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1   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

Increased postural stiffness during challenging postural tasks in patients with knee osteoarthritis with high pain sensitization

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2   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

ABSTRACT

Background: Postural stability is affected in knee osteoarthritis patients who present with pain but the link to pain sensitization is unclear.

Methods: Patients with knee osteoarthritis completed the Knee Injury and Osteoarthritis Outcome Score and pressure pain thresholds were assessed bilaterally at the knee, lower leg and forearm prior to standing quietly (one minute) on a force platform in four conditions: Firm surface with open eyes, firm surface with closed eyes, soft surface with open eyes, and soft surface with closed eyes. Pain intensity during standing was assessed via numerical rating scale. Postural stability was assessed by the range, velocity, and standard deviation of the Centre of Pressure (CoP) extracted from the force platform. The means of three repeated measures per standing condition were analysed. High-sensitization and low-sensitization groups were defined based on bilateral pressure pain thresholds from leg and arm.

Findings: Fifty-six patients were included. Compared with the low-sensitization group, the high-sensitization group demonstrated 1) smaller pressure pain thresholds at the knee (P<0.05) although the Knee Injury and Osteoarthritis Outcome Score and pain intensity were not significantly different between groups, and 2) smaller range of the CoP in the anterior-posterior direction during the soft surface with closed eyes condition (P<0.05).

Interpretation: Smaller CoP range suggest that patients with more widespread pain sensitivity have increased postural stiffness compared with the low-sensitization group. The greater stiffness found in high-sensitization patients under sensory restrictions (closed eyes and reduced proprioception) might relate to restricted integration of sensory information due to widespread pain sensitization.

Keywords

Center of Pressure, Pain Pressure Threshold, Vision, Foam, Balance

1. Introduction

Knee osteoarthritis (KOA) is a progressive degenerative joint disease (Davis, 1988) with related worsening of balance stability over time (Messier et al., 2002) partially related to ageing (Felson et al., 1987). Interestingly, the progressive degeneration of the joint structures (Davis, 1988) is correlate with proprioceptive acuity (Felson et al., 2009), which might be related to postural control impairments found in patients suffering from KOA (Masui et al., 2006). Vision and proprioception is important for postural stability in subgroups of KOA patients who report high pain intensity and present with large structural damage to the joint. Suboptimal environments, such as those with unstable floor surfaces and poor lighting, can limit the sensory information fed back to the central nervous system of these patients, impacting postural stability (Hirata et al., 2013). This indicates that the central nervous system is adaptive by reorganizing available sensory information to decrease postural sway (Oie et al., 2002); although to which extent widespread sensitization due to pain is responsible for these adaptations is still unknown. Altogether, the current literature suggests that although pain and structural changes in patients with KOA seem to increase postural sway, the sensory-motor integration/reorganization used to control such posture is not trivial in patients with sensitized knees. The level of widespread sensitization due to pain is often neglected in postural control studies even though patients with KOA, in general, have higher pain sensitivity compared with controls (Imamura et al., 2008) which are also correlated with high levels of pain (Petersen et al., 2016). Although the central mechanisms of widespread pain sensitization in KOA patients have multiple actions, it seems that widespread pain sensitization may impair the sensory influx of information to the central nervous system (Graven-Nielsen and Arendt-Nielsen, 2002) with

possible consequences for the motor output related to postural sway (Schabrun et al., 2016).

If and how widespread sensitization affects postural sway in patients with KOA and how these patients reorganize the available sensory information is still not known. A better understanding of these mechanisms in patients with KOA can possibly improve the identification of those patients at greater risk of falling. This new knowledge may positively enhance future rehabilitation protocols aiming to improve postural sway and reduce fall risk in this population. The aim of the present study was to investigate postural control reorganization in different sensory conditions in KOA patients with high and low widespread sensitization. It was hypothesized that patients in the high-sensitization group would have larger postural sway in conditions where the sensory information is suboptimal compared with the low-sensitization group.

2. METHODS

2.1. Study design

This cross-sectional study evaluated baseline postural sway in KOA patients from a randomized controlled trial (Skou et al., 2016). The study conforms to the STROBE statement for reporting cross-sectional studies. Full details of the recruitment, eligibility criteria, randomization and allocation concealment have been published previously in the study protocol (Skou et al., 2012).

