Abstract

Objective. The aim of this study was to use quantitative sensory testing (QST) to explore the range and prevalence of somatosensory abnormalities demonstrated by patients with advanced knee OA.

Methods. One hundred and seven knee OA patients and 50 age- and sex-matched healthy participants attended a 1-h QST session. Testing was performed on the medial side of the knee and the pain-free forearm. Light-touch thresholds were assessed using von Frey filaments, pressure pain thresholds using a digital pressure algometer, and thermal sensation and pain thresholds using a Thermodot MSA. Significant differences in median threshold values from knee OA patients and healthy participants were identified using Mann-Whitney U-tests. The z-score transformations were used to determine the prevalence of the different somatosensory abnormalities in knee OA patients.

Results. Testing identified 70% of knee OA patients as having at least one somatosensory abnormality. Comparison of median threshold values between knee OA patients and healthy participants revealed that patients had localized thermal and tactile hypoesthesia and pressure hyperalgesia at the osteoarthritic knee. Tactile hypoesthesia and pressure hyperalgesia were also present at the pain-free forearm. The most prevalent somatosensory abnormalities were tactile hypoesthesia and pressure hyperalgesia, evident in between 20 and 34% of patients.

Conclusion. This study found that OA patients demonstrate an array of somatosensory abnormalities, of which the most prevalent were tactile hypoesthesia and pressure hyperalgesia. Further research is now needed to establish the clinical implications of these somatosensory abnormalities.

Key words: knee, osteoarthritis, pain thresholds.

Introduction

OA is the leading cause of chronic pain in Europe, accounting for 34% of self-reported chronic pain [1]. The knee is the peripheral joint most commonly affected by OA, with ~10% of all adults aged >55 years experiencing painful knee OA [2]. The pathophysiology of osteoarthritic pain is complex, and local contributors to OA pain probably include synovial inflammation, raised intra-osseous pressure and mechanical stresses on IA and peri-articular ligaments and tendons [3–5]. In addition to these local mechanisms, quantitative sensory testing (QST) has provided evidence that there are neurogenic responses in OA pain, with changes in the modulation of nociceptive input contributing to pain severity [6–13].

QST is a psychophysical technique, which measures participants’ responses to external stimuli of controlled intensity. It can assess somatosensory responses to a range of stimuli, including pressure, temperature, electricity and vibration. This is an important property of QST because somatosensory abnormalities can be modality specific [14]. QST can record participants’ responses to both innocuous and noxious stimuli. Measuring responses to innocuous stimuli can identify hyperaesthesia (increased sensitivity), hypoesthesia (reduced sensitivity) and allodynia (the perception of pain in response to a stimulus that does not normally provoke pain). Measuring responses to noxious stimuli can identify altered pain sensitivity and provide evidence of changes in dynamic pain modulation such as temporal summation and diffuse noxious inhibitory controls (DNICs) [15]. QST can also determine whether somatosensory abnormalities are occurring at a
localized level (at or near to the site of tissue damage) or a more generalized level (at distant pain-free body sites). Therefore, QST can provide evidence of an array of somatosensory abnormalities and has the potential to cast light on the complex pain mechanisms occurring in OA. However, because there is uncertainty about which types of QST testing are of most relevance to OA, and how these tests might be interpreted in a way that is relevant to patient care, QST is not routinely used in clinical rheumatology and orthopaedics.

Within the literature research, there is a small number of studies that have found evidence of somatosensory abnormalities in patients with hip OA [7, 11, 12, 16] and knee OA [6, 7, 9, 10, 13, 17]. However, the small patient numbers tested in these studies (between 11 and 69 OA patients) limits the conclusions that can be drawn from the data. Also the statistical analysis performed in these studies involved comparing average QST data between OA patients and healthy participants, thereby enabling identification of somatosensory abnormalities at the group level. In addition to this method of analysis, the German Research Network on Neuropathic Pain (GRNNP) [18–21] suggests that when analysing QST data, it is of value to z-transform the data and compare the results from a single patient to the group average of healthy participants, to allow prevalence of somatosensory abnormalities to be explored. Therefore, the aim of this study was to use a variety of QST modalities and analysis techniques to explore the range and prevalence of somatosensory abnormalities demonstrated by patients with knee OA.

