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Spreading of pain as a sign of central sensitization in patients with knee osteoarthritis pain

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Abstract

Background: Spreading of pain is considered a sign of central sensitization (CS). The relationship between patient's recording of symptom location and CS in people with knee osteoarthritis (OA) pain has been poorly investigated.

Objective: To examine whether the extent of pain assessed using pain drawings (PDs) relates to CS and clinical features in patients with knee OA pain.

Design: Cross-sectional study.

Methods: Fifty-three subjects with knee OA pain scheduled to undergo primary total knee arthroplasty were studied. All participants were asked to complete PDs using a novel digital device for PDs acquisition and analysis. Pain frequency maps were generated separately for women and men. Patients completed self-administration questionnaires and were assessed by quantitative sensory testing. Spearman's correlation coefficients were computed to reveal possible correlations between pain extent and quantitative sensory testing and clinical features.

Results: Besides local knee symptoms, pain frequency maps revealed enlarged areas of pain, especially in women. A significant positive correlation was found between pain extent and knee pain severity (.325, $P < 0.05$) and stiffness (.341, $P < 0.05$). Pain extent was also significantly correlated with pressure pain thresholds measured at the knee (-.306, $P < 0.05$) and distantly

from the knee (-.308, P < 0.05) and the degree of subjective CS pain descriptors as assessed with the Central Sensitization Inventory (.456, P < 0.01).

Limitations: Firm conclusions about the predictive role of PDs on knee OA pain cannot be drawn.

Conclusion: Spreading of pain measured by PDs was correlated with widespread hyperalgesia and centrally mediated symptoms in patients with knee OA pain. PDs may constitute an easy way for the early identification of CS in people with knee OA pain.

Key words: Knee osteoarthritis, chronic pain, pain location, central nervous system sensitization.

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Introduction

There is compelling evidence that central sensitization (CS) is present in a subgroup of people with knee osteoarthritis (OA) pain, especially in those with more advanced knee OA, and may be associated with knee OA symptom severity.[1,2] These conclusions were mainly derived from studies using quantitative sensory testing (QST) within laboratory conditions.[3] However, there is currently a lack of established criteria or gold standard for the diagnosis of CS in knee OA.[4] Recently, a set of criteria to assist clinicians on the classification of CS pain have been published,[5] but the suitability of this classification algorithm to the OA knee pain population is unknown. One criterion included for the classification of CS pain is diffuse pain distribution (i.e. large pain areas with a neuroanatomically illogical distribution) as identified from the clinical history and/or a body chart.[5] Spreading of pain is a well-recognized sign of CS[4,6,7] and, in this regard, pain drawings (PDs) might be useful to identify extended areas of pain distribution in patients with knee OA.

PDs have been used to obtain a graphic representation of pain distribution and location in people with knee OA pain.[8-14] In PD patients indicate the location of their pain by shading the painful area.[15] Several methods and instruments have been described to record the location and classify the pattern of knee OA pain, with knee pain diagrams on paper being the most commonly used.[8,10,11] Despite a wide variety of assessment methods, the medial knee region seems to be the most frequently reported pain location amongst people with knee OA pain,[10,11,16,17] though generalized or diffuse knee pain is also commonly reported.[8,10] However, the location of pain is heterogeneous with no

single pattern of pain location being pathognomonic for knee OA.[10] This is probably due to the multiple sources of pain in knee OA.[11]

Recently, the presence of widespread pain as recorded on PDs, was most frequently reported by a subgroup of patients with high levels of (in particular bilateral) knee OA pain during daily tasks and low level of structural damage on radiography.[18] Widespread pain in this subgroup of patients was attributed to a variety of etiological factors, including abnormal central pain processing mechanisms. Wood and colleagues found that subjects with knee OA reporting generalized knee pain with radiation had more persistent and severe pain and higher anxiety levels, which was also interpreted as reflecting altered central pain processing mechanisms.[10]

To our knowledge, only the two above mentioned studies[10, 18] related central pain mechanisms to patient's recording of symptom location and distribution. If CS was the dominant pain mechanism in a patient with knee OA pain, this should reflect in more extended areas of pain mapped in PDs as compared to people with a lesser degree of pain sensitization. However, this hypothesis has not been previously tested.

