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Patients with knee osteoarthritis who score highly on the PainDETECT questionnaire present with multi-modality hyperalgesia, increased pain and impaired physical function

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Abstract

Objectives: PainDETECT is a self-report questionnaire that can be used to identify features of neuropathic pain. A proportion of patients with knee osteoarthritis score highly on the PainDETECT questionnaire. This study aimed to determine whether those with a higher 'positive neuropathic' score on the PainDETECT questionnaire also had greater pain, hypersensitivity and reduced function compared to individuals with knee OA with lower PainDETECT scores.

Methods: 130 participants with knee OA completed the PainDETECT, Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Pain Quality Assessment Scale (PQAS) questionnaires. Quantitative sensory testing was carried out at three sites (both knees and elbow) using standard methods. Cold and heat pain thresholds were tested using a Peltier thermode and pressure pain thresholds using a digital algometer. Physical function was assessed using three timed locomotor function tests.

Results: 22.3% of participants scored in the 'positive neuropathic' category with a further 35.4% in the unclear category. Participants in the 'positive neuropathic' category reported higher levels of pain and more impaired function based on the WOMAC questionnaire ($p<0.0001$). They also exhibited increased levels of hyperalgesia at the knee and upper limb sites for all stimulation modalities except heat pain thresholds at the OA knee. They were also slower to complete two of the locomotion tasks.

Discussion: This study identified a specific sub-group of people with knee OA who exhibited PainDETECT scores in the 'positive neuropathic' category. These individuals experienced increased levels of pain, widespread, multi-modality hyperalgesia and greater functional impairment than the remaining cohort. Identification of OA patients with this pain phenotype may permit more targeted and effective pain management.

(264 words)

Keywords

PainDETECT, neuropathic pain, knee osteoarthritis, multi-modality hyperalgesia, functional impairment

Introduction

Osteoarthritis (OA) is a common arthritic disorder [1, 2], often associated with pain and local tenderness or pressure hyperalgesia around the affected joint(s) [3, 4]. Although knee OA has been considered the archetypal model of inflammatory or nociceptive pain [5], it is increasingly apparent that people with knee OA may present with different pain phenotypes. It is now recognised that some individuals with knee OA exhibit features of neuropathic pain [6] and it has been suggested that neuropathic pain in OA may be the result of damage to sensory neurons in subcortical bone as a result of the degenerative pathology [7-9]. This relates to the concept of neuropathic pain being, "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [10].

One approach to evaluating the presence of neuropathic pain has been to use self-report questionnaires such as PainDETECT, Doleur Neuropathic 4 (DN4) and the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS). These questionnaires predominantly evaluate the degree to which the individual reports phenomena such as burning pain, shooting or lancinating pain, tactile allodynia and other features that are normally associated with neuropathic pain states.

The PainDETECT questionnaire uses a combination of visual analogue scale, body diagram and Likert-type questions to ask about everyday frequency of symptoms such as 'electric shocks' or 'painful light touch'. A total score is calculated, with subjects scoring ≤12 classified as 'negative neuropathic' and those scoring ≥19 as 'positive neuropathic'. The group with intermediate scores (13-18) is classified as unclear or possible neuropathic [11]. A number of studies have evaluated people with knee OA using the PainDETECT questionnaire and demonstrated that some individuals score in the 'positive neuropathic' range. The percentage of people with increased PainDETECT scores (≥19) in the 'positive neuropathic' category appears to vary between OA cohorts, ranging from 5.4% to 32%

although the majority of studies suggest a percentage at the higher end of this range [6, 7, 12]. Similar percentages have also been identified using the DN4 questionnaire (29.4%) [13] and the S-LANSS questionnaire (30%) [14].

Previous research also suggests that increased PainDETECT scores in individuals with knee OA are associated with changes in quantitative sensory testing (QST) measures suggestive of increased pain sensitivity and with higher scores on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [14, 15]. However, these studies have not clearly differentiated between PainDETECT categories in terms of QST measures and functional capacity.