**Patients and methods**

**Recruitment**

Ethics approval for this study was obtained from the Local Research Ethics Committee (Southwest 4 Research Ethics Committee) and all participants provided informed, written consent. Patients on the waiting list for a primary total knee replacement (TKR) because of OA at a large orthopaedic centre were recruited into this study by postal invitation. Healthy participants (defined as people who had no pain in either knee and had not previously had a TKR) were included to provide normative somatosensory data and were recruited through three methods: from friends and family of knee OA patients participating in the study; from upper limb, urology or skin pigmentation clinics; and from colleagues of the research team. As gender and age can influence somatosensory function [22, 23], only healthy participants aged >50 years were approached for recruitment.

Exclusion and inclusion criteria were established via self-report on a screening questionnaire. An inclusion criterion for OA patients and healthy participants was being pain free in their right forearm (to allow testing of somatosensory function at a body site distant to the osteoarthritic knee). As QST involves the full co-operation of participants, individuals who had cognitive impairment or dementia were excluded.

**Questionnaires**

Before testing, all participants completed questions about pain in nine other joints (both knees, hips, shoulders, hands and neck/back). In addition, OA patients completed the WOMAC pain scale [24], the 11 sensory pain descriptors from the short-form McGill pain questionnaire (SF-MPQ) [25] and information on the duration of knee pain.

**QST**

All participants attended the hospital for a 1-h QST session, and underwent an identical testing protocol. QST was performed at two body sites: the volar surface of the right forearm and the medial side of the index knee (the osteoarthritic knee listed for replacement in the OA patients or the left knee in healthy participants). These body sites were chosen because they could provide evidence of somatosensory abnormalities occurring locally (the skin over the painful osteoarthritic knee) and at a pain-free distant body site in knee OA patients. The medial side of the knee was tested because 60–70% of weight-bearing load is transmitted through this compartment and therefore it is the most common knee compartment to be affected by OA [26]. Also it has been demonstrated to be the most sensitive area of the knee to pressure pain stimulation in patients with severe knee OA [10].

Mechanical and thermal stimuli were used to assess sensation and pain thresholds. In order, light touch, thermal detection, thermal pain and pressure pain thresholds were tested at both body sites. Sensation thresholds were tested before pain thresholds to minimize sensitization of receptors by noxious input. These tests were chosen because they have previously been found not to differ systematically over 1 week at the knee and/or forearm in knee OA patients and healthy participants [27].

**Light touch thresholds**

Von Frey monofilaments (Somedic, Sweden) were used to measure participants’ light touch thresholds using the ascending method of limits. Participants were asked to close their eyes, and each monofilament, beginning with the smallest diameter monofilament, was applied to the skin until the monofilament buckled. Monofilaments of increasing diameter were applied until the light touch threshold (gram per square millimetres) was reached, which was when the participant felt three out of four stimuli [17].

**Pressure pain thresholds**

Pressure pain thresholds were measured using a digital algometer (Somedic, Sweden). A 1-cm² probe was held perpendicular to the skin and force applied at a constant rate of 10 kPa/s. The patient was instructed to say stop when the sensation of pressure became the very first sensation of pain. Pressure algometry was repeated three times at each body site, and between each reading the position of the algometer on the skin was altered very slightly to avoid sensitization of the test area. The first
Thermal detection and pain thresholds

Thermal detection and pain thresholds were assessed using a QST analyser (Thermotest Modular Sensory Analyzer, Somedic, Sweden). The same thermode size (25 x 50 mm²) was used in all tests. The thresholds were tested in the order of: warm detection, cold detection, hot pain and cold pain thresholds. The method of limits algorithm was used, and the thermode adaptation temperature of 32°C rose or fell at a rate of 0.5°C/s, as this rate of temperature change minimizes intra-individual variation [29]. Each stimulus was generated after a randomized 4- to 6-s interval, the four sensations were tested four times at each body site and a mean value from the last three readings was calculated. The MSA thermotest has in-built safety cut-off temperatures of 5 and 50°C to ensure no harm could occur to the participants. If these temperature limits were reached and the participant did not report any sensation, the data were recorded as a no response. Since a large number of participants (between 20 and 29 participants, depending on body site and participant group) did not perceive cold pain before the safety cut-off temperature of 5°C, cold pain thresholds were excluded from the analysis.

Statistics

Using a Kolmogorov–Smirnov test, it was found that the QST results were predominately non-parametric and therefore medians (interquartile ranges) are presented, and non-parametric statistical tests used throughout, except for the analysis of age (data were parametric). Body region and QST modality were analysed separately to identify any modality- or region-specific somatosensory abnormalities.