Therefore the primary aim of the study was to examine whether the extent of pain and pain location assessed using PDs relates to direct (QST) and indirect (self-reported questionnaires, neuropathic pain symptoms) measures of CS in patients with chronic knee OA pain. As a secondary aim, the association between extent of pain/pain location and clinical features (including the level of knee pain, disability and psychosocial variables) were also investigated. Such psychosocial variables have been suggested as negatively influencing OA-related pain and disability[19] with their presence in the pre-surgical phase

negatively influencing post-surgical outcome measures after total knee replacement surgery.[20]

Methods

Study design

This study was a cross-sectional study. Baseline data from a randomized controlled trial about the effects of neuroscience education on subjects with chronic knee pain related to osteoarthritis were analyzed. The randomized controlled trial was approved by the Ethics Committee of the Hospital (blinded) and was registered in the Clinical Trials database (NCT02246088).

Subjects

Fifty-three subjects with chronic knee OA pain of more than 3 months duration and scheduled to undergo primary total knee arthroplasty participated in the study. The sample size used for the current study was derived from the sample size calculation as performed for the randomized controlled trial. G*Power 3.0.18 Software was used and conditioned pain modulation was taken as the primary outcome measure. Sample size calculation corresponding to the randomized controlled trial design (2 groups of intervention, power of 0.8, alpha level of 0.05), resulted in 22 patients per group (44 patients in total). Considering an estimated increase of a 20% in case of losses, a total of 53 patients with chronic knee OA pain was finally recruited.

Knee OA was diagnosed by a surgeon according to the American College of Rheumatology classification.[21] All participants were recruited from

the Orthopedic Surgery Service of the Hospital (blinded) between January 2014 and February 2015.

Patients were excluded from study participation if they had previously undergone knee joint replacement surgery of the affected joint or any other lower limb surgery within the past 6 months, co-existing inflammatory, metabolic, neurological or severe medical conditions hindering the ability of the patient to participate in the study or comorbid conditions or cognitive disturbances that could influence with completion of the PDs.

Before study participation, subjects carefully read an information leaflet. Written informed consent was obtained from all participants before testing in accordance with the Declaration of Helsinki.

Procedure

Demographic information including age, sex, body mass index and pain duration were collected by self-report. Participants additionally completed a 11-point numeric rating scale to quantify their current pain intensity and were asked to complete a PD to illustrate their area of pain. The patient-reported numeric rating scale demonstrated good psychometric properties for evaluating functional disability in people with hip and knee osteoarthritis.[22]

Patients then completed the following self-administration questionnaires in a standardized order: the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale, Pain Catastrophizing Scale (PCS), Central Sensitization Inventory (CSI), painDETECT (PD-Q), Tampa Scale for Kinesiophobia (TSK), Pain Vigilance and Awareness Questionnaire (PVAQ) and the Chronic Pain Acceptance Questionnaire (CPAQ).

Afterwards, a standardized physical examination was performed on each participant consisting of range of motion measurement for both active knee flexion and extension and the Timed Up and Go test. The reliability and validity of goniometry to measure range of motion has been documented for knee flexion and extension.[23] The Timed Up and Go test is reliable and has a minimum detectable change that is adequate for clinical use.[24]

Finally, all subjects were assessed by QST to examine pressure pain thresholds, temporal summation and conditioned pain modulation. All QST was carried out by the same researcher in one individual session in the laboratories of the Hospital Universitario de La Ribera (Alzira, Spain). At the time of examining the patients, the assessor was blinded to the questionnaire data including the PDs analysis. Statistical analysis of the PDs data was performed by a researcher who was blinded from the QST data.

Measurements

Pain extent and location

A novel method for obtaining and quantifying the extent and location of pain using a digital tablet was used.[25] Test-retest reliability of this method for acquisition of PDs was recently demonstrated in people with chronic neck and low back pain.[25] PDs were completed on a digital tablet (iPad 2, Apple Computer, Cupertino, CA, USA) using a stylus pen for digital tablets (CS100B, Wacom, Vancouver, WA, USA) and a commercially available sketching software (SketchBook Pro). Depending on the gender of the subject, a male or female body chart with different views of the knee region (frontal, dorsal) was

chosen and opened in the sketching software. The type, size and colour of the pen stroke were standardized across all participants.

