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ABSTRACT

1 **Widespread hyperalgesia** has been found in patients with painful hip osteoarthritis (OA) which can
2 be normalized after total hip arthroplasty (THA) if patients have no residual postoperative pain.
3 This study **characterized the preoperative somatosensory profiles and provided possible**
4 **interpretation of underlying pain mechanisms** that might influence the development of postoperative
5 pain. Forty hip OA patients with unilateral pain were assessed before and 6 weeks post-THA and
6 compared with forty asymptomatic control subjects. Hip pain intensity at rest and while walking
7 was assessed on a visual analogue scale (VAS). Bilateral cuff algometry from the thighs were used
8 to assess the cuff pressure pain thresholds (cPPT), pressure values at VAS scores equal with 6 cm
9 (PVAS6), cuff pressure tolerance (cPTT), and temporal summation of pain (TSP) quantified by an
10 increase in VAS scores to repeated phasic cuff stimulations. Correlations between hip pain VAS
11 post-THA and preoperative QST results were analyzed. Post-THA hip pain VAS scores decreased
12 ($P<0.05$) compared to pre-THA. The cPPT, PVAS6, and cPTT were significantly lower bilaterally
13 in both pre-THA and post-THA patients compared with controls ($P<0.05$). TSP was facilitated
14 bilaterally in pre-THA patients compared with controls and normalized following THA in
15 postoperative pain-free patients ($P<0.05$). Postoperative hip pain VAS scores correlated with
16 preoperative **ipsilateral** TSP ($r=0.44$, $P<0.05$). Bilateral pressure pain hypersensitivity and
17 facilitated TSP were demonstrated in **preoperative** hip OA patients. **Although persistent**
18 **postoperative pain is known as multifactorial, greater preoperative TSP was associated with greater**
19 **pain and less reduction in pain after THA.**
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Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty

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ABSTRACT

1 Widespread hyperalgesia has been found in patients with painful hip osteoarthritis (OA) which can
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3 be normalized after total hip arthroplasty (THA) if patients have no residual postoperative pain.
4

5
6 This study characterized the preoperative somatosensory profiles and provided possible
7
8 interpretation of underlying pain mechanisms that might influence the development of
9
10 postoperative pain. Forty hip OA patients with unilateral pain were assessed before and 6 weeks
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12 post-THA and compared with forty asymptomatic control subjects. Hip pain intensity at rest and
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14 while walking was assessed on a visual analogue scale (VAS). Bilateral cuff algometry from the
15
16 thighs were used to assess the cuff pressure pain thresholds (cPPT), pressure values at VAS scores
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18 equal with 6 cm (PVAS6), cuff pressure tolerance (cPTT), and temporal summation of pain (TSP)
19
20 quantified by an increase in VAS scores to repeated phasic cuff stimulations. Correlations between
21
22 hip pain VAS post-THA and preoperative QST results were analyzed. Post-THA hip pain VAS
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24 scores decreased ($P < 0.05$) compared to pre-THA. The cPPT, PVAS6, and cPTT were significantly
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26 lower bilaterally in both pre-THA and post-THA patients compared with controls ($P < 0.05$). TSP
27
28 was facilitated bilaterally in pre-THA patients compared with controls and normalized following
29
30 THA in postoperative pain-free patients ($P < 0.05$). Postoperative hip pain VAS scores correlated
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32 with preoperative ipsilateral TSP ($r = 0.44$, $P < 0.05$). Bilateral pressure pain hypersensitivity and
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34 facilitated TSP were demonstrated in preoperative hip OA patients. Although persistent
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36 postoperative pain is known as multifactorial, greater preoperative TSP was associated with greater
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38 pain and less reduction in pain after THA.
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INTRODUCTION

1 Osteoarthritis (OA) of the knee and hip is the most common musculoskeletal joint disease
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3
4 worldwide [5; 8]. Total hip arthroplasty (THA) is normally an effective surgical intervention to
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6
7 provide pain relief [34], which offers superior outcomes compared with total knee arthroplasty
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10 (TKA) 1 year after surgery [6]. Several recent large, well-designed reports indicate however that
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13 8-17% of patients continue to experience persistent moderate or severe pain 1 to 4 years after THA
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16 [31; 38; 49]. In a systematic review, postoperative follow-up assessments after 3 months and up to 5
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19 years later reported postoperative pain in about 9% of patients after THA and about 20% of patients
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22 after TKA [4].
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26 Painful OA often show pain sensitization [2; 14] associated with postoperative pain or
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28 reduced function of the joint [48]. Perioperative treatment with pregabalin may reduce the
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30 development of chronic post-operative pain indicating sensitization could be important for the pain
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33 outcomes after THA and TKA [7; 44]. Quantitative sensory testing (QST) used to assess widespread
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36 pain hypersensitivity [2; 14; 17], temporal and spatial pain summation [2; 39; 40], and efficacy of
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39 descending pain modulation [2; 14; 39] may help with profiling patients and determining the degree
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42 of sensitization. Recent reviews conclude that painful OA is associated with lower pressure pain
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45 thresholds (PPT) outside and locally over the symptomatic joint [3; 43]. Other studies demonstrated
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48 that widespread pain hypersensitivity, facilitated temporal and spatial pain summation, and impaired
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51 conditioning pain modulation (CPM) exist in patients with painful OA, which may be normalized
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54 after successful TKA with total pain relief [14; 39].
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3 In hip OA patients, Kosek et al. reported local mechanical and thermal hyperalgesia [24] and
4
5 impaired CPM compared with controls which were normalized after successful THA [25].
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7 Aranda-Villalobos et al. [1] reported normalization of decreased PPTs after THA along with clinical
8
9 and functional improvements. A recent study showed a weak correlation between preoperative
10
11 widespread pressure pain hypersensitivity and the severity of movement pain 12 months after THA
12
13 [52] However, no studies have evaluated the pain summation mechanism in hip OA patients
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16 although this parameter has been shown to be facilitated in painful knee OA [2; 14; 33] and to be
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19 predictive for development of chronic post-operative pain [33].
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25 The aim of this study was to assess widespread pain hypersensitivity, temporal and spatial
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27 pain summation, and CPM 1) in hip OA patients compared with matched control subjects, 2) before
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29 and 6 weeks after THA, and 3) to evaluate the value of QST for predicting postoperative pain after
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METHODS

Study participants

Forty consecutive patients with hip OA (mean age 68 years [range 45-81 years]; 20 men) undergoing THA were recruited at the outpatient clinic at the Orthopaedic Clinic in Farsø, Aalborg University Hospital, Denmark. All patients were diagnosed as having hip OA either unilaterally or bilaterally based on radiographic assessments and all met the American College of Rheumatology criteria for hip OA. Patients suffering for at least 3 months from unilateral hip pain while walking

with a pain intensity of 4 cm or more on a 0-10 cm visual analogue scale (VAS) were included.