2.2. Subjects

One hundred patients were initially enrolled. Patients were recruited from one of two specialized public outpatient clinics by an orthopedic surgeon. Patients with symptomatic KOA were included if they presented with a Kellgren-Lawrence (KL) score of 1 or greater on standing, weight-bearing x-rays, and not found eligible for total knee replacement by an orthopedic surgeon, although experiencing more than mild symptoms and functional limitations (Skou et al., 2016). More than mild limitation was defined as a score equal to or below 75 on the Knee injury and Osteoarthritis Outcome Score (KOOS$_4$) calculated as the average score of the subscale scores for pain, symptoms, activities of daily living and quality of life (0-100 worst to best scale (Roos et al., 1998)). Major exclusion criteria were less than mild limitations (>75 KOOS), previous ipsilateral knee replacement, and a mean knee pain intensity in the previous week greater than 60 mm on a 100 mm visual analogue scale (VAS). Subjects were given a detailed verbal and written explanation prior to data collection. Signed informed consent was obtained before enrollment in the study conducted in accordance with the Helsinki declaration, approved by the local Ethics Committee of The North Denmark Region (N-20110085), and registered at ClinicalTrials.gov (NCT01535001).

2.3. Protocol for postural control analysis

The study consisted of one session lasting approximately 45 minutes. Patients were asked to stand barefoot as quiet as possible on a force platform for 60 s with their feet together under four sensory conditions (Hirata et al., 2013): (i) firm surface with open eyes; (ii) firm surface with closed eyes; (iii) soft surface with open eyes; and (iv) soft surface with closed eyes. During the soft surface condition, a pillow of foam (5 cm high) was placed on top of

the force platform. The patients performed a total 12 postural control trials grouped in 3 blocks of 4 trials each. Each block consisted of one trial from each of the 4 sensory conditions. The order of each sensory condition was randomized for every subject.　The patients were asked to sit for at least one minute every time one block was finished. . During the eyes open conditions, the patients were asked to focus on a circular black mark (diameter of 12 cm) positioned on a wall 1.5 m away from the subjects and adjusted to their eye height. The patients were instructed not to talk during the 60 s of data collection unless any problem was reported and to open their eyes and/or take a step if necessary to avoid a fall. The trial was repeated if the subjects failed to stand quietly for 60 s. The feet position was marked to ensure the same position was used during all trials and the arms were relaxed along the body. The foam was also marked to ensure it was placed in the same position on the top of the of force plate during the experiment. Prior to data collection, all patients performed at least 1 familiarization trial (10 s) in each condition.

2.4. Postural control parameters

A triangular force plate (equal sides of 800mm) with four strain gauge transducer (Meititur Good Balance System, Finland) recorded and filtered the vertical forces during each trial. The data was recorded at 50Hz [as recommended by the International Society for Posture and Gait Research (ISPGR) standardization Committee (Scoppa et al., 2013)] and filtered with a three-point median filter and infinite impulse response (IIR) filter, with 20 Hz low-pass cut-off frequency.

. Knowing the position of the sensors and the magnitude of the force on each of them, the center of pressure (CoP) position in time for both medial-lateral and anterior-posterior direction was estimated from the filtered data during the intermediate 30 s of each trial

(from 15th to 45th s) by a dedicated software (Metitur Good Balance System®, Finland). This is a valid and reliable system for postural sway measurements (Era et al., 2006; Ha et al., 2014) with accuracy better than 1mm for the Center of pressure (CoP) position measurement (this information was extracted from the Good Balance System User Manual). Standard deviation, range and velocity in both medial-lateral and anterior-posterior directions were extracted from the CoP data and averaged over the 3 trials.

2.5. Pain intensity

Immediately after every 4th trial, the patients were asked to verbally rate their pain during the standing task for each lower limb (left and right side) using a numerical rating scale (NRS). The "0" score indicated no pain and "10" the worst imaginable pain (total of 3 scores for each leg). The NRS scores were averaged between the 2 legs and 3 time points for further analysis.

