, sensory dysfunction, contraindication to MRI or other chronic pain condition e.g. fibromyalgia, rheumatoid arthritis, were excluded at the time of recruitment. All patients were asked not take any analgesic medication 24 hours prior to the assessment. Healthy controls were free of any major medical, neurological or pain related conditions.

Protocol

All subjects completed the self-reported questionnaire PainDETECT to assess for neuropathic pain-like symptoms in OA pain. Subjects were asked to record their responses in respect to their pain in the last four 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 ≤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, 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 subjects lying on a couch in the supine position in a quiet room. QST data was collected blinded with the examiner unaware of the PainDETECT questionnaire scores of all the subjects. PPTs were recorded local and distant to the knee. Cuff algometry assessing pain thresholds and tolerance was done on the lower legs [20]. Temporal summation of pain (TSP) assessment was based on visual analogue scale (VAS) scores following ten sequential cuff stimulations. Conditioning pain modulation (CPM) was assessed by cuff pain conditioning on one leg and assessment on the contralateral leg. Finally, the degree of temporal summation to cutaneous von Frey stimulation was assessed.

On average 57 (12.8 to 116) days elapsed between the assessment procedures and TKR. All patients were invited to return for follow up assessment 6-months post 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 to the pain free healthy controls scores 6 months after TKR surgery to assess if there had been any normalization of the sensitization profiles in those individuals or if some degree of pain sensitization remained post-surgery. Patients reporting significant postoperative knee pain

with a VAS score ≥4 assessed at the six-month follow up with a definitive change in pain quality post-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 hand-held pressure algometer (Somedic AB, 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 OA patients, PPTs were recorded on the side of the affected knee due to be replaced, however the left side was chosen for the healthy controls. Five sites were assessed. Site 1: 3 cm medial to mid-point of the medial edge of patella. Site 2: 2 cm proximal to superior lateral edge of patella. Site 3: 2 cm proximal to superior medial edge of patella. Site 4: 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-s 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, 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, Denmark) 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 knee OA patients 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 automatically inflated by a computer at the rate of 1 kPa/s until a maximum pressure limit of 100 kPa was reached. The subjects 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 subjects 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 PTT were delivered to the lower leg below the affected knee due to be replaced in OA patients and the left side in controls. Subjects 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 following the individual cuff stimuli was extracted. For the analysis of TSP the mean VAS score of the 1st to 4th cuff stimulations (VAS-I) was subtracted from the mean VAS score of the 8th to 10th cuff stimulations (VAS II), as previously used in similar studies [38, 52].

Conditioning Pain Modulation by Cuff Algometry

Two 13 cm wide cuffs were used to conduct CPM assessment with one 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 cPTT. Simultaneous re-assessment of the subject's cPDT was performed with a second cuff on the ipsilateral lower leg (test stimulus). CPM was defined as the difference between the cPDT during the conditioning stimulus and the initial trial without it.

Von Frey induced Temporal Summation of Pain

A weighted 25.6 g von Frey stimulator (Aalborg University, Aalborg, Denmark) was used to assess and induce cutaneous temporal summation of pain. The monofilament was applied directly to the affected knee (5 cm proximal to the centre of patella) in the OA patients or

the left knee in the healthy controls. All subjects 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 inter-stimulus interval. Subjects were asked to rate the pain intensity of the first stimulation and the 10th stimulation. Temporal summation was calculated by assessing the difference in the VAS score of the 10th stimulation to the 1st stimulation [6].

Statistical analysis

The OA patients were grouped based on the preoperative PainDETECT score. OA patients with a score ≥19 indicating neuropathic pain-like symptoms were assigned to the High PainDETECT group, and those with nociceptive or mixed pain based on PainDETECT score <19 were assigned to the Low PainDETECT group [17]. The healthy controls with no chronic pain condition or osteoarthritis were recruited for comparison.

The data was analysed using Prism 7.0. Parametric data was presented as the mean and standard deviation with median and interquartile ranges (IQR) being expressed for data that was non-parametric. 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 non-parametric data, was conducted for comparisons of age, BMI, PPTs, TSP and CPM between the three groups.

A mixed-model ANOVA was used to assess PPTs, cuff PDT'S cuff PTT, cuff TSP and von Frey induced TSP with group factors (High PainDETECT and Low PainDETECT) as well as repeated factor time (pre-TKR and post-TKR) for data that was normally distributed. The Wilcoxon Matched Paired Rank Tests for non-parametric data was used to assess pre and post-TKR changes for cuff CPM. Differences in gender distribution were assessed using a chi-square test. Pain Duration and VAS pain scores of the OA patients 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 questionnaires scores to the six-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 post-TKR. In those patients who reported a post TKR VAS score of ≥4 six months after surgery the pre and post TKR PainDETECT scores were assessed using a paired T –Test to identify if there had been a change in pain quality after surgery to confirm the diagnosis of chronic postoperative pain. Association between parameters was assessed by Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. $P< 0.05$ was considered significant. Pre-TKR correlations between pain characteristics and QST measures were assessed using pooled data from all three 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.