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3 Bilateral OA patients were included only if one hip was pain free (VAS = 0). The VAS was
4
5 anchored with “no pain” and “maximum pain” at 0 cm and 10 cm, respectively. Exclusion criteria
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7 were other ongoing pain problems, past history of a chronic pain condition, sensory symptomatic
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9 dysfunctions such as a nerve damage, and mental illnesses. Patients were requested not to take
10
11 analgesic medications 24 hours before the study assessment. Forty sex- and age-matched healthy
12
13 control subjects without a history of painful joint disorder were recruited from local communities
14
15 around Aalborg, Denmark (mean age 65 years [range 53-79 years]; 20 men). All participants
16
17 received a detailed written and verbal explanation of the experimental procedures and signed an
18
19 informed consent form. The study was conducted in accordance with the Helsinki Declaration and
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21 was approved by the local Ethics Committee (N-2012-0078).
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Characteristics of clinical pain

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39 All participants were interviewed to obtain medical and medication history, duration of pain
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41 symptoms, and present pain intensity rating at rest and while walking were assessed on the VAS.
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46 Post-THA patients were categorized as pain-free when presenting VAS scores at 0 at rest. The
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48 patients were asked to mark the pain distribution by filling in a body chart. The occurrence of pain
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51 in 11 different areas was registered as (Fig. 1). Previous clinical studies outlined the referral pattern
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54 of hip OA pain [15; 30] and similar categorization was used in this study. Moreover this
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57 categorization matches an experimental hip pain study also demonstrating referred hip pain[18].
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1 The frequency of pain occurrence in each area and the number of pain areas in each patient were
2
3 extracted. Some typical patterns of pain distribution were categorized as 1) hip (including groin,
4
5 buttocks, and greater trochanter), 2) hip and thigh, 3) hip and below thigh, 4) hip and thigh and
6
7 below thigh. The quality of pain was assessed by completion of the Danish version of the McGill
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9 Pain Questionnaire [9]. Moreover, the PainDETECT [12] questionnaire was completed for the
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11 purpose of identifying patients with potential neuropathic pain components although this
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13 questionnaire has recently been criticized when used in OA [29].
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Protocol for quantitative sensory assessment

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27 The subjects were carefully familiarized with the methods before the start of assessments. All
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29 assessments were performed with subjects lying down on a bench in either supine or lateral
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31 decubitus position. Quantitative sensory assessment consisted of 7 modalities: 1) Pressure pain
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33 thresholds (PPTs) at several test sites on the lateral hip and control sites; 2) Cuff pressure pain
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35 sensitivity at the thigh; 3) Temporal summation of pain (TSP) using repeated cuff pressure pain
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37 stimulations on the thigh; 4) Spatial summation of pain (SSP) to cuff pressure stimulation (one and
38
39 two cuffs) on the thigh; 5) Cutaneous pin-prick pain sensitivity on the lateral hip; 6) Thermal
40
41 detection and pain thresholds on the lateral hip; 7) CPM where PPTs and cuff pressure pain
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43 sensitivity were re-assessed during tonic pain induced by cuff pressure pain on the contralateral arm
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45 (heterotopic stimulation to evoke conditioning pain modulation). Bilateral assessments were
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47 performed and the sequence (side and assessment modality) was randomized although CPM test
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1 was always performed last. Each measure, except the CPM test, was recorded three times and
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3 averages of the measurements were used for analysis.
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6 OA patients were assessed before and approximately 6 weeks after THA. For healthy control
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8 subjects, the “affected side” was randomly allocated to the right (N=20) and left (N=20) sides. The
9
10 same experimenter (MI) collected all the data.
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14 15 16 17 18 *Handheld pressure algometry* 19

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21 A handheld pressure algometer (Somedic, Hörby, Sweden) mounted with a 1-cm² probe (covered by
22
23 a disposable latex sheath) was used to record the PPT at 6 different locations on each side (Fig. 1).
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27 An interval of at least 20 s was kept between each PPT assessment. The PPT was defined to the
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29 subject as “the time point at which the pressure sensation changed into pain”. Pressure was
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31 increased gradually at a rate of 30 kPa/s until the pain threshold was reached and the subject pressed
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33 a button.
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44 *Cuff pressure algometry* 45

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47 The cuff algometry (NociTech and Aalborg University, Denmark) consisted of a double chamber
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49 13-cm wide tourniquet cuff (a silicone high-pressure cuff, separated lengthwise into two equal-size
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51 chambers, VBM Medizintechnik GmbH, Sulz, Germany), a computer-controlled air compressor,
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53 and an electronic 10-cm VAS (Aalborg University, Aalborg, Denmark). The cuff was connected to
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57 the compressor and wrapped around the thigh as proximal as possible (just below inguinal crease)
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1 and was automatically inflated at a rate of 1 kPa/s until a maximum pressure limit of 100 kPa. The
2
3 pressure-induced pain intensity was recorded with the electronic continuous VAS and sampled at 10
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5 Hz. Zero and 10 cm on the electronic VAS were defined as “no pain” and “maximal pain”,
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7
8 respectively. The subjects were instructed to rate the VAS pain intensity continuously, and press a
9
10 hand-held pressure release button when the pain was intolerable and the pressure was immediately
11
12 terminated. This pressure value was defined as cuff pressure tolerance (cPTT). If the cPTT was not
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14 reached before the maximum stimulation intensity, 100 kPa was used as a conservative estimate for
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16 cPTT in the further analysis. The VAS score at cPTT was defined as VAScPTT. The pressure at VAS
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18 equal to 2 cm was defined as the cuff pressure pain threshold (cPPT). The pressure value when the
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20 VAS score reached 6 cm was extracted and defined as PVAS6. Similar terminology has been used
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22 previously. [45]
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Assessment of pain summation by cuff algometry

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40 TSP was evaluated by ten sequential cuff pressure stimuli delivered at 0.5 Hz (1-s duration and 1-s
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42 break) to the thigh with the proximal single chamber. The intensity of the stimulus was set to the
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44 cPTT recorded in the same session. In line with previous studies [13; 35; 46], cPTT was used for
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46 induction of TSP to ensure that the first stimulation was perceived as painful by patients and control
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48 subjects, but it was not regarded extremely painful because of the short stimulation time. A constant
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50 non-painful pressure of 5 kPa was kept in the period between stimuli to prevent cuff movements.
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60 The subjects rated their pain intensity continuously during the sequential stimuli on the electronic
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1 VAS without returning it to zero after individual stimuli. The mean VAS score during the 1-s
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3 interstimulus interval after each of the 10 stimuli was extracted and normalized by subtraction of
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5 the VAS scores from the first stimulus. The accumulated VAS score (VAS-sum) over the ten stimuli
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7 was extracted.
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11 The ratio of thresholds (cPPT, PVAS6, and cPTT) from the double-chamber cuff divided by
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13 the thresholds from single-chamber cuff was used as an index for SSP. Lower ratios show a higher
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15 degree of SSP, indicating more sensitization.
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21 22 23 24 25 *Cutaneous pin-prick pain sensitivity*