2.6. Pressure Pain Thresholds

Pressure algometry is a reliable method to estimate pressure pain thresholds [PPTs; (Chesterton et al., 2007; Kosek et al., 1993)] and correlates with clinically meaningful variables evaluated in different chronic pain patients (Hooten et al., 2013; O'Neill et al., 2013)." PPTs were assessed with a handheld pressure algometer (Algometer Type II, Somedic AB, Hoerby, Sweden) with a 1 cm^2 probe. Prior to the actual assessment, one or two tests were performed at the dorsal aspect of the hand to ensure that the patient understood the procedure. A constant force rate (30 kPa/s) was applied perpendicular to the skin at 3 bilateralareas: (i) tibialis anterior muscle (5cm distal to the tibial tuberosity); (ii) four sites in the knee region (Figure 1A, 3cm medial to the midpoint of the medial edge of

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9   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

the patella; 2cm proximal to the superior edge of the patella; 3cm lateral to the mid-point of the lateral edge of the patella; and at the center of the patella); and (iii) on the extensor carpi radialis longus muscle. The subjects were asked to push a button when the pressure stimulation became painful (defining the PPT). The PPTs assessment was performed twice at all sites and the average of the 2 measurements was used in the analysis.

2.7. Subgrouping

A Two-Step Clustering Analysis procedure [SPSS software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp)] was used to divide the patients according to the degree of their spreading sensitization. The average PPTs from both tibialis anterior and extensor carpi radialis muscles was used as input for the model as indicators of spreading sensitization in patients with KOA (Arendt-Nielsen et al., 2010). Subgroups (clusters) were determined automatically by Schwarz's Bayesian Criterion with the distance between groups was measured with a log-likelihood approach (Fraley, 1998; Fraley and Raftery, 1998).

2.8. Statistics

Data is presented as mean (standard deviation, SD), otherwise indicated. Normality was tested in all variables by Q-Q plots. Age, body mass index (BMI) and KOOS scores were tested with independent T-test between *groups* (low vs high-sensitization). NRS scores of pain intensity during the task and KL scores were analyzed with a non-parametric Mann-Whitney U-test. Pearson's chi-squared test was used to identify if gender were significantly different between *group*s. A 3-way mixed-model analysis of variance (ANOVA) with *groups as a between subject factor, and surface* (firm vs soft) and *vision* (eyes-opened vs closed)

as within subject factors was applied for all CoP variables (Standard Deviation, range and velocity in both medial-lateral and anterior-posterior direction). A MANOVA was perfomed to test if there was a difference in PPTs at the 4 knee sites and 2 control points (bilaterally) between patients with bilateral or unilateral KOA. To test if PPTs (log10 transformed) at the 4 knee sites were different between the low and high sensitized groups, a 3-way mixed model ANOVA with *group as a between subject factor, and side* (left vs right) and *sites* (1 to 4) as within subject factors. Newman-Keuls (NK) correction for multiple comparisons was used in the post-hoc tests and the P-value was set at 0.05. All statistical analyses were performed with STATISTICA software [StatSoft, Inc. (2011). STATISTICA, version 10].

3. RESULTS

3.1. Patient characteristics

Forty-four patients [18 males, 16 females, 67.3 (SD 8.1) years old, 81.4 (SD 13.7) kg of body mass, 167.5 (SD 8.2) cm tall, KL score 2.5 (SD 1.1) and BMI of 30.0 (SD 4.1)]were excluded due to 1) corrupted or insufficient CoP data (n = 17), 2) incompliance by not showing up for the postural control test (n = 20), 3) inability to complete the postural task (n = 6), and 4) surgical intervention (total knee replacement) after enrolment into the study (n= 1). . Finally, fifty-six patients were included for analysis [64.9 (SD 9.4) years old, 90.2 (SD 17.2) kg of body mass, 171.4 (SD 8.9) cm tall and BMI of 30.7 (SD 6.1) kg/cm^2]. There was no significant difference between included vs not included patients for age, height, weight, KL score, BMI and all KOOS scores (Table 1). The included patients were in average 4 cm higher and 8 kilograms heavier than the not included patients. The corrupted/incomplete data problem occurred due to technical issues in the dedicated

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11   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

software used for collecting the postural control data. An updated version of the software was later implemented, solving the issues when recording the data. In total, 39% of the included patients presented with bilateral KOA.