Analysis was performed at both the group- and individual level. Group-level analysis involved the comparison of median QST threshold values between knee OA patients and healthy participants using a Mann-Whitney U-test to identify any somatosensory abnormalities. To enable comparison of individual patient’s QST results to normative data, independent of the unit of measurement, z-transformation was used. In line with previous analysis involving QST parameters, warm detection thresholds, cold detection thresholds and hot pain thresholds were expressed as the difference from the 32°C baseline temperature [18, 19]. For z-scores to be calculated, QST data for light touch detection, thermal detection and pressure pain thresholds were log-transformed to meet the assumptions of normality, as suggested by the GRNNP [18]. In line with these recommendations, hot pain thresholds were not transformed because logarithmic transformation would be inadequate as the temperature scale is arbitrary and there is no natural zero in the stimulus dimension [18]. The z-scores were then calculated for individual OA patients, with z-scores for the different QST modalities and body sites being calculated separately [18, 20]. The equation used to calculate the z-scores was:

\[ z = \frac{X_{\text{Patient}} - \text{Mean}_{\text{Healthy participants}}}{\text{S.D.}_{\text{Healthy participants}}} \]

After z-transformation, all OA patients’ QST results are presented as standard normal distributions (zero mean, unit variance). A z-score of 0 represents a result corresponding to the mean result of the healthy participants. The z-values between 0±1.96, i.e. mean ±1.96 x standard deviation, represent the range of scores that which are likely to include 95% of the healthy participant’s results. Therefore, any z-scores outside the 95% CI of the healthy participant data (i.e. z-score < -1.96 or >1.96) were classified as abnormal (with a positive value indicating hyper-sensitivity and a negative value indicating hyposensitivity). These abnormalities were defined as local if they were present at the knee, and distant if they were present at the forearm. All statistical analysis was performed with the use of SPSS (version 16.0; SPSS, Chicago, IL, USA).

Results

Participant demographics and clinical characteristics

In total, 107 knee OA patients and 50 healthy individuals participated in this study. The mean (s.d.) age of OA patients was 69 (8.5) years, which was not significantly different from the mean (s.d.) age of 68 (7.9) years for the healthy participants (P = 0.524). The gender distribution between the two groups was similar with 52% of OA patients being male, compared with 42% of healthy participants. In OA patients, the median (interquartile range) duration of pain in the knee listed for surgery was 6 (3–10) years. The median WOMAC pain score, on a scale of 0–100 (best to worst) was 60 (45–70) for the knee listed for surgery and 25 (4–46) for the contra-lateral knee. The contra-lateral knee had been replaced in 17 (16%) patients. OA patients had a median of 4 (2–5) painful joints (including the osteoarthritic knee), which was significantly more than the median of 1 (0–2) painful joint in healthy participants (P < 0.001).

The three SF-MPQ pain descriptors that were most frequently rated as moderate or severe by knee OA patients were aching (83% of patients), sharp (64% of patients) and stabbing (57% of patients). Neuropathic pain is often described using characteristic pain descriptors, such as hot-burning and shooting [30]. Of the pain descriptors on the SF-MPQ, 55% of patients reported that they experienced moderate or severe shooting pain in their knee, and 42% reported moderate or severe hot-burning pain in their knee, with 23% of these patients experiencing both types of pain.

QST results

A comparison of median thresholds from patients and healthy participants for each of the QSTs is displayed in Figs 1–5. The percentage of patients indentified as having local and distant somatosensory abnormalities in response to each different QST test is displayed in Fig. 6. Individual-level analysis revealed that 71% (76/107) of
OA patients demonstrated at least one somatosensory abnormality. Of the 10 possible somatosensory abnormalities (localized and widespread abnormalities for each of the five modalities tested), 27 patients had one, 19 patients had two, 19 patients had three, 7 patients had four, 3 patients had five and 1 patient had seven somatosensory abnormalities.

**Light touch thresholds**
OA patients had significantly higher median light touch thresholds than healthy participants, at both the knee ($P < 0.001$) and the forehead ($P < 0.001$), indicating local and distant tactile hypoaesthesia, respectively (Fig. 1). Individual-level analysis revealed that tactile hypoaesthesia was the most common somatosensory abnormality detected with the sensory perception tests, with 34% (36/107) of patients reporting local hypoaesthesia and 31% (33/107) reporting distant hypoaesthesia (Fig. 6). The percentage of patients reporting both localized and widespread tactile hypoaesthesia was 21% (23/107).