3.0 RESULTS

Demographic data and pain profiles

Analysis of the demographic data showed no differences in age (ANOVA: $F=9.9$, $p=0.0002$) between the High PainDETECT and Low PainDETECT OA patients (Tukey: $p=0.78$) but significant differences between the High PainDETECT patients and healthy controls (Tukey: $p=0.01$) and Low PainDETECT patients and healthy controls (Tukey: $p=0.0001$) were seen (Table 1). There were no differences in BMI (Kruskal-Wallis test: $H=10.73$ $p=0.005$) between the High PainDETECT and Low PainDETECT OA patients (Dunn's: $p>0.99$) but significant differences were seen between High PainDETECT patients and healthy controls (Dunn's: $p=0.02$) and Low PainDETECT patients and healthy controls (Dunn's: $p=0.01$). In addition, no significant differences in gender distribution were seen between groups (Chi-Squared Test: $p=0.818$). Comparing the two OA groups, the High PainDETECT group had a longer duration of pain symptoms (Mann Whitney U-Test: $p<0.02$) and higher peak pain VAS scores (Unpaired t-Test: $p<0.02$) compared with Low PainDETECT group. The structural radiological assessment of the knee showed no difference between the OA groups with both groups having a median K-L score of 4 (Table 1).

Forty-six patients returned for the re-assessment 6-months post TKR surgery (92% follow up). Regarding the four patients that failed to return; one was excluded from the study due to a fracture which required revision surgery and the other three patients we were unable to contact postoperatively. PainDETECT assessment based on their preoperative pain phenotype showed that 13/15 High PainDETECT patients and 33/35 Low PainDETECT

patients returned for follow up. High PainDETECT patients reported higher postoperative VAS pain scores six months after TKR surgery (4 cm [0.75-7]), compared to Low PainDETECT patients (0 cm [0-1]; Mann Whitney U-Test: p=0.0003).

Pressure Algometry

Pre-TKR assessments: Lower average PPTs around the knee PPT (Fig. 1; ANOVA: F =27.1, p<0.0001) were found in the High PainDETECT (Tukey: p<0.0001) and Low PainDETECT groups (Tukey: p<0.0001) compared with the healthy controls. Further, lower PPTs (ANOVA: F=15.0, p<0.001) were found at the tibialis anterior muscle for the High PainDETECT group compared with Low PainDETECT group (Tukey: p<0.02) and healthy controls (Tukey: p<0.001) and for Low PainDETECT group compared with the healthy controls (Tukey's: p<0.03). Assessment of the ECRL muscle showed lower PPTs (ANOVA: F=13.8, p<0.0001) in High PainDETECT (Tukey: p<0.0001) and Low PainDETECT groups (Tukey: p<0.008) compared to Healthy controls.

Post-TKR assessments: Six months post TKR lower PPTs values were seen over the knee (Fig. 1; ANOVA: F=16.0, p<0.0001) comparing the High PainDETECT group and healthy controls (Tukey: p<0.0001) and the Low PainDETECT group to the healthy controls (Tukey: p=0.001). Lower PPTs postoperatively were found over the tibialis anterior muscle (ANOVA: F=14.5, p<0.0001) in High PainDETECT (Tukey: p<0.0001) and Low PainDETECT groups (Tukey: p=0.02) compared with the healthy controls. Significantly lower PPTs were seen over the ECRL muscle (ANOVA: F=11.2, p<0.0001 in the High PainDETECT patients compared to the healthy controls (Tukey: p<0.0001). However, no differences were seen between the Low PainDETECT OA patients and healthy controls, indicating normalization of widespread hyperalgesia post TKR surgery in those OA patients with preoperative nociceptive or mixed OA pain.

Comparing pre and post-TKR assessments: A two-way ANOVA (Group: High PainDETECT vs Low PainDETECT groups) x (Time: Pre TKR vs Post TKR) was conducted to assess how the mean knee, TA and ECRL PPT scores differed between the two 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=0.02, such that the mean knee PPTs were significantly higher post TKR surgery (M=437.1 SD= 211.9) compared to pre TKR surgery (M=330.3 SD=174.1). There was no significant effect of Group: F(1,96) =1.53, p>0.05

suggesting the mean knee PPTs scores in both OA groups were similar. There was also no significant interaction effect F(1,96)=0.219, p>0.05.

For the tibialis anterior PPTs, no significant effect of group were seen F(1,96) = 0.5, p>0.05 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 (Pre vs Post TKR) F(1,96)=3.148 p>0.05 or interaction F (1,96) =0.116 , p>0.05.

Assessment of the ECRL PPTs showed a significant main effect of group F (1,96) = 14.77, p<0.001 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) = 0.264, p>0.05. The interaction effect was also not significant: F (1.96) = 0.203, p>0.05.