3.2. Clustering analysis

Low (n = 23) and high-sensitization (n = 33) groups were automatically generated after the TwoStep clustering analysis with good average silhouette (0.7), indicating that in average, all subjects were well matched to its own cluster A perfect matching is represented by a silhouette equals to 1.The characteristics for the fifty-six patients, in both groups, are described in Table 2. No significant difference was found between the low and high sensitization groups for age, BMI, KL scores, pain during the task and all KOOS scores (Table 2). There was a higher proportion of females in the high sensitization group compared with low sensitization group (Table 2, Pearson chi-square (15.7, 1), $P < 0.0001$). Likewise, the proportion of patients with bilateral KOA was higher in the high sensitization group compared with low sensitization group (Table 2, Person chi-square (4.2, 1), $P = 0.04$). For that reason, both gender and location of KOA (uni/bilateral) were used as co-variate in the statistical models for knee pain pressure thresholds and CoP variables. The patients in the high-sensitization group were 175.7 (SD 0.08) cm and thereby taller than the low-sensitization group who were 168.4 (SD 0.08) cm (t-score (54): 3.2; P: 0.002). Therefore, the patients' height was used as co-variant in our ANOVAs evaluating the CoP variables (Berger et al., 1992). No differences were found between groups for the variable weight [high-sensitization: 93.7 (SD 15.2) Kg; low-sensitization 87.8 (SD 19.8); t-test (54) = 1.2, $P = 0.2$).]

3.3. Pain Pressure Thresholds

There was no significant difference in any PPT site between patients with unilateral and bilateral KOA (Table 3: MANOVA: Wilks lambda = 0.7, F(12, 43) = 1,2, *P* = 0.3).: Therefore, the PPT values in all sites were averaged between sides for all patients for further analysis.

The average (SD) PPT values for bilateral tibialis anterior muscle for both groups were: (i) high-sensitization right side: 450 (SD 122) kPa, (ii) high-sensitization left side: 442 (SD 145) kPa, (iii) low-sensitization right side: 1034 (SD 320) kPa and (iv) low-sensitization left side: 972 (SD 256) kPa. For the extensor carpi radialis muscle, the PPTs values were: (i) high-sensitization right side: 288 (SD 101) kPa, (ii) high-sensitization left side: 306 (SD 89) kPa, (iii) low-sensitization right side: 586 (SD 222) kPa and (iv) low-sensitization left side: 627 (SD 262).

Averaged PPTs at both knee joints for both groups are showed in Figure 1B. Significant interaction between *site* x *group* indicated that PPTs at all 4 sites were lower in the high-sensitization group compared with the low- sensitization group (Figure 1B, ANOVA F(3, 156) = 5.6, *P* = 0.002, NK: *P* < 0.0001).

3.4. Centre of pressure

The CoP standard deviation, range and velocity in both directions for both groups during all 4 sensory conditions are shown in Figure 2. The CoP range in the anterior-posterior direction was larger in the low-sensitization group compared with the high- sensitization group during eyes closed and soft surface condition (Figure 2D. ANOVA for group*surface*vision interaction: F(1, 53)=8.1, *P* = 0.04, NK: *P* = 0.03).

4. DISCUSSION

This is the first study to investigate how patients with KOA with different degree of widespread sensitization, but similar pain intensity and structural damage adapted their postural sway in different sensory conditions. The high-sensitization group showed smaller CoP range (CopSD) than the low sensitization group during the most challenging sensory condition (eyes closed with unstable surface).

4.1. Postural sway and pain sensitivity in KOA patients

Severe KOA patients sway more than less severe group during the condition with eyes closed on an unstable surface (Hirata et al., 2013). Disease severity (high pain intensity and large cartilage degeneration at the knee joint) may impair postural stability by limiting the quality and amount of sensory information from the affected knees (Hurley et al., 1997) therefore decreasing the amount of sensory information available to estimate the body position space and increasing postural sway. Severe patients may be less capable of reorganizing their sensory information, i.e. reducing the importance of the potentially inaccurate information coming from the affected areas (knee) and increasing the importance of non-affected areas (Hirata et al., 2013). Although we acknowledge that these mechanisms play important roles for postural stability in patients with chronic knee pain, they cannot be used to explain our results since both groups (low and high-sensitization) showed similar pain intensity and structural damage during the experiment.