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27 A weight-calibrated pinprick device (Aalborg University, Aalborg) was used to apply punctate
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29 stimulation in the hip area (sites 2 and 4). The skin was stimulated by standardized application of
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31 25.6 g and 51.2 g pins (0.6 mm tip diameter tip), and the subjects scored the pin-prick sensation on
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33 a VAS from 0 to 10 cm, where 0 indicated “no sensation”, 5 cm indicated “pain threshold”, and 10
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35 cm equaled “maximum pain”.
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46 47 *Thermal pain sensitivity*

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49 A 3×3 cm (9 cm²) contact thermode (Medoc Advanced Medical Systems, Israel) was used to apply
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51 thermal stimulation. Cold detection threshold (CDT), warm detection threshold (WDT), cold pain
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53 threshold (CPT), and heat pain threshold (HPT) were assessed on the hip (site 4). CDT and WDT
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55 were measured first. Each stimulus began at 32 °C from which the temperature increased or
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1 decreased by 1 °C/s. The temperature could vary between 0 and 50 °C during stimulation. The
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3 subject was instructed to push a hand-held stop button when a cold or warm sensation was
4
5 perceived (CDT, WDT) and when the cold and heat sensation changed into pain (CPT, HPT).
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10 11 *Conditioned pain modulation*

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13 For conditioning stimulus, a 7.5-cm-wide tourniquet cuff (VBM, Germany) was wrapped around
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15 the contralateral arm at the level of the largest circumference of the biceps brachii muscle. The
16
17 computer-controlled cuff algometer (NociTech, Denmark) maintained a constant pressure at 60 kPa
18
19 for 2 min. If subjects could not endure the arm pain with 60 kPa, the pressure was reduced to 30 kPa.
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21 Cuff algometry was re-assessed once on the thigh after 60 seconds with the conditioning cuff
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23 inflation and pressure algometry at the hip (sites 2 and 4) was consecutively evaluated twice during
24
25 the same conditioning stimulus. The conditioning cuff was released immediately after the pain
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27 assessments were finished. The CPM-difference (i.e. conditioning minus baseline) of cPPT, PVAS6,
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29 cPTT and handheld PPTs were calculated for analysis.
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47 *Statistical analysis*

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49 Normally distributed data are presented as mean and standard error of the mean (SEM), and other
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51 data as median and interquartile range [0.25-0.75]. The VAS scores for clinical hip pain and
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53 cutaneous pin-prick pain sensitivity did not pass the Kolmogorov-Smirnov test for normal
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55 distribution and were analyzed by the Wilcoxon signed rank test and the Mann-Whitney U test.
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3 Three-way analysis of variance (ANOVA) was performed on PPTs using the factors of *study group*
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5 (OA and control), *side* (affected and contralateral), and *assessment site* (6 sites). A mixed-model
6
7 ANOVA was used to analyze PPTs before and after THA, with group factors *side* and *site* as well as
8
9 repeated factor *time* (before and after 6 weeks post THA). A similar approach was used for
10
11 comparing the parameters of cuff algometry (cPPT, PVAS6, cPTT), SSP ratio (cPPT, PVAS6, cPTT),
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13 and the CPM difference (cPPT, PVAS6, cPTT, PPT) between study groups or assessment time. Each
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15 parameter of these tests (in parentheses) was separately analyzed by ANOVA. The sequences of test
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17 side and assessment procedures were set as independent factors except for the CPM test. TSP was
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19 analyzed by a mixed-model ANOVA of the VAS scores with group factors of *study group* (OA and
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21 control) and *side* (affected and contralateral) as well as repeated factor *number of stimulation* (2-10).
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25 To compare before and 6 weeks after THA, a mixed-model ANOVA was performed with group
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27 factor *side* and repeated factors *number of stimulation*, and *time*. The VAS-sum was analyzed using
28
29 a similar approach. In addition, the relationship between postoperative pain and normalization of
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31 each parameter was analyzed by a mixed-model ANOVA with group factor *post-THA pain* (pain+
32
33 and pain-) as well as repeated factor *time*. The ANOVAs were adjusted for the gender and age. The
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35 Neuman-Keuls (NK) tests were used for post-hoc comparisons incorporating correction for the
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37 multiple comparisons when ANOVA showed significant factors or interactions. Correlations among
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39 demographic data (age, BMI), clinical pain parameters, and QST results were examined. The VAS
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41 scores for rest and walking pain before and after THA, pain duration, pain referral patterns (number
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43 of pain areas, pain distribution) and total score of painDETECT were included as parameters of the
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3 clinical pain profile and analyzed by Pearson's product-moment test with Bonferroni corrections to
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9 adjust for multiple correlations. $P \leq 0.05$ was considered significant.

10 **RESULTS**

11 *Demographic data and pain profiles in hip OA patients*

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13 No significant difference in the demographic data was noted between preoperative OA patients and
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19 control subjects. In hip OA patients, median pain VAS scores were 3.8 cm at rest, and 6.0 cm while
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22 walking (Table 1). The three most common words describing the quality of pain were shooting,
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25 tiring and spreading on the McGill pain questionnaire. Twenty-seven patients were classified as
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28 'nociceptive' (total score of painDETECT ≤ 12), 3 were 'neuropathic' (≥ 19), and 10 were 'unclear'
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31 (≥ 13 - ≤ 18), respectively. The pain was located not only around the hip but also spread to the thigh,
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35 knee, lower leg, foot, and lumbar area (Table 2) with 3.0 [2.8-5.0] pain regions per patient.

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38 Post-THA assessment: Thirty-six patients were included for the follow-up assessment
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41 approximately 6 weeks after THA. Two patients were re-operated for postoperative dislocation and
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44 periprosthetic fracture and were excluded. Two patients did not want to participate in the
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47 postoperative session for personal reasons. The median pain VAS scores at rest and while walking
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50 were significantly reduced (Wilcoxon: $P < 0.00002$, Table 1), which met minimal clinically important
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53 difference (MCID) as per IMMPACT criteria [10]. However, sixteen patients had pain at a level of
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57 VAS > 1 cm at rest and 8 patients had VAS > 4 cm while walking at the follow-up assessment, and
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60 in these cases 3 patients with rest pain and 6 patients with walking pain did not meet the MCID.

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3 Preoperative pain intensity, pain distribution, number of pain areas, and painDETECT score did not
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8 correlate with the post-THA pain intensity.

9 *Handheld pressure algometry of the lateral hip, lower leg, and arm*

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11
12 The ANOVA of PPTs demonstrated a significant group factor indicating that PPTs were bilaterally
13
14 reduced in OA patients compared with healthy controls at all sites (Fig. 2; ANOVA: $F[1]=46.7$,
15
16 $P<0.00001$; NK: $P<0.00001$). The assessment site factor was significant where Hip-3 and the arm
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19 $P<0.00001$; NK: $P<0.00001$). The assessment site factor was significant where Hip-3 and the arm
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21 showed lower PPTs compared with other sites, and Hip-1 was lower than the Hip-2 and Hip-4
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24 (ANOVA: $F[5]=36.4$, $P<0.0001$; NK: $P<0.002$).