Cuff Pressure Algometry

Pre-TKR compared with controls: No significant differences in cuff PDTs (Kruskal-Wallis Test: H=0.72 p>0.05) were seen comparing High PainDETECT (Dunn's: p>0.05) and Low PainDETECT (Dunn's: p>0.05) to healthy controls. The PPTs results also were not significantly different (Kruskal-Wallis Test: H=0.44 p>0.05) comparing High PainDETECT (Dunn's: p>0.05) and Low PainDETECT (Dunn's: p>0.05) to healthy controls.

Post-TKR compared with controls: Six months post TKR surgery both High PainDETECT and Low PainDETECT OA patients showed no significant differences in postoperative cuff PDT and PTT thresholds to cuff stimulation compared to the healthy controls (cuff PDT: p=0.23; cuff PTT: p=0.50; Kruskal-Wallis Test).

Pre-TKR and Post-TKR in OA patients: No differences were seen in the preoperative cuff PDT (ANOVA: F (1,42) = 2.463, p=0.124) and PTT (ANOVA: F (1,42) = 1.61, p=0.212) scores between the High PainDETECT and Low PainDETECT groups.

Temporal Summation of Pain by Cuff Algometry

Pre-TKR compared with controls: Higher cuff TSP scores (Kruskal-Wallis Test: H=10.64 p<0.005) were found in High PainDETECT (Dunn's: p<0.01) and Low PainDETECT groups (Dunn's: p<0.04) compared to healthy controls (Fig. 2).

Post-TKR compared with controls: No significant differences were found comparing the post TKR cuff TSP scores of High PainDETECT (Dunn's: p>0.999) or Low PainDETECT (Dunn's: p=0.784) groups to healthy controls (Fig. 2; Kruskal-Wallis Test: H=3.26 p=0.197).

Pre-TKR and Post-TKR in OA patients: A two-way ANOVA (Group: High PainDETECT vs Low PainDETECT) x (Time: Pre TKR vs Post 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) $F(1,96) = 8.69$, $p=0.004$, such that the cuff TSP were significantly lower post TKR surgery (M=1.11 SD=1.39) compared to pre TKR surgery (M=2.13 SD=1.75). There was no significant effect of Group: $F(1,96) = 0.75$, $p>0.05$ suggesting the cuff TSP scores in both the High PainDETECT and Low PainDETECT groups were similar were similar. There was also no significant interaction effect $F(1,96)=0$, $p>0.05$.

Von Frey induced Temporal Summation of Pain

Pre-TKR compared with controls: Higher preoperative von Frey induced TSP VAS scores (Fig. 3, ANOVA: $F=35.7$ $p<0.0001$) were seen in High PainDETECT patients compared to healthy controls (Tukey: $p<0.0001$) and Low PainDETECT patients and healthy controls (Tukey: $p=0.0006$).

Post-TKR compared with controls: Increased (ANOVA: $F= 8.3$, $p=0.0006$) von Frey induced VAS scores were seen in High PainDETECT patients post-TKR surgery compared with healthy controls (Tukey's: $p=0.02$) but no difference was seen comparing Low PainDETECT with healthy controls (Tukey's: $p=0.36$).

Pre-TKR and Post-TKR in OA patients: A two-way ANOVA (Group: High PainDETECT vs Low PainDETECT) x (Time: Pre TKR vs Post TKR) was conducted to assess how the von Frey induced 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) $F(1,96) = 8.82$, $p=0.004$, such that the von Frey induced TSP scores were significantly lower post TKR surgery (M=2.13 SD=2.22) compared to pre TKR surgery (M=3.54 SD=2.29). There was no significant effect of Group: $F(1,96) = 0.75$, $p>0.05$ with similar von Frey induced TSP scores in both High PainDETECT (M 3.17 SD 2.31) and B (M=2.73 SD 2.31). There was also no significant interaction (Group x Time) effect $F(1,96)=0$, $p>0.05$.

Conditioning Pain Modulation

Pre-TKR compared with controls: Preoperative assessment of conditioning pain modulation showed impaired CPM in High PainDETECT patients compared to healthy controls (Dunn's: p=0.012), (Fig. 4; Kruskal-Wallis Test: H=8.68, p=0.013) but not the Low PainDETECT compared with healthy controls.

Post-TKR compared with controls: Following TKR surgery no significant differences in CPM scores were found between High PainDETECT patients and healthy controls (Dunn's: p=0.1687) or Low PainDETECT patients and healthy controls (Dunn's: p=0.434; Kruskal-Wallis Test: H=4.09, p=0.129).

Pre-TKR and Post-TKR in OA patients: No significant differences were found between the pre TKR CPM results between High PainDETECT and Low PainDETECT OA patients, (Dunn's: p=0.5198) (Fig. 4; Kruskal-Wallis Test: H=8.68, p=0.013). Six-months post TKR surgery no significant differences were seen when comparing the pre and post TKR CPM scores of High PainDETECT patients (p=0.3804, Wilcoxon) and Low PainDETECT patients (p=0.4992, Wilcoxon).