The current study sought to explore the relationship between self-report of neuropathic pain (based on PainDETECT scores) and pain report, sensory impairment, multi-modality hyperalgesia and impaired physical function in individuals with knee OA.

The primary aim of the study was to determine if there were differences in measures of pain, hyperalgesia, sensation and function between three sub-groups of participants categorised by PainDETECT scores ('negative neuropathic' (≤12), 'unclear neuropathic' (13-18) and 'positive neuropathic' (≥19).

Materials and Methods

Participants

One hundred and thirty participants with painful knee OA were recruited from the Perth community. Participants were assessed for suitability by a Rheumatologist, using the American College of Rheumatology (ACR) classification system [16]. People who were diagnosed as having knee OA based on the ACR criteria and who reported pain ≥4 /10 were included in the study. Exclusion criteria included: history of systemic inflammatory conditions; neurological disorders affecting sensory or motor function; recent (<6 months) lower limb injury or surgery; or history of other chronic pain disorders (e.g. fibromyalgia).

All participants provided written informed consent before participating in the study. Ethical approval was provided by Royal Perth Hospital Medical Research Ethics Committee (EC2009/100 and REG 13-005) and by Curtin University Human Research Ethics Committee (HR26/2010 and 79/2013).

Study Design and Procedure

The study used a cross-sectional design, with subjects attending for one test session. Participants underwent a washout period equal to five half lives of their analgesic or NSAID medication before testing. They were able to use paracetamol (acetaminophen) for analgesia if required during this washout period but were asked to refrain from its use for 12 hours before testing. All subjects initially completed the WOMAC Osteoarthritis Index for the Knee [17], the PainDETECT questionnaire [11] and the Pain Quality Assessment Scale (PQAS) [18]. They then completed a series of QST measures and a series of tests of physical function.

Self-Report Questionnaires

PainDETECT is a validated self-report tool with good internal consistency and high sensitivity and specificity that has been used to identify neuropathic pain features in a range of conditions [11]. The maximum score is 30 with scores ≥19 being designated as 'positive neuropathic'.

PQAS was also used to provide data regarding the type of spontaneous pain experienced [18]. The questionnaire includes 17 questions about the type of pain plus additional numerical rating scales for unpleasantness and surface versus deep pain. Three pain sub-scores are then calculated [18]: paroxysmal, surface and deep. The questionnaire has demonstrated good reliability and excellent internal consistency for all of the sub-scales [18]. It has been suggested that differences between the deep and surface or paroxysmal subscale scores may differentiate nociceptive-type and neuropathic-type pain [18].

WOMAC was used to evaluate subjective pain, stiffness and functional limitation . This OA-specific self-report scale has been widely used to measure pain and disability from knee OA, demonstrating good internal validity and test-retest reliability [17]. A higher score denotes greater functional limitation.

Physical Function Tests

The *Aggregated Locomotor Function (ALF) test* [19] was used as a measure of observed locomotor function. The score was calculated by summing the time (seconds) taken to complete 3 locomotor tasks: walk 2-metres to a chair, sit, stand and walk back 2-metres; 8-metre return walk; ascend / descend 10 stairs. All instructions were standardized, with subjects asked to complete each task "as briskly as possible". The score has good inter-rater reliability and is moderately well correlated with both WOMAC and SF-36 function indices, and is reported to be responsive to change following intervention over a short time period [19].

Quantitative Sensory Tests

All quantitative sensory tests were applied using standardized instructions at standardized sites: at the OA knee and the contralateral knee (medial joint line) and at the ipsilateral elbow over the extensor carpi radialis brevis (ECRB) muscle [20]. Triplicate measures were obtained. Order of testing was randomized between QST modalities and between test sites.