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28 Post-THA assessment: The ANOVA of the PPTs in OA patients before and after THA resulted
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31 in a significant time factor where the PPTs increased after THA regardless of side and assessment
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34 site (Fig. 2; ANOVA: $F[1]=7.7$, $P<0.01$; NK: $P<0.01$). The PPTs were lower on the affected side
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37 compared with the contralateral side (ANOVA: $F[1]=4.5$, $P<0.04$; NK: $P<0.05$). The PPTs at all
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40 assessment sites were different except the comparison between Hip-2 and Hip-4 (ANOVA:
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43 $F[5]=52.9$, $P<0.0001$; NK: $P<0.02$). However post-THA pain was not a significant factor for
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46 normalization of the PPTs, therefore no difference of PPTs was seen between patients with
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49 postoperative pain and those without pain.
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57 *Cuff pressure algometry*

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60 The single cuff stimulus-response curve relating the pressure and VAS scores (cPPT, PVAS6, cPTT

1 and VAScPTT) was bilaterally left-shifted in preoperative OA patients compared with control
2 subjects (Fig. 3). Significant group factors were found for cPPT, PVAS6, and cPTT with the single
3 cuff stimulation and for cPPT with the double cuff stimulation indicating that OA patients showed a
4 significantly lower threshold compared with control subjects (Fig. 3; ANOVA: $F[1]>3.4$, $P<0.05$;
5 NK: $P<0.02$). In addition, a significant group factor was demonstrated for the VAScPTT with the
6 single cuff stimulation indicating higher VAScPTT in control subjects compared with preoperative
7 OA patients (Fig. 3; ANOVA: $F[1]=4.0$, $P<0.04$; NK: $P<0.05$). The assessment side was not
8 detected as a significant factor.

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25 Post-THA assessment: No significant difference of the cPPT, PVAS6, cPTT, or VAScPTT was
26 seen between preoperative and postoperative OA patients. Moreover, post-THA pain was not a
27 significant factor for normalization of the cPPT, PVAS6, cPTT, and VAScPTT, which means there
28 was no difference for each parameter between patients with postoperative pain and those without
29 pain.
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44 *Temporal summation of cuff induced pain*

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47 The VAS score of the first stimulation was 1.1 ± 0.2 cm in OA patients and 1.0 ± 0.3 cm in control
48 subjects, with no significant difference between the groups. A significant interaction between the
49 factors group and cuff stimulation number showed that the normalized VAS scores to sequential
50 cuff stimulation were progressively increasing to a higher level for stimulation 5 to 10 in
51 preoperative OA patients bilaterally compared with healthy subjects (Fig. 4; ANOVA: $F[9]>4.3$,
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3 P<0.00003; NK: P<0.04). The VAS-sum was 22.4 ± 2.5 cm (affected) and 25.9 ± 3.3 cm
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5 (contralateral) in preoperative OA patients and 8.6 ± 2.1 cm (affected) and 8.9 ± 2.1 cm
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7 (contralateral) in control subjects; significantly higher in preoperative OA patients bilaterally
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9 compared with control subjects (ANOVA: $F[1]=31.5$, $P<0.00001$; NK: $P<0.00001$).

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11 Post-THA assessment: Postoperatively compared with pre-THA, the normalized VAS scores
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13 to sequential cuff stimulation were significantly decreased for stimulation 4 to 10 on the affected
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15 side in 20 OA patients who achieved complete pain relief (Fig. 4; ANOVA: $F[9]=3.8$, $P<0.0003$;
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17 NK: $P<0.002$), but this change was not seen in the other 16 patients who still experience pain. The
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19 VAS sum was 11.6 ± 2.8 (affected) and 15.9 ± 3.3 cm (contralateral) in postoperative pain-free OA
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21 patients while 22.4 ± 5.3 (affected) and 25.3 ± 4.8 cm (contralateral) in 16 patients with some pain.
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23 In pain-free patients, the VAS sum significantly reduced on the affected side after THA compared
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25 with preoperative assessments (ANOVA: $F[1]=5.7$, $P<0.03$; NK: $P<0.04$). However, such a
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27 reduction was not observed in 16 patients with postoperative pain.
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44 *Spatial summation of cuff induced pain*

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46 Although SSP effect was seen in OA patients and control subjects, there was no significant
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48 difference in the degree of summation between both groups (Supplementary table 1). No significant
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50 difference of the SSP ratio was seen between preoperative and postoperative OA patients, and
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57 post-THA pain was not a significant factor for normalization of the SSP ratio.
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Pin-prick pain sensitivity on the lateral hip

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3 The VAS scores for 26 g and 51 g pin-prick stimulation were less than 5 cm in preoperative OA
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5 patients and healthy subjects indicating that this was not painful stimulation. A significantly higher
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7 VAS score was seen in OA patients compared with healthy subjects (Supplementary table 3;
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9 Mann-Whitney: $P < 0.04$).

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12 Post-THA assessment: The VAS scores for 26 g and 51 g pin-prick stimulation significantly
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14 reduced compared with preoperative OA patients (Supplementary table 3; Wilcoxon: $P < 0.002$), but
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16 post-THA pain was not a significant factor for normalization of the VAS scores for pin stimulation.
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Thermal detection and pain threshold on the lateral hip

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29 A significant group factor was demonstrated in WDT indicating that preoperative OA patients
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31 showed a higher threshold compared with healthy subjects (Supplementary table 3; ANOVA:
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33 $F[1]=4.1$, $P < 0.05$; NK: $P < 0.05$). No other significant interactions or factors were observed in CDT
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35 and HPT between groups.
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44 Post-THA assessment: No significant difference of the CDT, WDT, and HPT was seen between
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46 preoperative and postoperative OA patients, and post-THA pain was not a significant factor for
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48 normalization of each parameter. CPT was mostly not detected within the temperature limit of the
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50 apparatus (0°C) and only 5 patients reported pain in both assessment periods during cold
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57 stimulation. Consequently, the data were not statistically analyzed.
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Conditioned pain modulation

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3 All patients were confirmed to have constant arm pain at a VAS score above 7 cm during
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6 conditioning. No significant difference of the CPM-difference was found in the comparison
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9 between preoperative OA patients and healthy subjects (Supplementary table 2). No significant
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12 difference was seen between preoperative and postoperative OA patients, and post-THA pain was
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15 not a significant factor for normalization of the CPM-difference.
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Correlation among demographic data, clinical pain profile and QST in OA patients

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25 Demographic data including age and BMI showed no significant correlation with clinical pain
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28 profiles (VAS scores) or QST results in this cohort. Preoperative rest pain intensity was negatively
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31 correlated with PPTs around the affected hip ($r=-0.42$, $P<0.05$) and mean of all PPT sites ($r=-0.38$,
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34 $P<0.05$). The duration of pain was not correlated with any other clinical pain profile and QST
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37 parameters. The pain distribution but not the pain intensity, correlated with the total score of
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40 painDETECT ($r=0.37$, $P<0.05$).
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Correlation between postoperative pain and preoperative parameters in OA patients

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50 Age, BMI, and clinical pain profile did not correlate with postoperative pain. The VAS score of
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53 postoperative rest and walking pain significantly correlated with preoperative cuff VAS-sum (Fig.5;
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56 $r=0.44$, $P<0.05$). The degree of pain relief at rest (i.e. difference of rest pain VAS before and after
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59 THA) negatively correlated with preoperative cuff VAS-sum (Fig 5; $r=-0.52$, $P<0.05$). The other
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preoperative QST parameters did not correlate with postoperative pain.