Incidence of Chronic Postoperative Pain after TKR surgery in all OA Patients

Fourteen patients (30.4%) were defined as having chronic postoperative pain six months following TKR surgery with a VAS knee pain score of ≥4, with eight patients originating from High PainDETECT group (53.3%) and six from Low PainDETECT group (17.1%) preoperatively. A change in pain quality was identified in these OA patients with chronic postoperative pain six months after TKR surgery assessed using the PainDETECT questionnaire. These fourteen patients preoperatively had a mean and SD PainDETECT score of 19.1 +/- (7.8) and 6 months post TKR their PainDETECT scores were 12.1 +/- (8.5), p=0.005, (paired T-Test). Based on the thresholds used in the PainDETECT scoring those patients that 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 following TKR surgery in keeping with the IASP 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 five (15.6%) from High PainDETECT group. Six months post-TKR

the PainDETECT questionnaire was repeated in all forty-six patients that returned for follow up. The OA patients with High PainDETECT score preoperatively showed a significant change in their pain quality post-surgery with a post-TKR PainDETECT scores of 13.7 +/- 8.6 (mean and SD), which was a -9.85 (+/-8.7) point improvement in their score, (p=0.002, paired T-Test).

The Low PainDETECT group patients also showed a significant reduction in their PainDETECT scores post TKR (Pre op mean and standard deviation PainDETECT score 9.3 (+/-4.4) to Post op PainDETECT 3.9 (+/-4.3), p<0.0001, (paired T-Test).

Pre-TKR correlations between pain characteristics and QST

The preoperative PainDETECT score correlated with OA pain duration (Spearman's R= 0.6519, p<0.0001) and preoperative pain VAS score (Spearman's R= 0.7836, p<0.001).

Table 2 outlines the correlations between preoperative pain VAS scores to each of the pre-TKR QST assessments.

Correlations between pre-TKR and post-TKR pain characteristics and QST

Correlation analysis revealed that preoperative PainDETECT (R = 0.397, p = 0.003), VAS (R = 0.413, p = 0.004), mean knee PPT (R = -0.262, p = 0.039) and von Frey induced TSP (R = 0.343, p = 0.010) were significantly associated with postoperative pain. A linear stepwise regression, including preoperative significant associated parameters found that preoperative PainDETECT was only independent factor associated with postoperative pain (crude coefficient: 0.132 (Standard error: 0.46), adjusted coefficient: 0.397 (t = 2.873), p= 0.006).

4.0 DISCUSSION

This explorative study found that knee OA patients with preoperative neuropathic pain-like symptoms displayed higher knee pain intensity and duration, widespread hyperalgesia, facilitated TSP, and impaired CPM preoperatively. This group of patients also demonstrated higher postoperative pain intensities post-TKR compared with knee OA patients with facilitated von Frey induced TSP six months after surgery compared with healthy controls. 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 (e.g. 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 OA patients had a PainDETECT score ≥19 suggesting they had features of neuropathic pain. Previous studies assessing pre-TKR OA patients has demonstrated that the percentage of patients with high PainDETECT scores ≥19 ranges from 5-34% indicating that our study findings are consistent with previously published data. OA patients with neuropathic pain like symptoms reported longer knee OA pain duration and higher subjective knee pain intensity scores prior to TKR surgery which may have contribute to the observed group differences seen postoperatively. It has been reported that higher knee pain intensity scores preoperatively are predictive for 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 two confounding factors seen in knee OA patients with neuropathic pain like symptoms may influence their outcomes six months post TKR but from our regression model neither were independently predictive unlike the PainDETECT questionnaire which demonstrated an association with the development of chronic postoperative pain after TKR surgery.

A high PainDETECT ≥19 is however, not diagnostic of neuropathic pain and the questionnaire can only be used as an assessments tool to identify the symptoms in OA patients that are neuropathic pain-like. Treede *et al.* proposed an initial grading system for neuropathic pain [51] which has recently been updated [16] and identified three categories of possible, probable and definite neuropathic pain. Possible neuropathic pain is based on the anatomical 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 OA patients following TKR surgery, however, the reported estimates vary, ranging from 1-63% [13, 23, 57]. Buvanendran *et al* showed that six months post TKR surgery the rate of neuropathic pain characteristics was 5% in a prospective series of 120 patients [13] and Wylde *et al.* reported the incidence of neuropathic pain characteristics was 6% three to four years after TKR in a retrospective study of 632 patients [57].