**Pressure pain thresholds**
OA patients had significantly lower median pressure pain thresholds than healthy participants at the knee ($P < 0.001$) and the forehead ($P < 0.001$), indicating local and distant pressure hyperalgesia (Fig. 4). Individual-level analysis revealed that pressure hyperalgesia was the most common somatosensory abnormality detected with the pain perception tests, with 31% (33/107) of patients reporting local pressure hyperalgesia and 20% (21/107) reporting distant pressure hyperalgesia (Fig. 6). The percentage of patients reporting both localized and widespread pressure hyperalgesia was 14% (15/107).

**Thermal detection thresholds**
In response to both the warm and cold stimuli, OA patients had significantly higher median detection thresholds than healthy participants at the knee ($P = 0.049$ and 0.02, respectively), but not the forehead ($P = 0.2$ and 0.084, respectively), indicating local thermal hypoaesthesia (Figs. 2 and 3). Individual-level analysis revealed that in response to cold stimuli, 13% (14/107) of patients demonstrated localized hypoaesthesia and 8% (9/107) demonstrated widespread hypoaesthesia (Fig. 6). The percentage of patients demonstrating both localized and widespread cold hypoaesthesia was 3% (3/107). In response to warm stimuli, 7% (8/107) of patients demonstrated localized hypoaesthesia and no patients demonstrated widespread hypoaesthesia (Fig. 6).

**Hot pain thresholds**
There was no significant difference in median hot pain thresholds between OA patients and healthy participants, at either the knee ($P = 0.13$) or the forehead ($P = 0.689$), indicating that OA patients have no abnormalities in processing hot pain (Fig. 5). Individual-level analysis revealed that 5% (5/107) of patients had heat hyperalgesia at the knee and 9% (10/107) had heat hyperalgesia at the forehead (Fig. 6). The percentage of patients reporting both localized and widespread heat hyperalgesia was 4% (4/107).

**Discussion**
This study identified 71% of knee OA patients as having at least one somatosensory abnormality. The assessment of sensory and pain perception thresholds using mechanical and thermal stimuli uncovered an array of somatosensory

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*Fig. 1* Comparison of median light touch threshold (g/mm²) of knee OA patients and healthy participants (**$P < 0.001$**).
abnormalities. Group-level analysis of thresholds at the osteoarthritic knee revealed that patients demonstrated thermal and tactile hypoaesthesia, alongside pressure hyperalgesia. This apparently contradictory finding of hypoaesthesia alongside hyperalgesia has been found previously [6, 17]. The altered sensitivity of the skin and muscle surrounding the osteoarthritic knee likely reflects changes at the localized level of the spinal cord. Tactile hypoaesthesia and pressure hyperalgesia were also present at the pain-free forearm, indicating more widespread

**Fig. 2** Comparison of median warm detection threshold (°C) of knee OA patients and healthy participants (*P < 0.05).

**Fig. 3** Comparison of median cold detection threshold (°C) of knee OA patients and healthy participants (*P < 0.05).
changes within the CNS. Individual-level analysis revealed
that the identified somatosensory abnormalities were not
a universal occurrence across the patient sample, with no
evidence of somatosensory abnormalities in 29% of
patients.

The most common somatosensory abnormality identified
in the sensory testing was tactile hypoesthesia, which
was present at the knee in 34% of patients and at the
forearm in 31% of patients. Localized tactile hypoesthesia
in the presence of pain sensitization has previously been
reported in knee OA patients [17], and is likely due to descending inhibitory systems. These systems are activated to counteract the enhanced excitation of peripheral afferents in response to noxious stimuli, but in doing this they also reduce the sensitivity of afferents to innocuous stimuli [17, 31].

The pain perception tests revealed that knee OA patients demonstrate pain sensitization at the knee and the forearm in response to pressure stimuli. Localized pressure pain sensitization was demonstrated by 32% of patients and distant pressure pain sensitization by 20% of patients. The small number of previous research studies that have assessed pressure pain thresholds in OA patients have also found evidence of pressure hyperalgesia at the osteoarthritic knee and other pain-free body sites [9, 10, 12]. Pain sensitization probably occurs because the continuous nociceptive input into the dorsal horn neurones from the osteoarthritic knee leads to changes in the neurones, such as increased excitability, lower activation thresholds and larger receptive fields [32]. The reduced pressure pain thresholds of the muscle overlying the osteoarthritic joint likely represents changes at the level of the spinal cord where convergence of skin, joint and muscle afferent fibres occurs [33]. The presence of pain sensitization at a pain-free distant site suggests more widespread changes in the CNS, and a neuropathic component to OA pain. The possibility of neuropathic pain mechanisms contributing to OA pain is further supported by the results from the SF-MPQ, which found that 23% of patients experienced moderate–severe pain that was shooting and hot-burning in quality, which is indicative of neuropathic pain [30]. Supporting evidence has also arisen from qualitative research through the finding that 34% of OA patients used pain quality descriptors that were suggestive of neuropathic pain [30]. However, this study did not test for the presence of allodynia, a hallmark symptom of neuropathic pain [34], which would have provided further evidence for the presence of neuropathic pain mechanisms in knee OA.