4.2. Effect of widespread sensitization on postural sway in KOA patients

Despite the higher number of patients suffering from bilateral KOA in the high-sensitization group compared with the low-sensitization group, there were no significant differences in

the PPT values of all sites analysed. That seems to indicate the larger widespread sensitization in the high-sensitization group might not be related to larger number of patients with bilateral KOA in that group. Similar to a previous study analyzing the PPTs at the knee region showed significantly lower pressure pain thresholds in the high-sensitization group compared with the low-sensitization group (Arendt-Nielsen et al., 2010). The grouping technique applied resulted in two different groups with similar pain intensity and KL scores, therefore allowing a unique interpretation on the influence of widespread sensitization on postural control in KOA patients. The results complements a previous study that evaluated postural sway in KOA patients groups with different pain intensity and KL scores (Hirata et al., 2013). Furthermore, similar to our previous study (Hirata et al., 2013), the two different groups could only be differentiated during conditions where the environment posed sensory challenges (eyes closed and soft surface). However, contrary to our hypothesis, the high-sensitization group showed smaller postural sway compared with the low-sensitization group in that condition. A previous study found an increased likelihood of losing balance with smaller CoP amplitude and velocity under fatigue and challenging environment conditions (Ritzmann et al., 2016). It is important to note that when maintaining balance, elderly subjects are known to prioritize postural control in order to avoid injuries from falls and that postural control is enhanced when the environment poses sensory challenges (Liston et al., 2014).

The effect of the widespread sensitization on the gathering of sensory information from the environment might have played an important role in the results reported. In a rat model of KOA pain, highly-sensitized rats showed significant electrophysiological changes in action potentials characteristics from the Aβ-fibers compared with normal control rats (Wu and Henry, 2010). Interestingly, the resting

membrane potential of the Aβ-fibers in the sensitized OA rats was significantly less depolarized compared with control rats, which indicates that less neuronal drive would be necessary to evoke an action potential in these rats (Wu and Henry, 2010). Indeed, more action potentials were elicited in rats suffering from OA compared with control rats, showing greater excitability of Aβ-fibers in presence of OA (Wu and Henry, 2012) and reduced mechanical threshold (Kelly et al., 2012). Additionally, such changes were found in the neuronal branches of Aβ, C and Aδ fibers related to the affected knee and adjacent areas (Wu and Henry, 2010). Although the translation of such findings to human experiments should be done cautiously, one may argue that the presence of sensitized central mechanisms in the patients found in the present study could potentially help to quickly identify small changes in the muscle length and body position over time, allowing them to have a stiffer control of the posture. It has been reported that KOA patients have lower perception threshold for knee movement in the most affected compared with the less affected side (Weiler et al., 2000). Such stiffness may also be beneficial in reducing movement and load in the painful area therefore minimizing pain sensation (Hirata et al., 2010). Although there is not clear causal relation between body sway and physical function, a previous study showed that smaller and slower body sway was correlated with worse physical function and stiffness in KOA patients (Petrella et al., 2017).

Ankle joints have been demonstrated to control the body sway in the anterior-posterior direction during quiet standing (Winter et al., 1996). The high-sensitization group significantly decreased their body sway in the anterior-posterior direction, probably indicating higher stiffness in the ankle joints compared with the low-sensitization group.