Reversal of Widespread Hyperalgesia after TKR Surgery

Increasing evidence suggests that preoperative widespread deep tissue hyperalgesia in knee OA patients normalises in pain-free patients who respond well to TKR surgery compared with healthy controls [21, 32]. A recent study has shown that OA patients with neuropathic pain-like symptoms based on the PainDETECT showed widespread hyperalgesia with lower PPTs, and cold detection thresholds compared to OA patients nociceptive pain-like symptoms [36]. In the present study, OA patients with neuropathic pain-like symptoms exhibited preoperative widespread hyperalgesia and increased pain sensitivity than those OA patients with a more nociceptive/mixed pain phenotype. Further, no significant postoperative improvement was seen in widespread hyperalgesia in the neuropathic pain-like group, which was in contrast to 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 where most studies do not find this association but recent evidence have found similar findings in both patients undergoing total hip and total knee replacements [40, 58, 59].

Temporal Summation of Pain

Facilitated preoperative temporal summation of pain 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 temporal summation of pain using cuff algometry in OA subgroups based on neuropathic pain like symptoms. From the present study, normalization of TSP

occurs in those patients that have nociceptive or mixed 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 the association between the questionnaire and the central pain mechanisms in OA.

Conditioning Pain Modulation

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

PainDETECT and Central Pain Mechanisms

This study has shown that PainDETECT classifications are associated to central pain mechanisms in OA pain. Patients with high PainDETECT scores pre-TKR demonstrated local and widespread hyperalgesia, facilitated TSP and impaired CPM compared with healthy controls and that these patients seemed to be more pain sensitive than patients with nociceptive/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.* showed that knee OA patients with high PainDETECT scores demonstrated widespread sensitivity to PPTs [35] and this was complemented by work by

Hochman *et al.* who showed that 45.6% of eligible OA knee pain cases in their series had at least one sign of sensitised central pain mechanisms on QST assessment (widespread hyperalgesia, facilitated TSP or allodynia) [24]. In 20 patients with hip OA awaiting total hip replacement surgery, Gwilym *et al.* used functional brain MRI and a reduced version of the German Research Network on Neuropathic Pain (DFNS) QST protocol, to identify he relationship between PainDETECT score and signs of central mechanisms which were sensitized. Hip OA patients with preoperative PainDETECT scores above the sample median score showed significantly higher peri-aqueductal gray (PAG) activity and were more pain sensitive to punctate stimuli compared to those with low PainDETECT [22]. Brummett *et al* also studied the central pain mechanisms in OA and found that OA patients 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 outcome after TKR and total hip replacement (THR) surgery[11, 12]. The higher fibromyalgia survey score was the strongest predictor variable of poor outcome after TKR and THR surgery but as 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 pre-TKR surgery has been shown to predict poor outcome and postoperative pain 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 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 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 QST or neuropathic pain questionnaires like the PainDETECT questionnaire will allow the assessment of patients for

inclusion in future clinical trials evaluating new pharmacological and behavioural therapies to treat OA pain and allow the mechanistic profiling of joint pain to be conducted. With this mechanistic approach, it is hoped in the future we can offer patients awaiting TKR surgery an individualised medical treatment for their pain based on their OA pain subgroup peri-operatively which will improve their pain and reduce their risk of developing chronic postoperative pain after knee replacement surgery.

Study Limitations

This explorative study is limited by the small sample size of the knee OA patients and it is important that the results of this study should be interpreted with care. However, Petersen *et al* 2015 reported that preoperative TSP was significantly different between OA patients with severe chronic postoperative pain (mean: 2.18, SEM: 0.66) compared with OA patients with less chronic postoperative pain (mean: 0.85, SEM: 0.21) following TKR. A sample size calculation with a power of 95% and a significant level 0.05 yielded that 46 patients were needed for this study [39]. Longitudinal studies are at risk of patients being lost during the follow up period thus 50 patients were recruited in this prospective study to account for drop-outs. After recruitment of all OA patients and healthy controls it was noted that there was a significant difference in age in years between the two groups. However a recent study by Petersen *et al* 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[38].

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 neurological assessment of sensory deficits in knee OA patients.

CONCLUSIONS

OA patients with neuropathic pain-like symptoms demonstrated preoperative widespread hyperalgesia, facilitated temporal pain summation and impaired condition pain modulation and this patient group reported higher postoperative pain intensities after TKR surgery. We have demonstrated that preoperative PainDETECT scores are an independent predictor for postoperative pain after TKR surgery. Preoperative assessment of neuropathic pain like

symptoms and central pain mechanisms in knee OA patients 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 may lead to improved medical advice being given to OA patients with a stratified treatment approach and ultimately personalised therapy.

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FIGURE LEGENDS

Figure 1. Mean (+ SEM) pressure-pain thresholds assessed using pressure algometry OA patients (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 on the arm. Pre and 6-month post TKR PPTs are shown. Significantly different PPTs are illustrated (*, $p<0.05$).