An operator, who trained with the device in clinical practice one month prior to the start of the study, gave each subject a standardized verbal explanation on what the PD was and how to complete it using the digital tablet. The PD was presented to the patient as a tool where they should illustrate precisely where they had felt pain during the previous week. The assessor highlighted the importance of fully illustrating all pain sites. After a demonstration and brief training to familiarize the patients with the device, they were asked to complete their PDs. Patients were instructed as follows: '*Please draw where you felt your usual pain during the last week on this body chart and try to be as precise as possible*'. Patients were instructed to colour every part of the body where they perceived pain in the previous week, independently from the type and the severity of pain. Before saving and storing the PD, patients were asked if the PD corresponded to their real pain distribution/extent. If not, patients were given the possibility to correct the drawing using the "eraser" tool.

A custom software was used to compute the pain extent for each subject, and to generate two pain frequency maps (i.e. frontal and dorsal body chart) separately for men and women.[25] Pain extent was expressed as the number of pixels coloured inside the frontal and dorsal body chart perimeter. Pain frequency maps were obtained by superimposing the PD to illustrate the most frequently reported location of pain.

Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index (WOMAC)

The Spanish version of the self-administered Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis was used.[26] The WOMAC comprises of five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Total WOMAC score and scores from the pain, stiffness and functional subscales were considered. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. The reliability and validity of the WOMAC has been demonstrated in people with knee OA.[27]

Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale (PCS) is a valid and reliable instrument to measure pain catastrophizing in older adults with OA.[28,29] It comprises of 13 items each ranged on a 5-point scale with the end points (0) “not at all” and (4) “all the time” (range: 0-52). Higher scores indicate a higher degree of pain catastrophizing. The Spanish version of the PCS was used in this study.[30]

Central Sensitization Inventory (CSI)

The Central Sensitization Inventory is a self-report screening instrument to help identify patients with central sensitivity syndromes for which CS may be a common etiology.[31] It has high reliability and validity[31] and a cutoff score of 40 out of 100 was able to distinguish between patients diagnosed with central sensitivity syndromes and a non-patient comparison sample (sensitivity = 81%, specificity = 75%).[32] The Spanish version of the CSI was used in this study.

Neuropathic-like symptoms

The Spanish version of the PainDETECT questionnaire (PD-Q) was used to facilitate the identification of neuropathic-like symptoms related to knee OA.[33] The PD-Q is a self-administered questionnaire comprised of 9 items: seven evaluating pain quality, one pain pattern and one pain radiation, which all contribute to an aggregate score (range: -1 to 38). Sensitivity, specificity, and positive predictive values for neuropathic pain symptoms using the cut-off score of 19 were 85%, 80%, and 83%, respectively.[34] The relationship between PD-Q scores and signs of central sensitization in OA patients has been previously demonstrated.[35]

Tampa Scale of Kinesiophobia (TSK)

The Spanish version of the TSK-11 was used.[36] The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement and eliminates psychometrically poor items from the original version of the TSK,[37] thus creating a shorter questionnaire with comparable internal consistency. The TSK-11 has a 2-factor structure: activity avoidance and harm, and has demonstrated acceptable psychometric properties.[36] Higher scores indicate more fear-avoidance behavior.

Pain Vigilance and Awareness Questionnaire (PVAQ)

The Spanish version of the Pain Vigilance and Awareness Questionnaire (PVAQ) was used to evaluate patient's preoccupation with or attention to pain associated with pain-related fear and perceived pain severity.[38] The PVAQ comprises of nine items each rated on a scale from 0 (never) to 5 (always). Higher scores indicate a higher degree of pain vigilance and awareness.