Pressure Pain Threshold (PPT) was assessed using an electronic digital pressure algometer (Somedic AB, Sweden), a device with good test retest reliability [21]. A 1cm² algometer probe was applied at 90° to the skin at a rate of 40kPa/sec. Subjects were instructed to press the hand-held switch as soon as the sensation of pressure became one of painful pressure [22]. Lower PPT values indicate increased sensitivity.

Cold Detection and Cold Pain Thresholds (CDT & CPT) were measured using a Peltier thermode (Medoc, Israel) and standard Method of Limits [23]. The probe was attached to the

test site with a Velcro™ strap. The temperature reduced at a rate of 1°C/sec from a baseline temperature of 32°C to a minimum of 0°C. Cold detection threshold (CDT) was always measured first. Participants were instructed to press the hand-held switch as soon as they perceived any cooling change from baseline. For cold pain threshold (CPT), participants were instructed to press the switch as soon as the cooling sensation changed to one of painful cold. Some subjects failed to indicate cold pain before the thermode reached the minimum temperature of 0°C. These participants were assigned a cold pain threshold of 0°C. Higher CPT values indicate increased cold pain sensitivity.

Warm Detection and Heat Pain Thresholds (WDT & HPT) were measured with the Medoc Peltier thermode using similar methodology to cold testing (baseline 32°C, 1°C/sec ascending ramp), with maximum temperature set at 50°C. Warm detection threshold (WDT) was defined as the temperature (°C) at which participants first perceived an increase in warmth from baseline, whilst heat pain threshold (HPT) was defined as the temperature (°C) at which participants perceived that the heating sensation had become one of painful heat. Some subjects failed to indicate heat pain before the thermode reached the maximum temperature of 50°C. These participants were assigned a heat pain threshold of 50°C. Lower HPT values indicate increased heat pain sensitivity.

Statistical Analysis

Data were analyzed using SPSS version 22 (IBM Corp) with Alpha set at $p<0.05$. Participants were divided *post hoc* into three groups based on PainDETECT score (≤12, 13-18, ≥19). Data were evaluated to determine if they met the assumption of normality using the Shapiro-Wilk test. Those measures that were normally distributed were analysed using one way ANOVA with Dunnett t Post Hoc tests using the high PainDETECT group (≥19) as control. Data that were not normally distributed were analysed using the non-parametric independent samples Kruskal-Wallis test and the Mann-Witney U test.

Based on previous research it was predicted that 15-25% of participants would score in the 'positive neuropathic' category on PainDETECT [6, 7, 12]. With an estimated sample size of n=20 for the high PainDETECT group, it was calculated that the study would have 80% power to detect a between-groups mean difference of 38kPa (SD 57kPa) in PPT, a 5.4˚C (SD 2.3˚C) difference in CPT and a 7.8 mm (SD 16mm) difference in total WOMAC score [24]. These values equate to a 15-20% between group difference [24]. Based on the high PainDETECT group constituting 15% of the overall cohort a sample of 130 subjects with knee OA was recruited for the study.

Results

Subject demographics

The 130 participants (62 male: 68 female) had a mean age of 66 years (range 50-88 years). They reported moderate pain (WOMAC Pain 18.5/50) and functional disability (WOMAC function 60.6/250).

Based on PainDETECT score 29 participants (22.3%) were classified as 'positive neuropathic' (score ≥19), 46 as 'unclear neuropathic' (35.4%) (Score 13-18) and 55 as 'negative neuropathic' (42.3%) (Score ≤12).

Participants predominantly used paracetamol/acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) for pain management (Table 1). They reported a number of co-morbidities with diabetes and high blood pressure reported by a higher proportion of the 'positive neuropathic' group (Table 1).

Self-Report Questionnaires

There were significant differences between PainDETECT categories for WOMAC pain scores ($F_{2,127}$ =18.23, p<0.0001), function scores ($F_{2,127}$ =18.30, p<0.0001), stiffness scores ($F_{2,127}$=10.38, p<0.0001) and total scores ($F_{2,127}$=22.28, p<0.0001). Post hoc tests (Dunnett's

t) showed significant differences between the 'positive neuropathic' group and each of the other groups for pain, function, stiffness and total score (Figure 1).