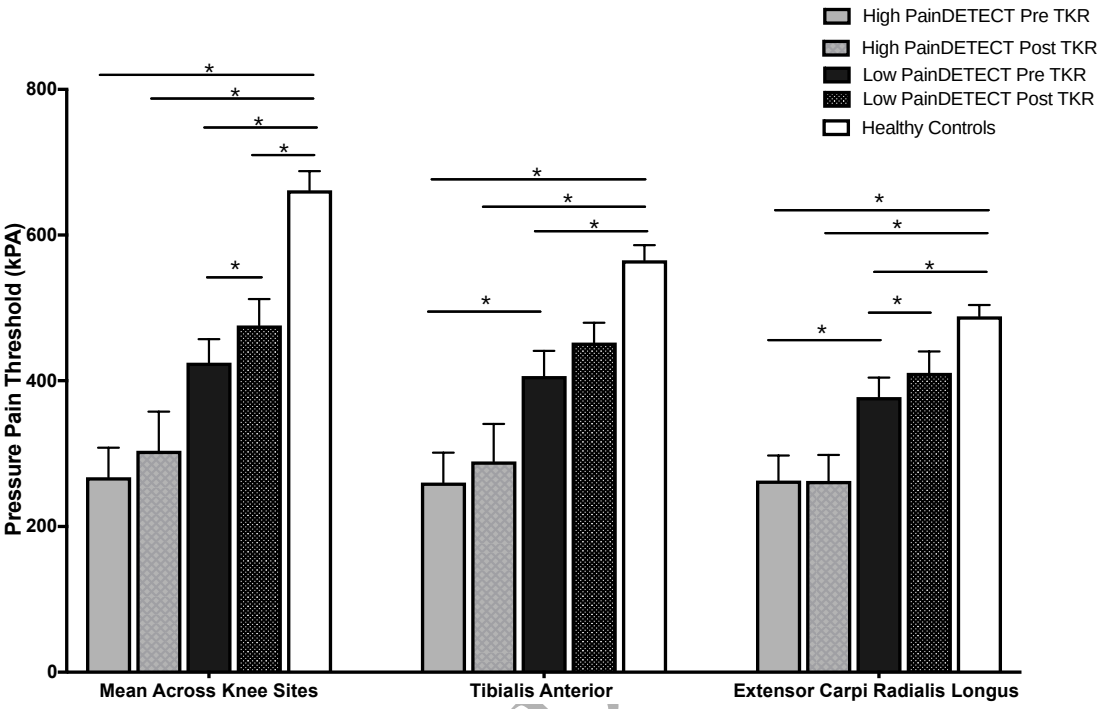

Figure 2. Mean (± SEM) cuff Temporal Pain Summation scores for both OA groups (High PainDETECT and Low PainDETECT) and Healthy controls Pre and Post TKR. Significantly differences are illustrated (*, $p<0.05$).