A limitation of this study is the number of not included subjects due to corrupted/incomplete data (17%) or no show (20%) for the postural control test. In order to

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16 *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

understand if such scenario might have biased our results, we investigated further if significant differences were found between included vs not included subjects. Since age, KL scores, KOOS scores and BMI were not different between the two groups, there is no clear indications that the excluded patients biased the presented results although the power of our analysis might have been reduced. The body center of mass position was not measured in the study, which could provide a more accurate estimation of the body position in space. Therefore, our study limited to relate the CoP displacement with the magnitude of the body sway during the quiet standing. Fear of fall was not evaluated in the study, which could have increased postural stiffness as a response to suboptimal sensory information provided by the environment. Finally, the sampling rate of 50Hz used in this study is the minimum recommended for reliable CoP data acquisition; sampling with higher rate would have enhanced the temporal definition of the CoP data, which could influence the values of the CoP velocity in this study

5. *Conclusions*

KOA patients with similar pain intensity and disease progression adapt their postural sway differently, according to the extent of spreading sensitization. Patients with a higher level of widespread pain sensitization increased postural stiffness compared with patients with a lower level of widespread pain sensitization. The increased postural stiffness found in high-sensitization patients only occurred in the sagittal plane and during the condition where the sensory information was suboptimal, suggesting that widespread pain sensitization in the high-sensitization patients may increase the risk of falls in these patients during challenging situations.

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Figure Captions

Figure 1

(A) Schematic representation of four sites in the knee region where pressure pain threshold were assessed: (1) 3 cm medial to the midpoint of the medial edge of the patella; (2) 2 cm proximal to the superior edge of the patella;(3) 3 cm lateral to the mid-point of the lateral edge of the patella; and (4) at the centre of the patella. (B) Mean ± SD (n = 56) for the pressure pain threshold in the 4 knee sites (averaged for both knees) for both low- and high-sensitization group. For all sites, the low-sensitization group had higher pressure pain threshold compared with the high-sensitization group ("*", NK: *P < 0.0001*).

Figure 2

Mean ± SD (n = 56) center of pressure standard deviation (A & B), range (C & D) and velocity (E & F) for both anterior-posterior and medial-lateral direction during 4 sensory conditions: (i) open eyes (OE) and "firm" surface, (ii) closed eyes (CE) and "firm" surface, (iii) OE and "soft" surface, and (iv) CE with "soft" surface is showed for both low- and high-sensitization group. The CoP range in the anterior-posterior direction increased more in the low-sensitization group compared with the high-sensitization group during eyes closed and soft surface condition (D, "*" NK: *P* < 0.05).

Table 1: Summary of the Independent t-test between included (n = 56) vs not included patients (n = 44).

	T-Score	P-Value
Age	1.3	0.2
Height	-2.192	0.3
Weight	-2.582	0.1
KL Score	1.56	0.1
BMI	-1.566	0.1
Symptom (KOOS)	0.369	0.7
Pain (KOOS)	-0.713	0.4
ADL (KOOS)	-0.545	0.6
SRA (KOOS)	-0.231	0.8
QL (KOOS)	-1.266	0.2

T-scores and P-values for the independent t-tests between included vs not included patients for: age, height, weight, KL score, body mass index (BMI) and all scores for the Knee injury and Osteoarthritis Outcome Score (KOOS): symptom, pain, activities of daily life (ADL), sports and recreational activities (SRA) and quality of life (QL). No significant differences were found between included vs not included patients.

Table 2: Patient characteristics (n = 56) for both Low (n = 22) and High (n = 34) sensitized groups.

	Low Sensitized KOA patients (n=22)	*High Sensitized KOA patients (n=34)*	*p-value*
Age [years, Mean (SD)]	64.9 (9.4)	64.2 (9.9)	0.56
BMI [kg/m*m, Mean (SD)]	30.1 (4.5)	31.1 (7.1)	0.72
Pain Intensity during the task (NRS, Median [Range])	2 [0-5]	1.4 [0-5]	0.67
KOOS - pain score [0-100, Mean (SD)]	59.3 (13.1)	49.8 ± 14.8	0.10
KOOS - symptoms score [0-100, Mean (SD)]	59.9 (14.9)	54.3 (19.6)	0.99
KOOS - daily living activities score [0-100, Mean (SD)]	63.1 (15.8)	55.9 (19.2)	0.99
KOOS - sports and recreational activities score [0-100, Mean (SD)]	22.9 (15.1)	24.8 (18.5)	0.99
KOOS - quality of life [0-100, Mean (SD)]	38.3 (11.7)	38.2 (15.3)	0.99
KL score (0-4, Median [Range])	3 [1-4]	3 [1-4]	0.61
Gender (number of male/female subjects)	20/2	11/23	**<0.0001#**
KOA (Unilateral/Bilateral)	17/5	17/17	**0.04#**