PQAS scores also showed differences between the PainDETECT groups for the paradoxical ($F_{2,127}$=18.66, p<0.0001) and surface ($F_{2,127}$=43.44, p<0.0001) pain categories but there was no significant difference for the deep pain category ($F_{2,127}$ =2.33, p=0.10). Post hoc tests showed significant differences (p<0.0001) between the 'positive neuropathic' group and each of the other PainDETECT groups for paradoxical pain and surface pain (Figure 1). There was a significant difference between the 'positive neuropathic' and 'negative neuropathic' groups (p=0.029) for deep pain but no difference between the 'positive neuropathic' group and the unclear group (p=0.141) (Figure 1).

Physical Function Tests

There was a significant difference between PainDETECT groups for the stair climb (p=0.001) and walk (p=0.004) components of the ALF, and the total score (p=0.007) but no significant difference for the sit-to-stand (p=0.676) component (Figure 1). Comparisons between the 'positive neuropathic' and 'negative neuropathic' groups followed the same pattern (stair p<0.001, walk p=0.002, sit-to-stand p=0.369, total p=0.003). There was also a significant difference between the 'positive neuropathic' group and the unclear group for the stair component of the test (p=0.024).

Quantitative Sensory Tests

Pain Thresholds

There were significant differences in pressure pain thresholds at the index knee ($F_{2,127}$=24.56, p<0.0001), contralateral knee ($F_{2,127}$=27.69, p<0.0001) and ECRB sites $F_{2,127}$=10.22, p<0.0001). Post hoc tests showed significantly (p<0.0001) lower PPTs (sensitized) for the 'positive neuropathic' group relative to the 'negative neuropathic' group at all test sites but

no significant difference between the 'positive neuropathic' group and the unclear group (Figure 2).

Cold pain thresholds were also significantly different between PainDETECT groups at all sites (Kruskal-Wallis Test: index knee $p<0.001$; contralateral knee $p<0.001$; ECRB $p<0.001$). CPTs for the 'positive neuropathic' group were significantly ($p<0.001$) higher (sensitized) than the 'negative neuropathic' group at all sites but there was no difference between the 'positive neuropathic' group and the unclear group at any site (Figure 2).

Similarly, there were significant differences in heat pain thresholds at the contralateral knee ($p=0.004$) and the ECRB site ($p=0.02$) but not at the index knee ($p=0.72$). HPTs for the 'positive neuropathic' group were significantly lower (sensitized) than the 'negative neuropathic' group at the contralateral knee ($p=0.001$) and ECRB sites ($p=0.007$) but not at the index knee ($p=0.472$). There was a significant difference between the 'positive neuropathic' group and the unclear group at the contralateral knee ($p=0.041$) but no difference at the other sites (Index knee $p=0.466$; ECRB $p=0.212$) (Figure 2).

Sensory Thresholds

Cold detection thresholds were not significantly different at any site (Index knee $p=0.935$; Contralateral knee $p=0.455$; ECRB $p=0.118$) (Figure 3). There was a significant difference in warmth detection thresholds at the contralateral knee ($p=0.005$) but not at the other sites (index knee $p=0.069$; ECRB $p=0.453$) (Figure 3). At the index knee ($p=0.033$) and the contralateral knee ($p=0.018$) there was a significant difference between the 'positive neuropathic' group and the 'negative neuropathic' group indicating some degree of sensory impairment but there was no difference between the 'positive neuropathic' group and the unclear group at any site.

Discussion

This study investigated levels of pain, hyperalgesia and physical function in participants with knee OA, grouped according to PainDETECT score. Those scoring in the 'positive neuropathic' category reported the greatest pain and disability, and demonstrated widespread hyperalgesia and greater functional limitations.