Psychometric properties of the PVAQ were previously reported showing good internal consistency[39], reliability[38] and validity.[38]

Chronic Pain Acceptance Questionnaire (CPAQ)

The Chronic Pain Acceptance Questionnaire (CPAQ) is the questionnaire most often used to measure pain acceptance in chronic pain populations.[40] It comprises of 20 items each rated on a scale from 0 to 6 and it has a two-factor structure: activities engagement and pain willingness. The total score results from the sum of these two factors with higher scores indicating a higher degree of chronic pain acceptance. The Spanish version of the CPAQ, which has shown to be reliable and have valid construct validity, was used in this study.[40]

Pressure pain threshold (PPT)

Two test sites in the peripatellar region (3 cm medial and lateral to the midpoint of the medial and lateral edge of patella, respectively) and one control distant site on the ipsilateral extensor carpi radialis longus (5 cm distal to lateral epicondyle of humerus) were selected for PPT measurement.[12] The PPT was measured using an analogue Fisher algometer (Force Dial model FDK 40 Push Pull Force Gage, Wagner Instruments, P.O.B. 1217, Greenwich CT 06836) with a surface area at the round tip of 1cm^2. The algometer probe tip was applied perpendicular to the skin at a rate of 1kg/cm^2/s until the first onset of pain. PPT was measured three times on each site with a 30 s interstimulus interval between each measurement. The mean of the three measurements was used in the statistical analysis.

Temporal summation of pain and Conditioned pain modulation (CPM)

For measuring bottom-up excitability and efficacy of endogenous pain inhibition, the temporal summation (TS) and Conditioned Pain Modulation (CPM) paradigms were used. TS and CPM are established ways of measuring bottom-up excitability and pain inhibition, respectively[41,42].

First, PPTs were measured at the peripatellar region and the ipsilateral extensor carpi radialis longus as described above. Second, TS was provoked by means of 10 consecutive pulses at previously determined PPT at each location. TS started 2 min after PPT measurement. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the determined PPT and maintained for 1 s before being released (1 s interstimulus interval). Pain intensity of the first, fifth, and tenth pulse was rated on a numerical rating scale (0: no pain to 10: worst possible pain). Afterwards, a rest period of 5 min was given.

Third, CPM was induced by combining the TS procedure (test stimulus) and an inflated occlusion cuff around the subject's arm, contralateral to the side of the affected knee, to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mm Hg/s until 'the first sensation of pain' and maintained for 30 s. Afterwards, pain intensity, as a result of cuff inflation, was rated on a numerical rating scale. Next, cuff inflation was increased or decreased until the pain intensity was rated as 3/10. TS assessment was then repeated during maintenance of the cuff inflation.

The details and data supporting the test-retest reliability and validity of the protocol for examining TS and CPM are described elsewhere.[43]

Statistical analysis

Distribution of the data was tested with the Shapiro-Wilk test and non-normally distributed data were identified. Descriptive statistics were used to describe the baseline characteristics of the OA patients. A Mann-Whitney U test was run to determine if there were differences in baseline clinical variables between males and females. Pain frequency maps were generated considering male and female patients separately. TS was calculated as the difference between the 10th and the 1st pain rating score before occlusion.[43] The outcome measure for CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th during occlusion.[43] Spearman's correlation coefficients were computed to reveal possible correlations: (1) between pain extent and direct measures of CS (i.e. PPT knee, PPT epicondyle, knee TS, epicondyle TS, knee CPM, epicondyle CPM), (2) between pain extent and indirect measures of CS (i.e. CSI and PD-Q) and (3) between pain extent and clinical features (i.e. VAS, WOMAC, WOMAC pain subscale, WOMAC stiffness subscale, WOMAC functional limitation scale, PCS, TSK, PVAQ, CPAQ). Statistical analyses were performed using SPSS 22 (SPSS INc, Chicago, IL, USA). The significance level was set at $P < 0.05$.

Results

Fifty-three patients with knee OA (34 woman and 19 men) were enrolled in the study. Patient baseline characteristics are detailed in Table 1. Median scores for pain extent, ROM for active knee flexion, Timed Up and Go test, and WOMAC were significantly different between males and females ($p<.05$). Pain frequency maps for the patients with knee OA are illustrated in Figure 1 and

correlations between pain extent and measures of CS and clinical features are reported in Table 2.