The knee osteoarthritis (KOA) patients were divided in two groups (low- and high-sensitization) according to their pressure pain threshold values from bilateral tibialis anterior muscle and carpi radialis muscles using a TwoStep Clustering Analysis. Age, body mass index (BMI), pain intensity during the task, Knee Injury and Osteoarthritis Outcome Score (KOOS) scores, Kellgren-Lawrence (KL) score, gender and number of patients with unilateral or bilateral KOA are reported for both groups. The incidence of females and bilateral KOA among the low-sensitization group is significantly lower compared with the high-sensitization group ("#", Pearson chi-squared test).
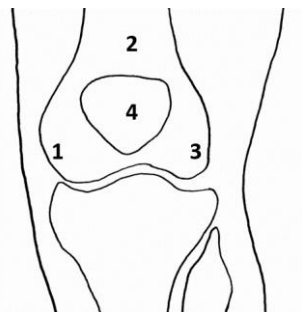
Table 3: Mean [Confidence Interval] for all pressure pain threshold (PPT) points for patients with unilateral (n = 34) and bilateral (n = 22) knee osteoarthritis (KOA).

	Unilateral		Bilateral	
	Right	Left	Right	Left
Site 1 (kPa)	600 [503-697]	529 [459 598]	453 [332 573]	369 [283 456]
Site 2 (kPa)	769 [657 890]	792 [691 894]	543 [393 694]	638 [512 764]
Site 3 (kPa)	699 [588 810]	712 [616 807]	471 [333 608]	526 [407 644]
Site 4 (kPa)	777 [665 889]	704 [613 795]	526 [388 665]	566 [453 679]
TA (kPa)	773 [652 895]	722 [611 832]	560 [409 712]	563 [425 700]
CRL (kPa)	470 [399 514]	503 [425 581]	317 [299 406]	337 [240 435]

PPTs at all knee sites (1-4) and bilateral tibialis anterior (TA) and extensor carpi radialis longus (ECR) muscles. There was no difference in any PPT site between patients with unilaretal and bilateral KOA (MANOVA: Wilks lambda = 0.7, $F_{(12, 43)}$ = 1,2, P = 0.3)

23   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization.*

Figure 1

A

B

Postural stiffness in patients with knee osteoarthritis and widespread sensitization.

Figure 2

ACCEPTED MANUSCRIPT

25   *Postural stiffness in patients with knee osteoarthritis and widespread sensitization*.