DISCUSSION

The present study showed bilateral pressure pain hypersensitivity and facilitated TSP in hip OA patients. The facilitated preoperative TSP correlated with post-operative pain intensity 6 weeks after THA. Moreover, facilitated TSP was normalized after THA only in postoperative pain-free patients.

Hyperalgesia in hip OA

PPTs have been used to assess local and spreading hyperalgesia in painful OA [2; 14; 17] and normalized after THA [1; 24], which is consistent with the current study. However post-THA pain was not a significant factor for normalization of the PPTs, possibly because PPTs are not sensitive enough to detect the effect of mild postoperative pain on the normalization. Obesity is considered a risk factor for OA progression but the present analysis did not find correlations between BMI and pain or pre- and postoperative PPTs, which is partly consistent with a recent large study that found no association between preoperative BMI and postoperative complications [11].

Regardless of the assessment side, the stimulus-response curve showed a significant left shift and the VAScPTT was significantly lower in preoperative OA patients compared with control subjects. OA patients stopped the cuff stimulation earlier at a lower pain intensity, suggesting that they were not willing to accept the higher pain intensity potentially because they were inflicted with daily pain which is in line with previous findings of OA patients [20]. Individuals with e.g. pain

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3 catastrophizing place excessive focus on the negative aspects of the pain experience and emphasize
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5 pain sensations, which disables them to cope effectively with pain [20; 42].

6 In contrast to the normalization of PPTs, no significant right-shift was found between pre- and
7
8 postoperative patients by the stimulus-response analysis. Although follow-up period was shorter
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10 compared with some previous studies which showed normalization of PPTs after TKA and THA [1;
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12 14; 24], this novel finding possibly suggests that mechanisms for normalization of pressure
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15 hypersensitivity are not identical between PPT and supra-threshold pain process. Further studies
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18 with longer follow-up period are warranted to evaluate when and how is the supra-threshold pain
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21 process normalized.
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27 The current study found that OA patients showed pin-prick hyperesthesia and thermal
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29 hypoesthesia compared with control subjects. Sensitivity to thermal detection and pain thresholds
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31 were different among previous OA studies compared with healthy controls. Kosek et al. [24]
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34 reported increased sensitivity to warm detection and cold pain but not to cold detection. Conversely,
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37 Wylde et al. [51] showed decreased sensitivity to warm and cold detection but not to heat pain.
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40 Furthermore King et al. [23] and Kuni et al. [26] reported no hyper or hyposensitivity to warm, cold
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43 detection and heat, cold pain. Thus both facilitated and inhibited alteration of superficial tissue
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46 sensitivity surrounding osteoarthritic joint has been reported controversially so that mechanisms of
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49 this change have not fully known.
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55 Similar to previous reports [16; 43], clinical pain and QST were not consistently matching.
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58 The complex nature of chronic postsurgical pain described by multiple confounders such as
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3 demographic, socioeconomic, and psychosocial factors [52] is possibly accounting for the reason of
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5 this finding. Hübscher et al. [16] suggested that evoked pain by QST might not necessarily reflect
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7 the clinical pain because it has been reported that the typical areas of the brain activated during
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9 spontaneous pain is different from evoked pain [32]. This may be a limitation of QST studies
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12 focused on pain perception abnormalities.
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Pain referral patterns and sensitization

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19 Referred pain is a typical findings of hip OA, much more frequent compared with knee OA [19].
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22 Similar to previous reports [15; 21; 22; 30], patients in the present study showed patterns of pain
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25 referral to the thigh, knee, lower leg, and lumbar region. So far no studies have described the
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28 association between referred pain patterns and QST results in hip OA patients. No significant
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31 correlation was found between pain referral patterns and QST results indicating that mechanisms
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34 controlling the sensitivity of these manifestations are not directly linked. Likewise, the area of pain
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37 referral was not associated with the pre- and postoperative pain intensity. Street et al. [41] reported
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40 that in 236 patients undergoing THA, 32% of patients presenting with primary knee pain had
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43 significantly poorer 2-years clinical outcome compared with patients who had hip and thigh pain.
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47 However, this study did not clarify that their knee pain was purely referred from the affected hip.
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50 From the present findings, preoperative widespread sensitization may not be a primary factor of
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53 wider pain referral. Interestingly, a weak correlation was seen between pain distribution and the
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56 total score of PainDETECT. Although this questionnaire has been criticized when used in OA [29],
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3 it may be interpreted that extensive pain referral is possibly associated with neuropathic
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9 components of hip OA pain.

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Summation of pain

This is the first study to evaluate temporal and spatial summation of pain in hip OA pain patients.

Compared with other QST modalities, TSP seemed most sensitive to detect a sensitized central mechanism and its normalization after THA. Previous studies using lower pressure intensities than cPTT for induction of TSP demonstrated less efficient temporal summation of pain [27; 39].

Moreover, the VAS score of the first stimulation in this study was around 1.0 cm and not significantly different between patients and controls. These data suggest that a ceiling effect is not likely in the current modality for TSP induction [28].

There was a significant association between the degree of preoperative TSP and the postoperative pain intensity at rest and while walking, which was a consistent finding with a recent report of knee OA patients evaluated 1 year after TKA [33]. Moreover, a significant correlation was found between preoperative TSP and the degree of rest pain relief following THA, which was not detected in a recent study when assessing the preoperative PPTs on the forearm [52]. The degree of walking pain relief was not significantly associated with preoperative TSP possibly because 8 patients had pain with VAS > 4 cm at the follow-up assessment so that the degree of pain relief was yet not enough. These correlations between TSP and postoperative pain are clinically important for predicting patients who may develop pain after replacement surgery. Interestingly, normalization of

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3 TSP was observed only in postoperative pain-free patients. No other preoperative QSTs associated
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5 with postoperative pain outcome.