Pain extent and direct and indirect measures of CS

Significant correlations were identified between pain extent and PPT at the knee (-.306, P < 0.05) and epicondyle (-.308, P < 0.05). No significant associations were observed between pain extent and TS or pain extent and CPM, both at the knee and epicondyle. A significant correlation was identified between pain extent and the CSI score (.456, P < 0.01).

Pain extent and clinical features

Significant associations were observed between pain extent and the pain (.325, P < 0.05) and stiffness (.341, P < 0.05) subscale of the WOMAC.

Discussion

Several methods for illustrating the location and extent of pain in patients with chronic OA pain have been used with no gold standard in this regard. We explored, for the first time, the utility of a novel digital device using two-dimensional body charts for PD acquisition and analysis[25] in a sample of patients with chronic OA pain. Through a digital tablet using a user-friendly digital device, participants reported their pattern of pain on a body chart. Other systems such as the photographic knee pain map have shown good validity and reliability for patients with regional knee pain to identify its location.[11] Future research is warranted to evaluate the clinimetric properties of PDs used in the

current study in people with knee OA pain. However the reliability of this method has been established in other patient groups.[25]

Pain extent and direct and indirect measures of CS

The results of this study showed a significant positive correlation between pain extent and some direct and indirect measures of CS. On the one hand, a greater extent of pain was correlated with lower PPT at a remote site from the knee (i.e. epicondyle), which reflects widespread hyperalgesia and therefore supports the validity of PDs for assessing CS in patients with knee OA pain. Indeed, increased pain sensitivity distantly from the knee provides direct evidence of CS in people with knee OA.[3,4] In addition, we found that a greater extent of symptoms was associated with a higher degree of subjective CS pain descriptors as assessed with the CSI questionnaire, again supporting the validity of PDs for assessing CS in knee OA. The CSI was recently shown to be a useful and a valid instrument for screening patients with central sensitivity syndromes.[44] In addition, OA patients with preoperative high levels of comorbid centrally mediated symptoms measured by the CSI showed severe pain, increased analgesic requirements and were at higher risk of persistent pain after total knee arthroplasty in the early postoperative period.[45]

Previous studies have established associations between PDs and central pain mechanisms, although in non-OA populations. For instance, a significant correlation between nonorganic PDs and higher scores with the Waddell's nonorganic physical signs was found in patients with chronic low back pain.[46] Nonorganic PDs were defined as those with poorly defined pain patterns, bizarre or non-anatomical pain areas. In addition, nonorganic PDs were

associated with maladaptive psychosocial factors (i.e. high levels of catastrophizing, anxiety and depression) in patients with chronic neck-shoulder and lower-back/lower limb pain[47] and chronic low back pain.[48] However, maladaptive psychosocial factors including magnified symptom behavior as assessed with the Waddell's scale provide no direct evidence for CS. In fact, psychosocial factors were not included as essential criteria for classification of CS pain as they are also prevalent in nociceptive and neuropathic pain.[5]

Some studies have inferred CS based on neuropathic pain descriptors of symptoms.[49,50] Contrary to what may have been expected, we did not find an association between pain extent and neuropathic symptoms in this study. This lack of correlation may be due to the fact that we used the PD-Q and not the *modified* version of this questionnaire (*m*PD-Q) recently recommended for an OA pain population.[49] Like the original PD-Q, the *m*PD-Q is comprised of nine items but with some modifications adapted to people with OA, such as those related to framing of questions. Also, widespread pain in OA patients may reflect non-neuropathic CS rather than neuropathic pain, making the lack of association between the scores obtained from the PDs and the PD-Q plausible.

No significant associations were observed between pain extent and TS or pain extent and CPM. Pain associated with knee OA is recognized as a complex phenomenon encompassing several mechanisms such as CS. [51,52] The quantification of CS is in turn multidimensional by including several objective QST techniques such as pain and tolerance thresholds, spatial summation, TS or CPM.[4] These methods assess different aspects of CS, which could justify that spreading of pain as assessed with PDs was not correlated with some pain biomarkers of CS such as TS and CPM.