Participants with knee OA in this study demonstrated a range of PainDETECT scores from 0 to 30 (of a maximum score 30), reflecting very heterogeneous pain experiences. 22.3% of the participants scored in the 'positive neuropathic' category, suggesting that they may be experiencing features of neuropathic pain. In previous studies the percentage of participants scoring in the 'positive neuropathic' pain category has ranged from 5.4% to 32% [6, 7, 12]. The findings from this study are therefore a little less than some previous studies but nevertheless within the previously published range.

When tested across a range of other self-report measures, participants in the 'positive neuropathic' pain category reported increased pain and decreased function relative to the remaining patient cohort. WOMAC pain, stiffness and function sub-scores were elevated for this group. There are no previous studies that have evaluated minimum clinically important differences (MCID) between patient cohorts, but the 32% reduction in WOMAC total score between the 'positive neuropathic' group and the intermediate group is considerably larger than the 16% MCID for reduction in total WOMAC score following drug treatments [25]. The 'positive neuropathic' pain group also reported significantly higher scores than the remaining cohort for the surface and paradoxical pain quality subscales of PQAS, both of which are thought to reflect features of neuropathic pain [18]. It therefore appears that this group experiences not just increased pain severity but also distinctive pain qualities that are often associated with neuropathic pain.

In addition to WOMAC self-report of reduced functional capacity, participants in the 'positive neuropathic' group were slower to complete physical tasks. They exhibited slower times for the stair climb and walk components of the ALF test and had significantly increased total times. This further emphasizes that they were experiencing greater functional limitation associated with their pain.

Participants in the 'positive neuropathic' category also exhibited widespread, multi-modality hyperalgesia or increased pain sensitivity relative to those in the 'negative neuropathic' category. In addition to increased pain sensitivity at the OA knee, these participants were also more sensitive to measures of pressure pain threshold, cold pain threshold and heat pain threshold at the distant ECRB test site in the upper limb. Differences in PPT between groups exceeded the reported MCID of 114kPa [26] at both knees but not at the ECRB site. Interestingly, there was no significant difference in heat pain threshold at the index knee. This was a somewhat surprising finding given the clear differences that were present at the other test sites and the other test modalities. In a recent publication we have demonstrated that a sub-group of patients with increased cold pain thresholds also present with widespread multi-modality hyperalgesia and increased PainDETECT scores [27]

However, a 'positive neuropathic' score on the PainDETECT questionnaire alone is not diagnostic of pain that is neuropathic in origin. Treede et al. have proposed a grading system with categories of possible, probable and definite neuropathic pain [10]. Inclusion in the probable neuropathic pain category requires the presence of a measured sensory deficit in an area clearly related to the area of neuropathic pain report. Definite neuropathic pain also requires the existence of imaging or other findings showing a clear causative neuropathology [10].

The current study's findings suggest that while some individuals with knee OA may score highly on the PainDETECT questionnaire there is limited evidence of associated sensory impairment. There were no marked changes in sensory thresholds for cold although there were differences in warmth detection thresholds suggesting some impaired sensation in the 'positive neuropathic' grouping. However these findings are inconclusive. It should be noted that sensory testing was only carried out at one knee location (medial joint line). Since the area around the knee is innervated by multiple peripheral nerves [28], a single test site is unlikely to adequately evaluate sensory deficits. It is also important to acknowledge a limitation of the study in that comprehensive testing of light touch, pinprick and vibration sensations was not carried out. Further research is therefore warranted to explore more closely the relationship between pain and neurological deficits in patients with knee osteoarthritis. In addition to sensory deficits the concurrent presence of proprioceptive deficits might also be explored. Is it notable that deficits in proprioceptive function have previously been identified in patients with knee OA [29]. Future studies would also benefit from including data from a control cohort to account for normal variations in sensation amongst an older cohort.