6 In a knee OA study, facilitated SSP and its normalization after TKA were found by cuff
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8 algometry applied on the lower leg [14]. However, similar findings could not be detected in the
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10 present hip OA patients. This inconsistency may be caused by a difference in assessment site. Most
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12 of the included hip OA patients perceived severe groin and thigh pain before surgery. In an
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14 experimental hip pain study [18], the cuff algometry assessed on proximal thigh was sensitive to
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16 hyperalgesia in the groin and thigh regions due to experimental hip-related pain, which may reduce
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18 the effect of SSP due to a saturation or ceiling effect (i.e. single cuff stimulation excited major parts
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20 of the pain system that cannot be excited much further by the double cuff stimulation).
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34 *Conditioning pain modulation*

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37 The degree of CPM showed no significant difference among pre- and postoperative OA patients and
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39 control subjects, which was inconsistent with an early report by Kosek et al. [25]. In the previous
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41 study patients may be more sensitized since they presented with preoperative hip PPTs around 250
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43 kPa [25] which are substantially lower than in the present study. The included OA patients were
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45 followed up 6 weeks after THA meaning many of them still experienced some pain. Although their
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47 median rest and walking pain VAS were 0 and 2.0 cm, this may be the reason why the
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57 normalization of CPM was negative in the present study.
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Limitations

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3 First, small sample size and short follow-up period should be noted. Although this study provided
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5 significantly different TSP and supra-threshold pressure hypersensitivity, further investigations are
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7 needed to establish its predictive value for persistent post-THA pain. Second, clinical outcome
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9 measures for OA pain and disability was not included, and psychosocial variables were not
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11 evaluated, which has been reported as potential confounders for pain sensitivity and postoperative
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13 pain intensity [36; 37]. In this study, a priority was given to psychophysical approach towards hip
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15 OA pain. Since the QST assessments required 1 hour, these useful questionnaires were reluctantly
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17 left out to minimize the load on the patients. Third, patients with bilateral radiological OA was
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19 included, if one hip was pain free. Although it was not a structurally normal joint, a fully
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21 asymptomatic hip would not influence the bilateral changes of the QST results. Finally, test-retest
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23 reliability of QSTs was not presented in this paper. However, adequate-to-excellent interclass
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25 correlation coefficients of QSTs were reported in previous OA studies [47; 50]. Moreover, a recent
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27 study demonstrated good to excellent interclass correlations for cuff algometry, which constitutes a
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29 user-independent method for assessment of pain [13].
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Conclusion

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53 Bilateral pressure pain hypersensitivity was demonstrated in hip OA patients to supra-threshold
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55 single cuff stimulation. Greater preoperative TSP was associated with greater pain and less
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reduction in pain after THA. Furthermore, facilitated preoperative TSP was normalized after THA
only in postoperative pain-free patients.

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Conflict of interest statement

NociTech is partly owned by Aalborg University and KKP is partly employed by NociTech.

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Figure legends

Figure 1. Outline of body areas used for the analysis of pain distribution (right), and sites for assessment of the somatosensory sensitivity (left). The assessment sites for PPTs are: m. gluteus medius; 3 cm proximal to the tip of the greater trochanter (Hip-1). M. gluteus maximus; 3 cm posterior to the posterior edge of the greater trochanter (Hip-2). M. vastus lateralis; 3 cm distal to the distal edge of the greater trochanter (Hip-3). M. tensor fascia latae; 3 cm anterior to the anterior edge of the greater trochanter (Hip-4). M. tibialis anterior; 5 cm distal to the tibial tuberosity (TA). M. extensor carpi radialis longus; 5 cm distal to the lateral epicondyle of the humerus (arm). The body areas are (1) groin, (2) greater trochanter, (3) buttocks, (4) anterior thigh, (5) posterior thigh, (6) lateral thigh, (7) medial thigh, (8) knee, (9) lower leg, (10) foot, and (11) lumbar. Note that body areas and assessment sites are illustrated separately but assessed on both sides.

Figure 2. Mean (\pm SEM) pressure pain thresholds (PPTs) in OA patients and healthy control subjects (Upper). Significantly reduced compared with healthy controls at all sites on both sides (*; NK: $P < 0.00001$). Significantly lower compared with other sites (#; NK: $P < 0.005$) or Hip-2 and Hip-4 (§; NK: $P < 0.005$). Mean (\pm SEM) PPTs in OA patients at pre- and post-THA (Lower). Significantly increased after THA regardless of side and assessment site (*; NK: $P < 0.009$). Significantly lower compared with contralateral side (†; NK: $P < 0.04$).

Figure 3. Stimulus-response curve constructed by mean (\pm SEM) cPPT, PVAS6, cPTT, and