Pain extent and clinical features

A significant positive correlation between knee pain severity and stiffness and pain extent reported by patients was observed. Although pain extent, pain intensity and stiffness are variables assessing different constructs, it could be expected that patients with knee OA with more diffuse or widespread pain would report higher pain intensity and stiffness scores. The most common pattern of pain reported by our sample was anterior knee pain, in particular medial knee and peripatellar pain, which is in accordance with previous research.[10,11,16,17] Interestingly, besides local knee symptoms, many participants also perceived enlarged and distant pain areas as can be seen in Figure 1. This spreading of pain to larger areas supports the notion that CS may be present in these patients.[4] Although using an experimental pain design, Bajaj and colleagues also showed significantly larger referred pain areas after intramuscular hypertonic saline infusion in subjects with knee OA, when compared with controls.[53] Referred pain is a phenomenon attributed to CS.[4,6] In addition, distally radiating knee pain was observed in individuals with knee OA pain, in particular in those with more persistent and severe symptoms.[10] In our study, enlarged areas of pain were especially noticeable in women. This finding is consistent with previous research where the most sensitized-groups of subjects with knee OA pain contained more women than men.[54,55]

Psychosocial variables were unrelated to pain extent in our study. This lack of correlation between pain extent and psychological factors is in accordance with previous research done in non-OA pain populations, where no correlation between pain extent and the individual psychological state was demonstrated.[56] Indeed, a recent systematic review on PDs did not support the

assumption that unusual or extensive pain drawings indicate disturbed psychological state.[15]

There are several methodological factors of this study which should be considered. First of all, we didn't collect information on the reliability or stability of pain location over time in our sample of patients. Reliability was assumed based on previous studies using this method for PD analysis in other chronic pain populations.[25] In addition, as positive and negative predictive values of PDs were not calculated and the study design was cross-sectional, firm conclusions about the predictive role of PDs on knee OA pain cannot be drawn. Future studies could for instance explore the possible association between PDs and outcome measures after treatment (i.e. surgery), to determine the real clinical utility of PDs for people with knee OA. In this regard, Skou and colleagues found that subjects with pain after re-total knee arthroplasty demonstrated significantly more pain sites using a region-divided body chart when compared to participants without pain.[13]

In conclusion, we have shown that pain extent reported by patients with knee OA is correlated with some clinical features and direct and indirect measures of CS. Given the significant role CS plays in a subgroup of patients with knee OA and that CS can mediate treatment responses (i.e. after surgery[57,58]), classification of people with knee OA pain in terms of pain mechanisms is a research priority[14,59,60]. However, since costly and unattainable laboratory equipment is usually necessary for diagnosis, identification of CS is clinically challenging. In this regard, PD may constitute an easy and cost-effective way for the early identification of CS in people with knee OA pain.

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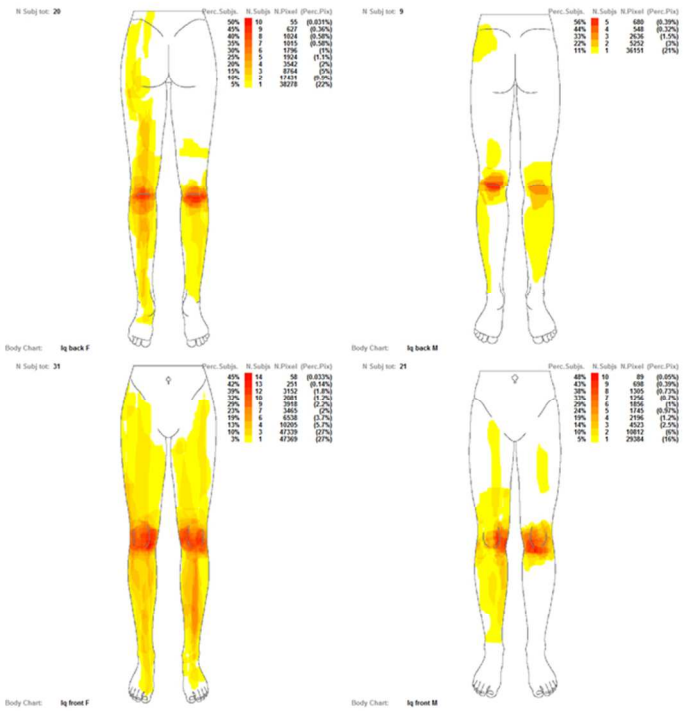
Figure and Table legends

Figure 1. Pain frequency maps generated for all patients with knee OA pain. Pain frequency maps have been generated for men and women separately. The colour bar represents the frequency of coloured areas. Dark red represents the most frequently reported area of pain.