It may also be the case that an increased PainDETECT score in association with widespread multimodality hyperalgesia may simply reflect a centrally augmented pain state [14, 15] rather than the presence of neuropathic pain. This may reflect enhanced central sensitization and possibly also impaired pain modulation [4]. Further research is required to evaluate the development of widespread pain sensitivity and impaired pain modulation to determine if these findings are also present in individuals who do not present with increased PainDETECT scores.

Although this study evaluated a relatively small cohort, the findings clearly suggest that scores on the PainDETECT questionnaire may be a useful indicator of those with a more severe pain state. These findings add further support to the concept that people with knee OA present with different pain phenotypes and so may have significantly different experiences of osteoarthritic pain [9]. In particular, they suggest that a sub-cohort of patients with knee OA experience more severe 'neuropathic-type' pain that has a greater impact on physical function than other individuals with the same condition. A previous study showed that patients with ongoing pain more than one year post joint replacement surgery showed that this group had higher PainDETECT scores and more functional impairment than patients with minimal pain following surgery [30]. This suggests that a standardized approach to pain management might result in some patients with knee OA receiving inadequate treatment and highlights the need for further research to develop clear criteria to diagnose neuropathic pain in knee OA and to optimize the management of pain in this patient group. In particular, it may be appropriate to consider the use of neuropathic pain medications in a sub-group of people with knee OA. Further research is warranted to evaluate this grouping in larger patient cohorts and clinical trials evaluating the efficacy of drugs used to manage neuropathic pain in this sub-group of OA sufferers.

Conclusion

Individuals with knee OA may report markedly different scores on the PainDETECT questionnaire. Those who score highly on the questionnaire tend to report increased pain, different pain qualities, more functional impairment and more widespread, multimodality hyperalgesia and pain sensitivity than other people with a diagnosis of knee OA. Further research is needed to determine whether these individuals can be clearly classified as having neuropathic pain if they would benefit from more targeted pain management.

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Figure Legends

Figure 1. Comparison between the 'negative neuropathic' (≤12), unclear (13-18) and 'positive neuropathic' (19+) PainDETECT categories for scores obtained in the subcategories of the WOMAC questionnaire (Panel a), the PQAS questionnaire (Panel b) and the ALF test (Panel c) (* $p<0.05$, ** $p<0.001$, *** $p<0.0001$).