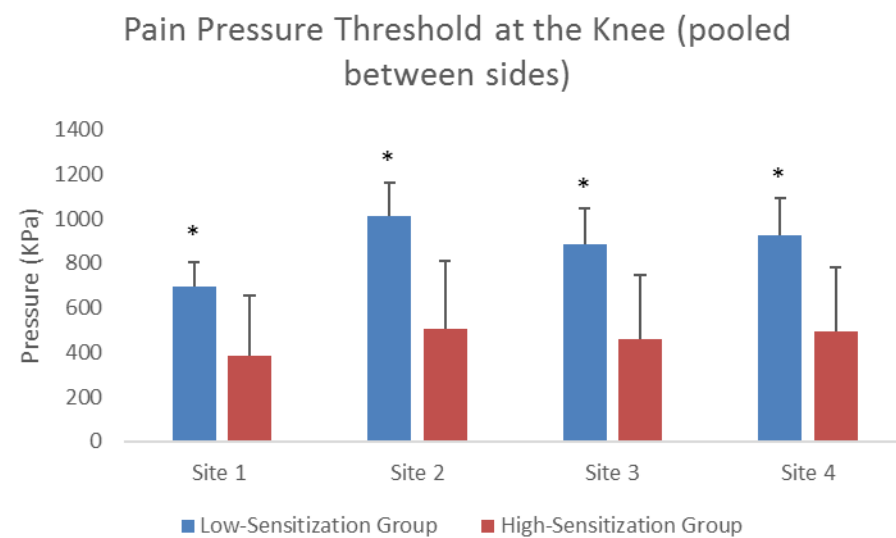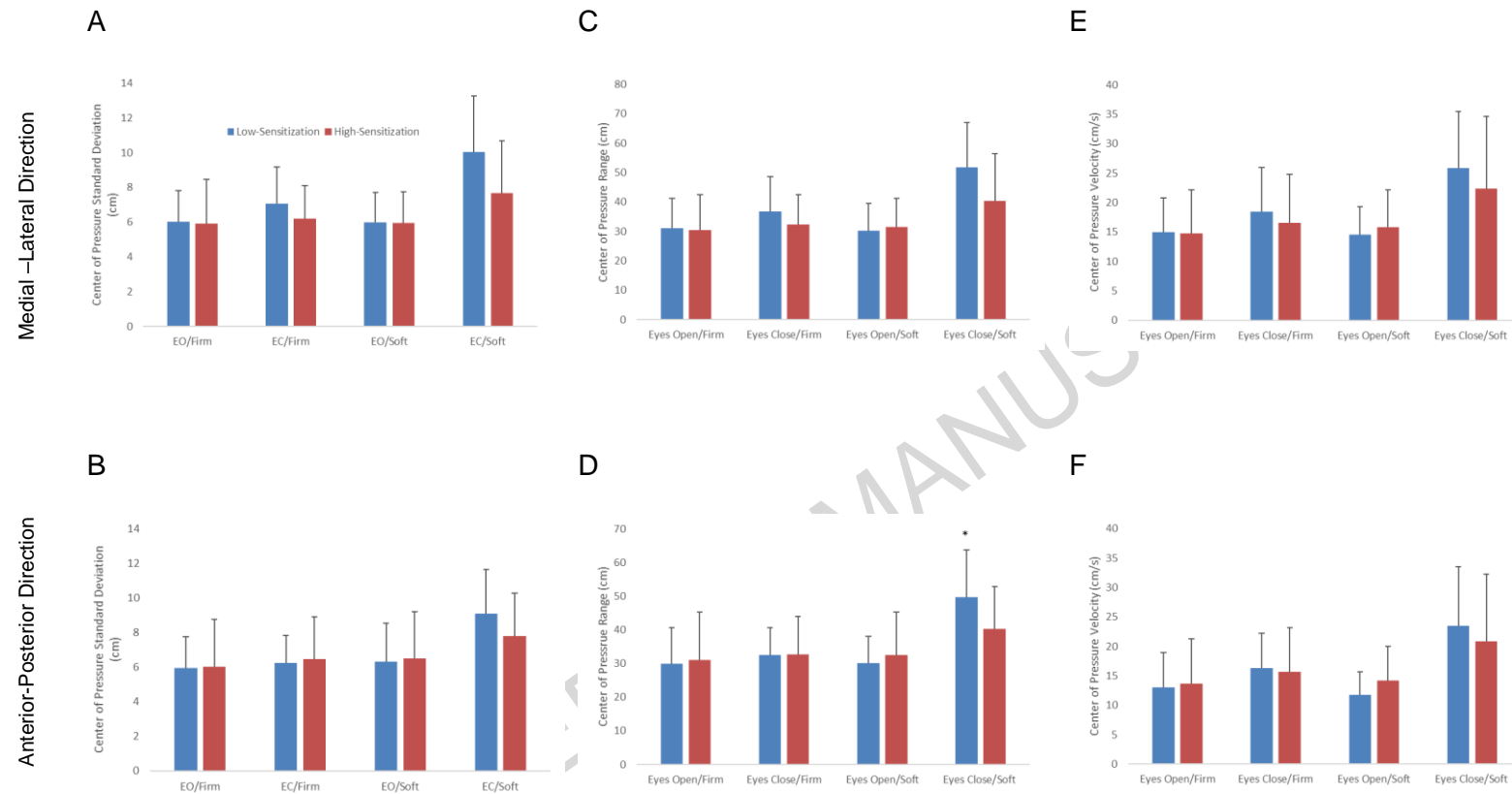**Highlights**

- Larger anterior-posterior postural sway compared with medial-lateral direction.

- Larger widespread pain sensitization relates to higher knee pain sensitivity.

- Larger widespread pain sensitization relates to increased postural stiffness.