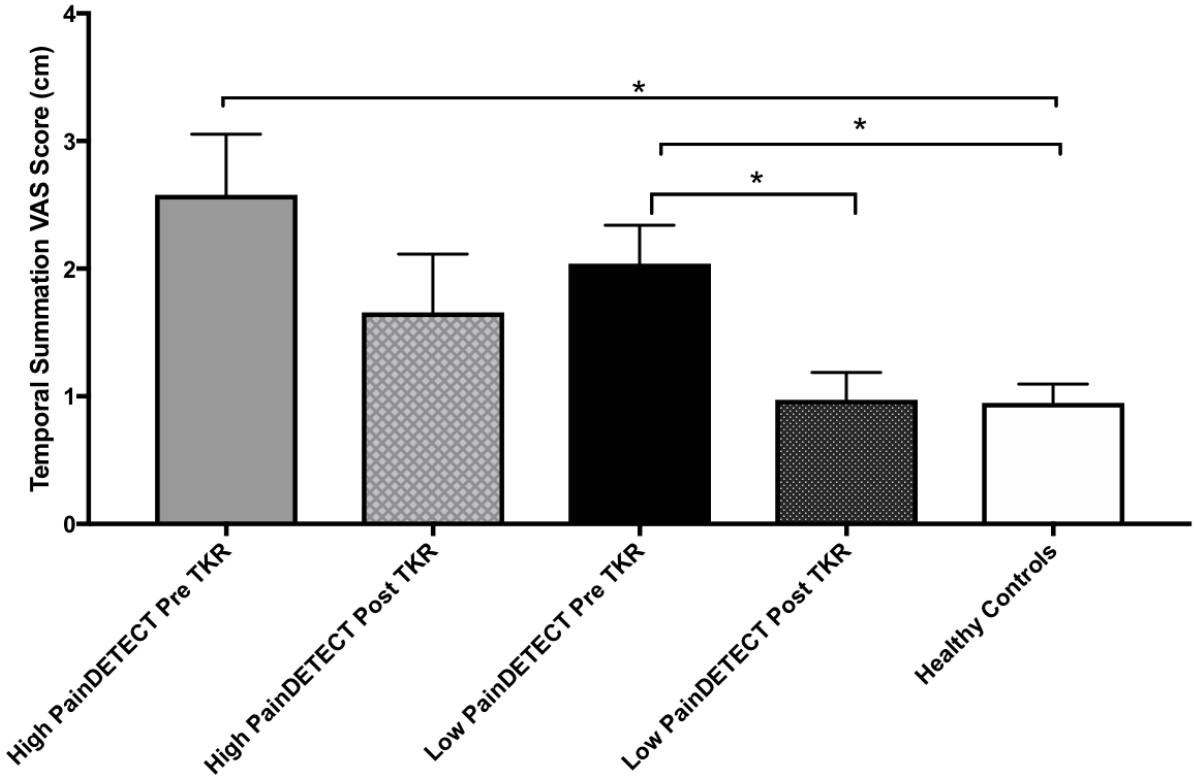

Figure 3. Mean (± SEM) Von Frey induced Temporal Summation of pain for both OA Groups (High PainDETECT and Low PainDETECT). Pre and Post TKR compared with Healthy controls Significantly differences are illustrated (*, p<0.05).

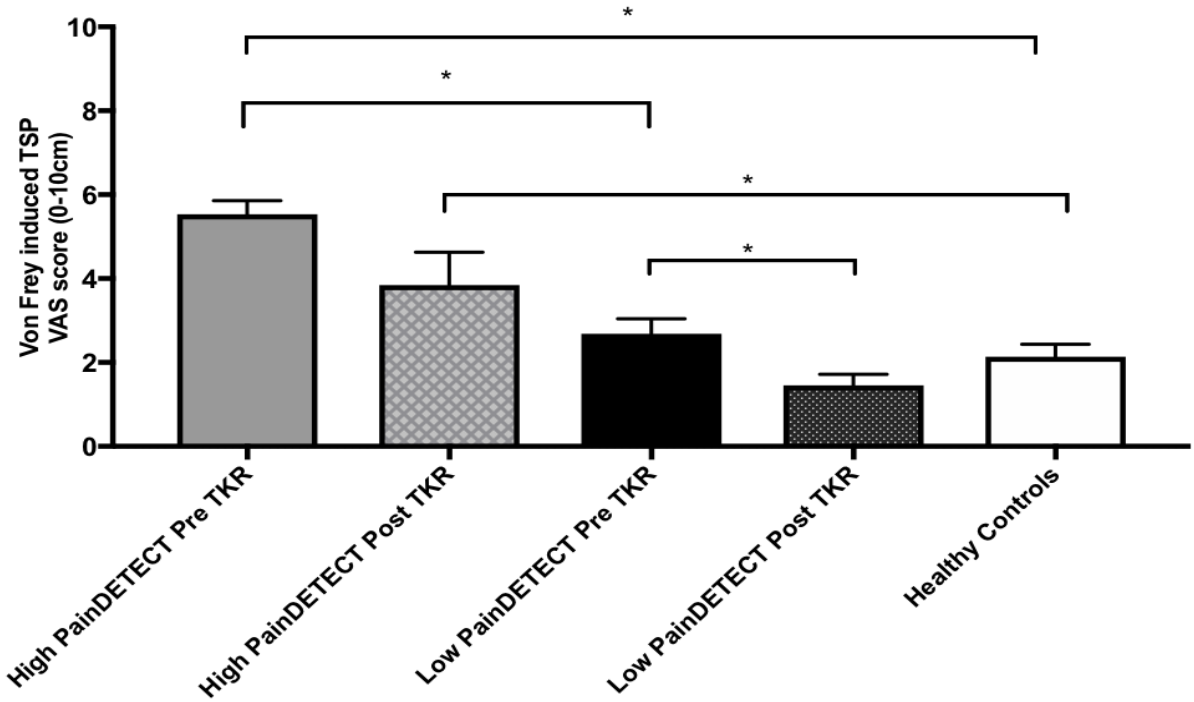

Figure 4. Mean (± SEM) Condition Pain Modulation Pre and Post TKR for OA Patients groups (High PainDETECT and Low PainDETECT) and Healthy controls Kruskal-Wallis ANOVA by Ranks Test. Significantly differences are illustrated (*, p<0.05).