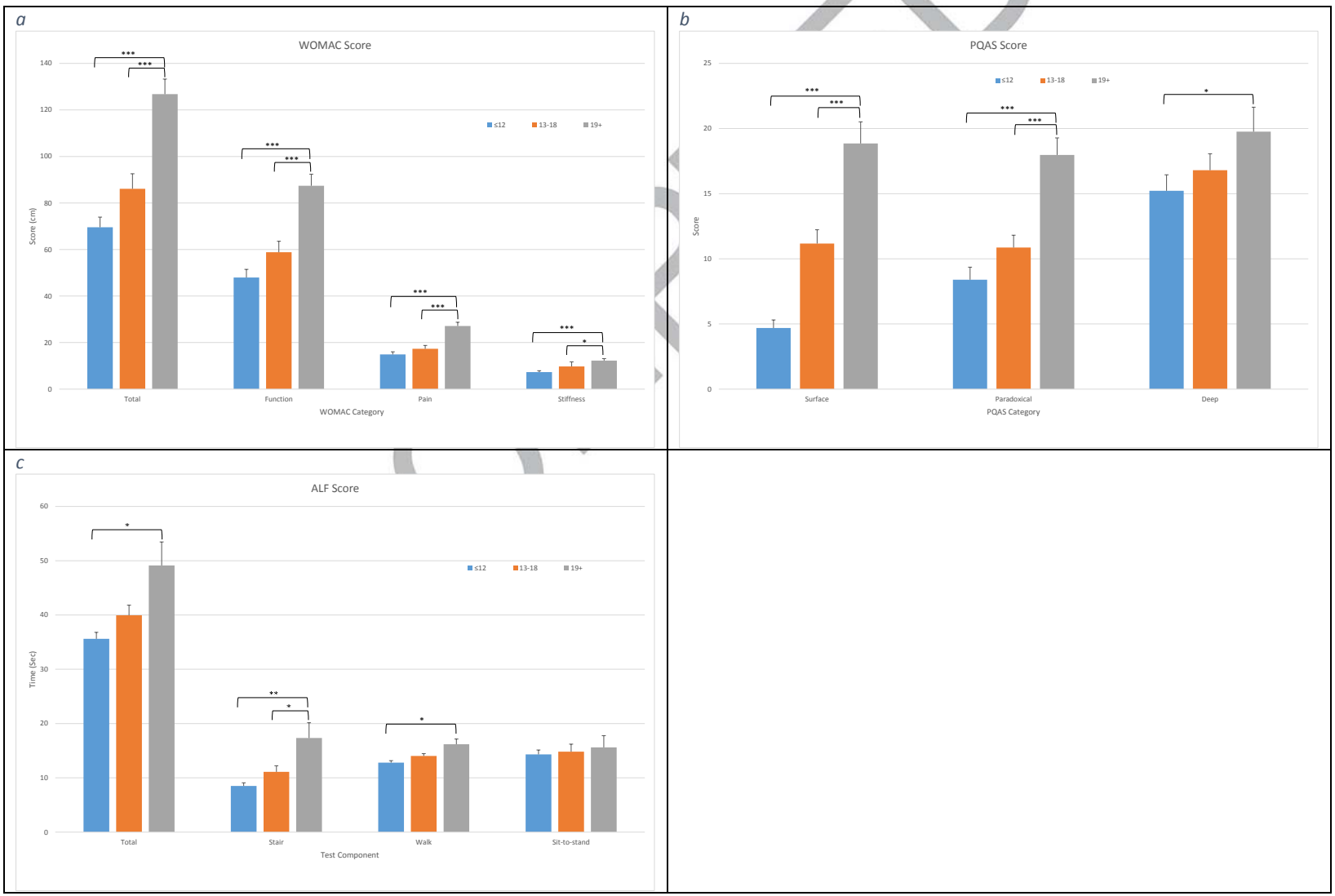
Figure 2. Comparison between the 'negative neuropathic' (≤12), unclear (13-18) and 'positive neuropathic' (19+) PainDETECT categories for pressure pain thresholds (Panel a), cold pain thresholds (Panel b) and heat pain thresholds (Panel c) at each of three test sites (* $p<0.05$, ** $p<0.001$, *** $p<0.0001$).

Figure 3. Comparison between the 'negative neuropathic' (≤12), unclear (13-18) and 'positive neuropathic' (19+) PainDETECT categories for cold sensation thresholds (Panel a) and warm detection thresholds (Panel b) at each of three test sites (* $p<0.05$, ** $p<0.001$, *** $p<0.0001$).