When interpreting the results of this study, there are some characteristics of the participant groups that need to be acknowledged as they could have potentially influenced the results obtained. First, patients were not instructed to stop analgesics on the day of testing, because the team thought it would be inappropriate to ask patients listed for knee replacement because of chronic pain to stop taking their pain medication. As a consequence, some patients may have taken pain medication before the testing, which could have potentially altered pain perception thresholds. However, this potential limitation applies to many of the other studies of QST in OA, although recent studies have requested that patients stop taking pain medications 24 h before the study [10]. Secondly, a potentially confounding characteristic of the healthy participants was that although they were pain free at the body sites tested, they were not completely pain free, with an average of one painful joint. The presence of a painful joint may have affected healthy participants’ QST results, because noxious input from the painful joint may have led to pain sensitization which would have made differences between the healthy participants and the OA patients more difficult to detect. However, because of the high prevalence of painful conditions in the elderly population [35], logistical difficulties were experienced in recruiting older individuals who had no bodily pain. Thirdly, there was the potential for bias in

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**Fig. 6** Percentage of patients with abnormal local sensitivity (at the knee) and distant sensitivity (at the forearm) to each QST stimuli (based on z-scores). Bars below the line indicate hyposensitivity (reduced sensitivity) and bars above the line indicate hypersensitivity (increased sensitivity). LTT: light touch thresholds; WDT: warm detection thresholds; CDT: cold detection thresholds; HPT: hot pain thresholds; PPT: pressure pain thresholds.
the study as the QST examiner was not blinded to whether participants were knee OA patients or healthy participants. Finally, the knee OA patients who participated in this study were all listed for TKR and therefore may not have been representative of the general knee OA population. Despite these limitations, the QST tests demonstrated that some knee OA patients have somatosensory abnormalities. Strengths of the study include the relatively large number of patients tested, the good age- and sex matching of OA patients and healthy participants and the use of z-score analysis to allow identification of somatosensory abnormalities on an individual level, and to demonstrate that even when significant differences in median thresholds between OA patients and healthy participants exist, not all patients have evidence of a somatosensory abnormality.

The findings of this study have potential clinical implications for the treatment of OA pain, because of the importance of differentiating between nociceptive and neuropathic pain for effective pain management. OA has traditionally been treated as a nociceptive pain condition, with the assumption that pain perception is driven solely by noxious input from the periphery. Due to this assumption, the treatment of OA pain usually involves pharmacological agents, such as NSAIDs, which target the peripheral afferent nerves. However, studies have shown that these treatments fail to significantly reduce OA pain in the long term in the majority of patients [36]. Furthermore, some patients do not obtain pain relief from other interventions, including major surgical procedures such as joint replacement, whereas others get good pain relief [37–39]. This study suggests that some patients may be failing to respond to standard pain treatments because they had a neuropathic component to their pain, and would therefore benefit from an intervention which was targeted at reversing the CNS changes that contribute to pain severity. However, these patients would first need to be identified, as this study found only a subgroup of patients to have widespread central changes in the modulation of heat pain (9%) and pressure pain (20%). Based on the results of this study, pressure algometry was more sensitive than hot pain testing in identifying pain sensitization in knee OA patients, and therefore is the more relevant test stimuli for application in OA.

Further research is now needed to establish the clinical implications of these somatosensory abnormalities. For example, it is possible that pain sensitization contributes to the continuance of chronic pain after technically successful TKR that affects between 13 and 30% of patients [37, 38, 40]. This may be because once pain sensitization has developed, it can be maintained without nociceptive inputs from the periphery [41], and could therefore persist after joint replacement. In support of this theory, an increased sensitivity to electrical pain at the hand has been found to be predictive of chronic pain 12–18 months after TKR [42]. If the presence of pain sensitization was found to be a risk factor for the development of chronic pain after TKR, then patients with pre-operative pain sensitization could be identified using QST, and targeted with an intervention to reduce the risk factor before they undergo surgery.

### Rheumatology key message

- OA patients demonstrate an array of somatosensory abnormalities, including tactile hypoaesthesia and pressure hyperalgesia.

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### Disclosure statement

The authors have declared no conflicts of interest.

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