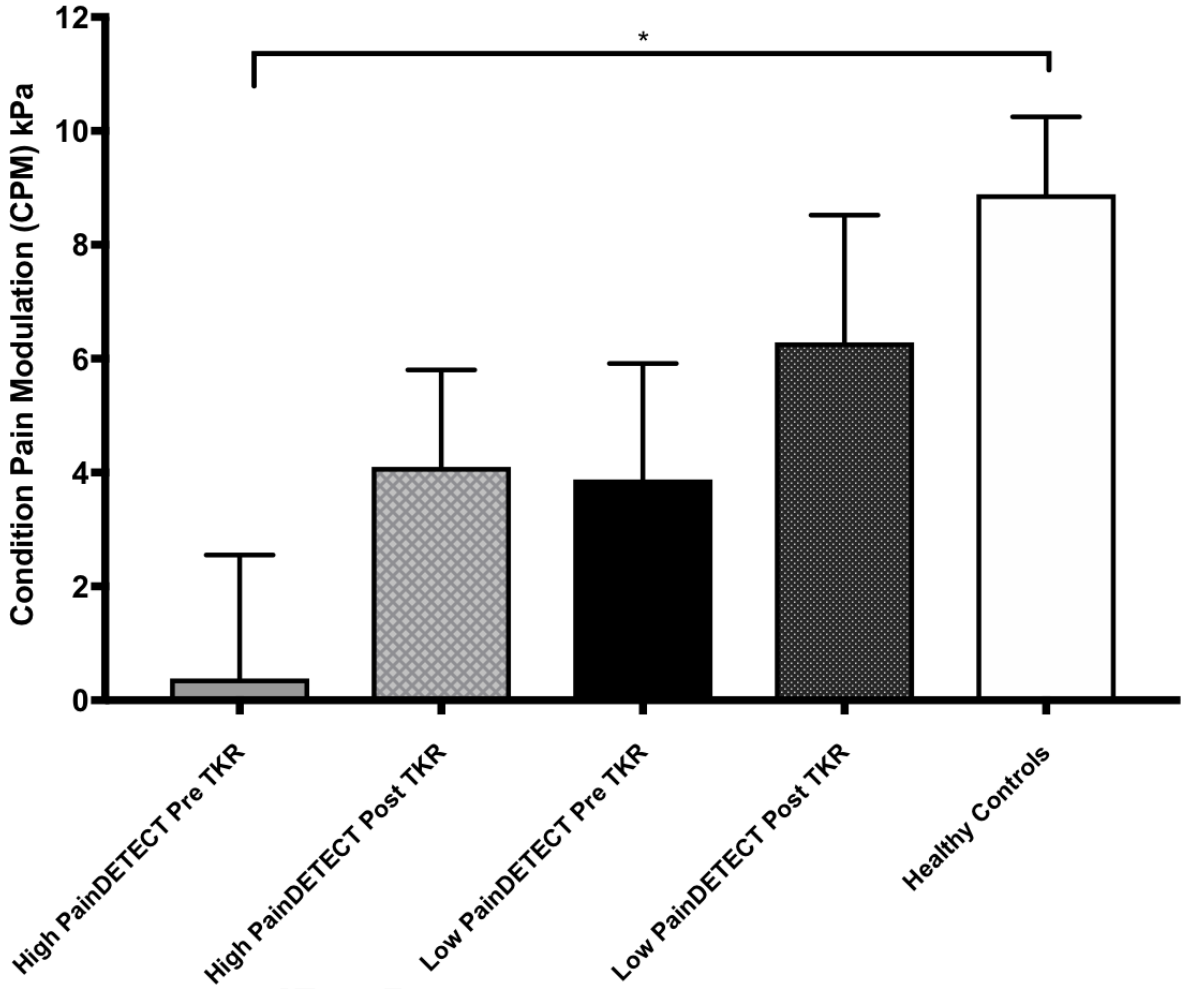

Table 1. Patient and Healthy controls demographics. Mean [Standard Deviation] or Median and (IRQ) are used to represent data. Significant different from High PainDETECT and Low PainDETECT groups (*, p<0.05). Significant differences between High PainDETECT and Low PainDETECT groups B (**, p<0.05)

	High PainDETECT Knee OA (n=15)	**Low PainDETECT Knee OA (n=35)**	**Healthy controls (n=22)**
PainDetect Score (0-38)	23 (21-27)	10 (6-13)	0 (0-0.25)*
Age (years)	65.1 [8.9]	66.9 [8.0]	56.7 [9.0]*
Male:Female %Female	5:10 66.6%	15:20 57.1%	9:13 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 (months)	61.4 (54.5-86.4)	54.5 (36.4-61.4)**	N/A
Peak pain VAS score (cm) in previous 24 h	6.5 [2.1]	4.7 [2.3]**	N/A

Table 2. Correlation of preoperative QST assessments to preoperative pain VAS scores. Based on pooled data from groups all three groups. Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. PPT: Pressure pain threshold. TSP: Temporal summation of pain. CPM: Condition Pain Modulation, PDT: Pain Detection Threshold, PTT: Pain Tolerance Threshold, NS: Not Significant

Preoperative Assessment	Pearson's/Spearman's	Correlation (r)	P Value
Mean Knee PPT	Pearson	-0.6792	<0.0001
Tibialis Anterior PPT	Pearson	-0.5251	<0.0001
ECRL PPT	Pearson	-0.5115	<0.0001
von Frey induced TSP	Spearman	0.5746	<0.0001
Cuff TSP	Spearman	0.4968	<0.0001
Cuff CPM	Spearman	-0.3403	NS
Cuff PDT	Spearman	-0.02078	NS
Cuff PTT	Spearman	0.04225	NS