Table 1. Patient baseline characteristics. BMI, Body Mass Index; VAS, Visual Analogue Scale; ROM, Range of Movement.

Table 2. Spearman's correlation coefficients between pain extent, computed using PDs, and measures of CS and clinical features for patients with knee OA pain. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.001 level (2-tailed).



254x190mm (96 x 96 DPI)

Table 1. Patient baseline characteristics. BMI, Body Mass Index; VAS, Visual Analogue Scale; ROM, Range of Movement.

Baseline characteristics of OA patients	**All subjects (n=53)** Mean (SD) Median (IQR)	**Female (n=34)** Mean (SD) Median (IQR)	**Male (n=19)** Mean (SD) Median (IQR)	**P- value**
Age (years)	70.2 (7.4) 72 (11.5)	71.2 (7.8) 73 (11.2)	68.5 (6.3) 70 (7)	.130
BMI (Kg/m^2)	29.9 (3.9) 30 (5.5)	30.4 (4.2) 30 (6.2)	28.9 (3.1) 28 (5)	.183
Pain extent (pixels)	12766 (13494) 8272 (12190)	15012 (14327) 10314 (12382)	8747 (11096) 5816 (7083)	<.05
Pain duration (years)	7.5 (6) 5 (10)	6.7 (5.7) 4 (10.3)	9.1 (6.3) 6 (11)	.127
VAS (mm)	59.2 (17) 59 (22.5)	61.9 (17.2) 60.5 (27.3)	54.4 (15.8) 58 (20)	.217
ROM active knee flexion (degree)	115.5 (11.4) 115.5 (10)	113.9 (9.8) 115 (8.7)	118.3 (13.5) 118.5 (9.2)	<.05
ROM active knee extension (degree)	-2.41 (6.3) -2 (7.9)	-3.2 (6.7) -2.6 (7.96)	-0.9 (5.4) -1.6 (5.3)	.30
Timed Up and Go test (seconds)	11.4 (5.7) 9.8 (5)	13.4 (6.2) 11.8 (5.5)	7.9 (1.6) 7.7 (2.6)	<.001
WOMAC (0-68)	49.4 (16.5) 49 (25)	54.1 (16.1) 56 (25)	41 (14) 38 (23)	<.05

Table 2. Spearman's correlation coefficients between pain extent, computed using PD, and measures of CS and clinical features for patients with knee OA pain. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.001 level (2-tailed).

		Correlation with pain extent ρ
Direct measures of CS	PPT knee (Kg/cm^2)	**-.306***
	PPT epicondyle (Kg/cm^2)	**-.308***
	Knee TS (Kg/cm^2)	-.031
	Epicondyle TS (Kg/cm^2)	.204
	Knee CPM (Kg/cm^2)	-.066
	Epicondyle CPM (Kg/cm^2)	-.040
Indirect measures of CS	CSI	**.456****
	PD-Q	.266
Clinical features	VAS (mm)	.221
	WOMAC	.259
	WOMAC pain subscale	**.325***
	WOMAC stiffness subscale	**.341***
	WOMAC functional limitation scale	.183
	PCS	.145
	PVAQ	.100
	CPAQ	-.195
	TSK	-.195

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

Please insert the page numbers where the item can be found in your manuscript. If item does not apply, type "N/A."

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 1-2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4-5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6-1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6-1
Bias	9	Describe any efforts to address potential sources of bias N/A
Study size	10	Explain how the study size was arrived at Page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 13
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy N/A
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed N/A
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 13
		(b) Indicate number of participants with missing data for each variable of interest N/A
Outcome data	15*	Report numbers of outcome events or summary measures Page 13-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 13-
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A

Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14-
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 18
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.