1 VAScPTT of cuff algometry in OA pre-THA patients (black circle), OA post-THA patients (square),
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3 and healthy control subjects (triangle). Data from single cuff (Upper) and double cuff (Lower)
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5 assessments. Significant left shift in preoperative OA patients compared with control subjects (*;
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7 NK: $P < 0.03$). Significantly higher VAScPTT in control subjects compared with preoperative OA
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9 patients (#; NK: $P < 0.05$).
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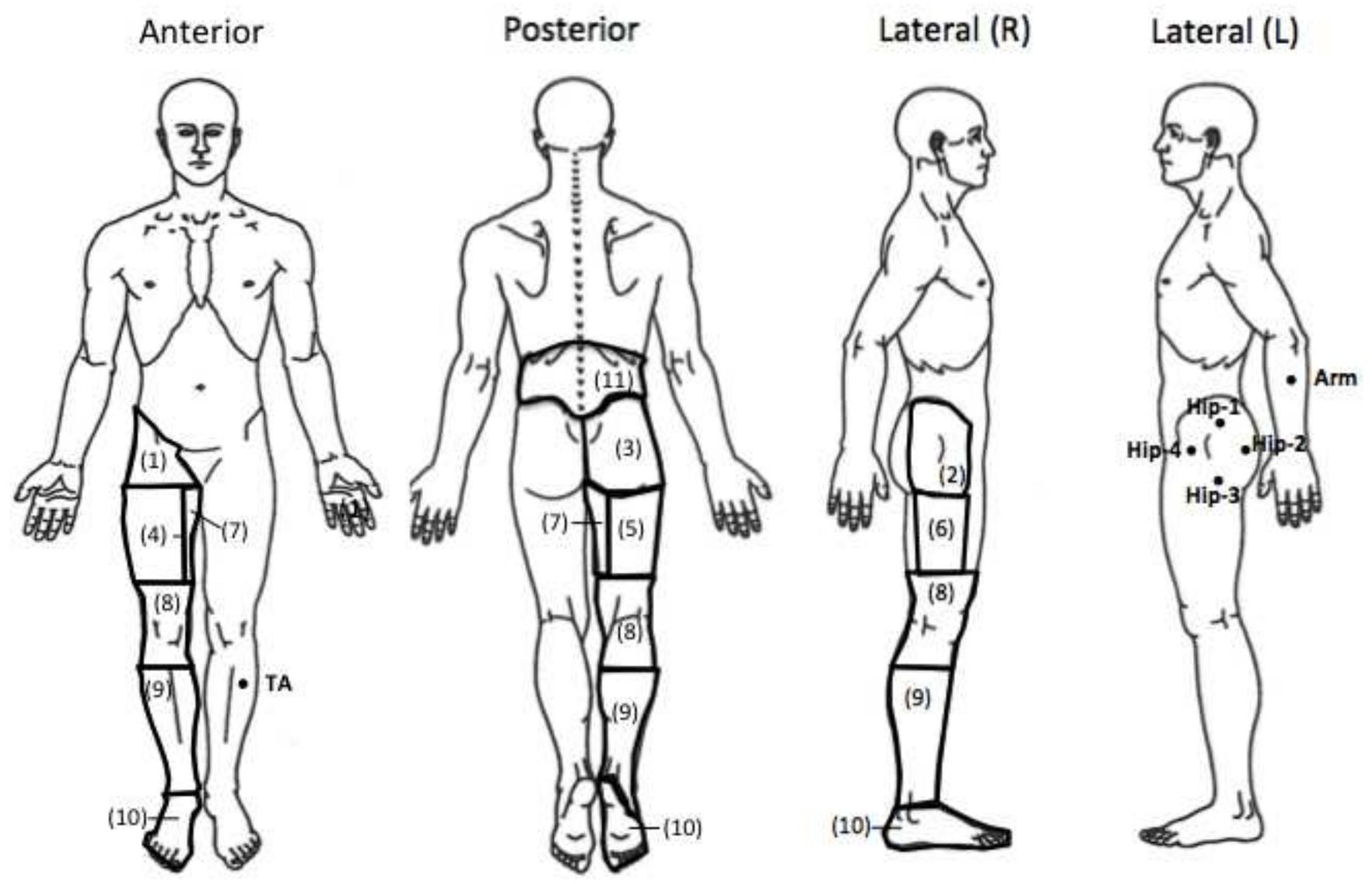
18 **Figure 4.** Temporal summation of cuff induced pain. Mean (\pm SEM) normalized VAS scores were
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20 significantly higher in preoperative OA patients (open circle) bilaterally compared with healthy
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22 subjects (triangle) (*; NK: $P < 0.05$). Postoperatively, the normalized VAS scores in pain-free OA
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24 patients (N=20, open square) significantly decreased on the affected side (#; NK: $P < 0.05$), but this