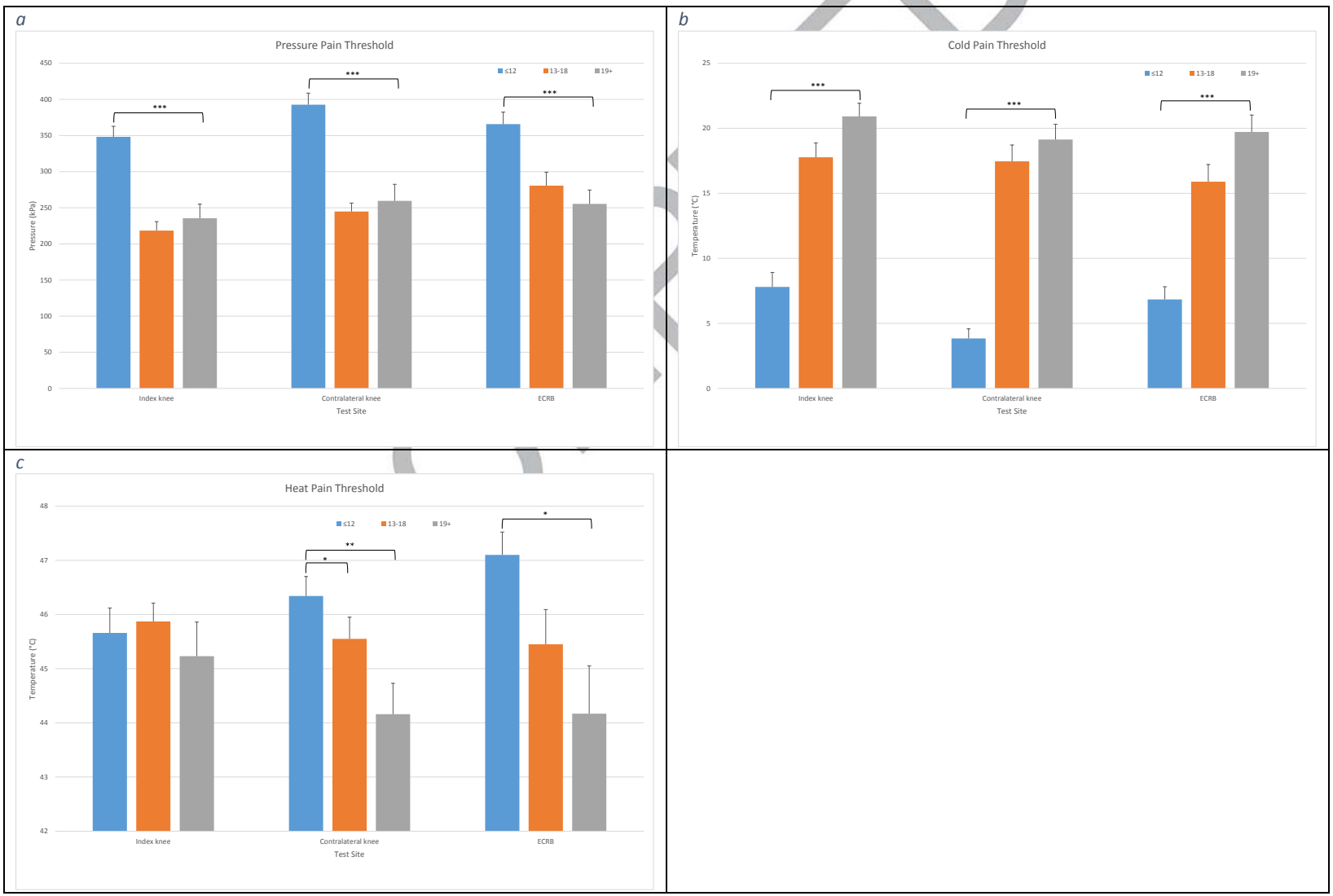
Table 1. Comparison of medication use and self-reported comorbidities for each of the three PainDETECT groups.

	Negative neuropathic (n=55)	**Unclear neuropathic (n=45)**	**Positive neuropathic (n=30)**	**Total (n=130)**	**% of total**	χ^2
Analgesia						
Paracetamol/ acetaminophen	22	20	15	*57*	***43.8***	p=0.671
NSAIDs	18	22	16	**56**	**43.1**	p=0.116
Tramadol	1	1	3	***5***	***3.8***	p=0.135
Co-morbidities						
Diabetes	8	6	10	***24***	***18.5***	p=0.076
BP	9	10	13	***32***	***24.6***	p=0.020
LBP	21	21	18	***60***	***46.2***	p=0.155
Neck pain	8	6	7	***21***	***16.2***	p=0.470
Migraines	6	3	4	***13***	***10.0***	p=0.614
Depression	7	9	8	***24***	***18.5***	p=0.271
IBS	2	4	3	***9***	***6.9***	p=0.442

Figure



Figure



Figure