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26 change was not seen in OA patients with some pain (N=16, black square).
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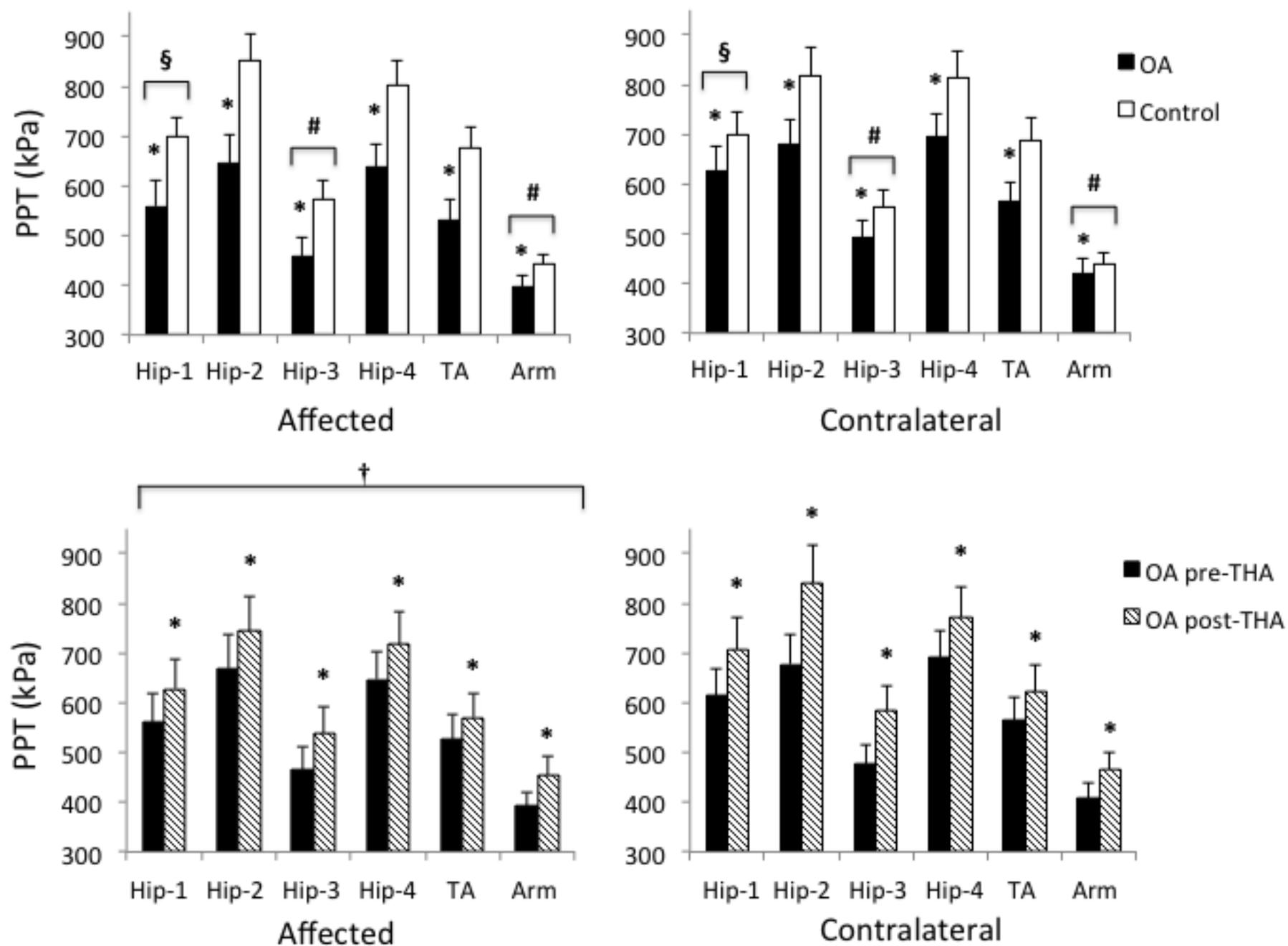
37 **Figure 5.** Scatter diagrams presenting correlations between preoperative VAS-sum and
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39 postoperative rest pain VAS, postoperative walk pain VAS, degree of rest pain relief (i.e. difference
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41 of rest pain VAS before and after THA). Each symbol represents an individual OA patient.
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44 Significant correlation was found between preoperative temporal summation of pain (VAS-sum)
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47 and postoperative pain intensity at rest, walk and pain reduction.
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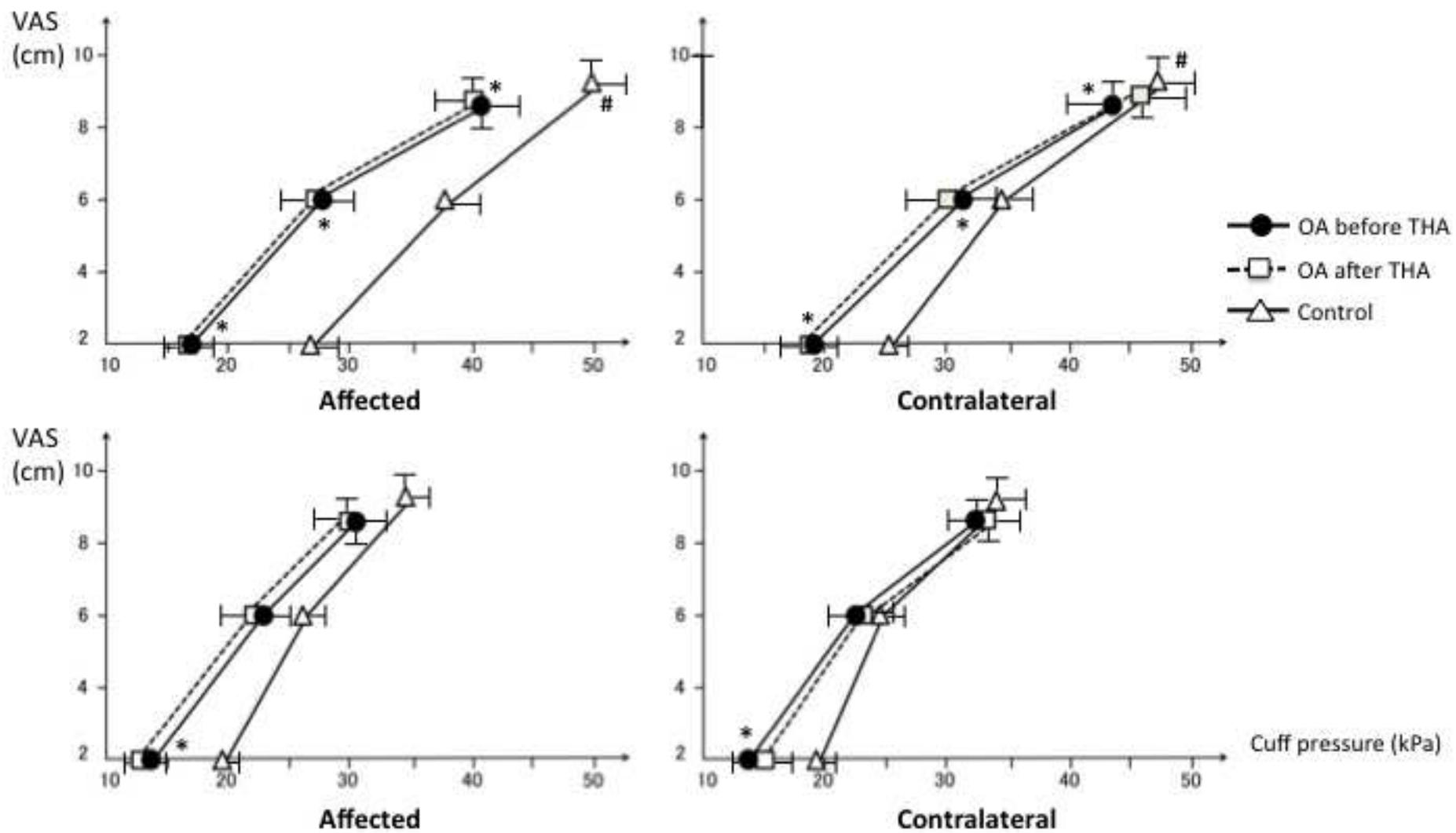
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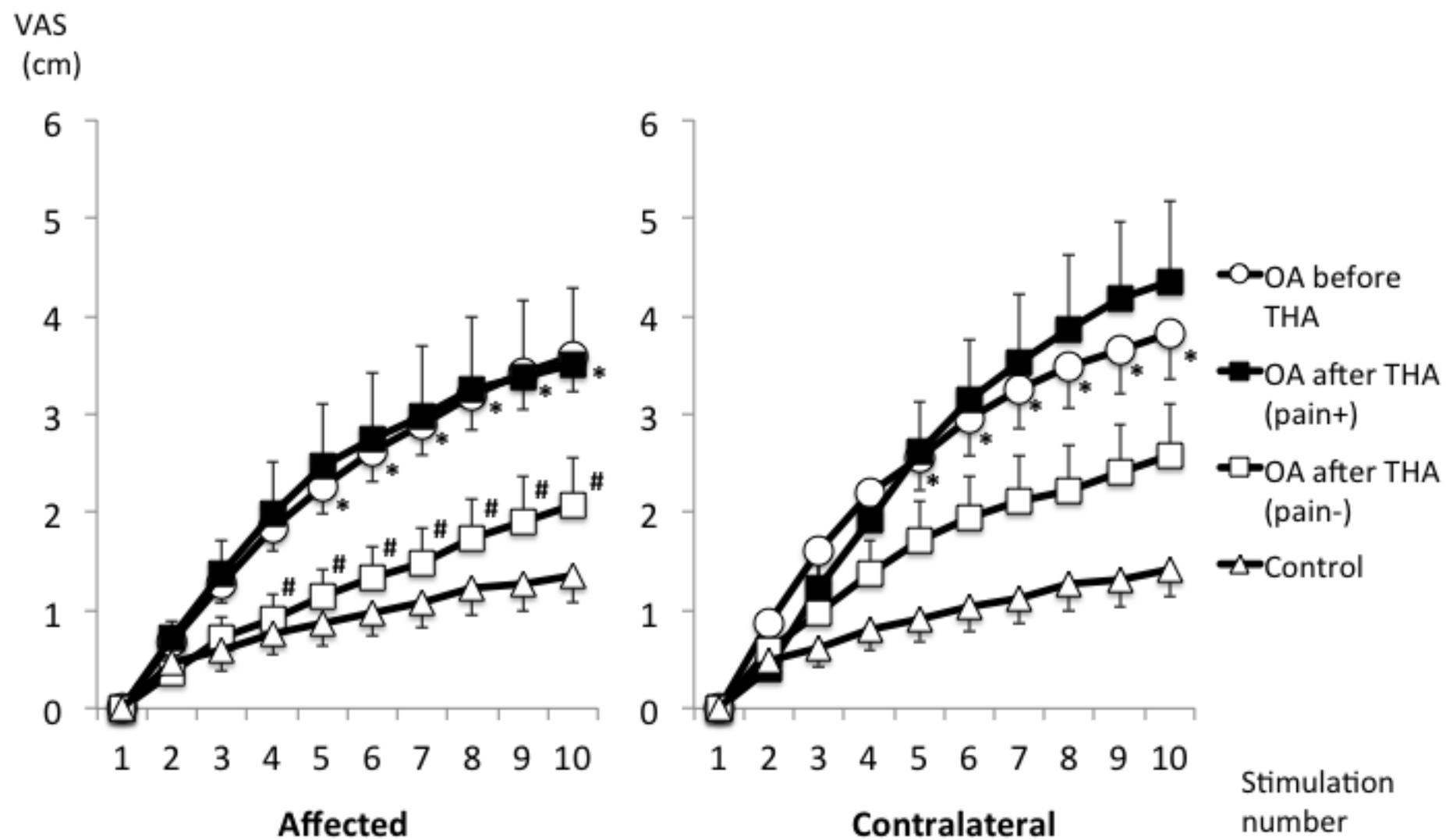
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Greater preoperative temporal summation of pain was associated with greater pain and less reduction in pain after THA.









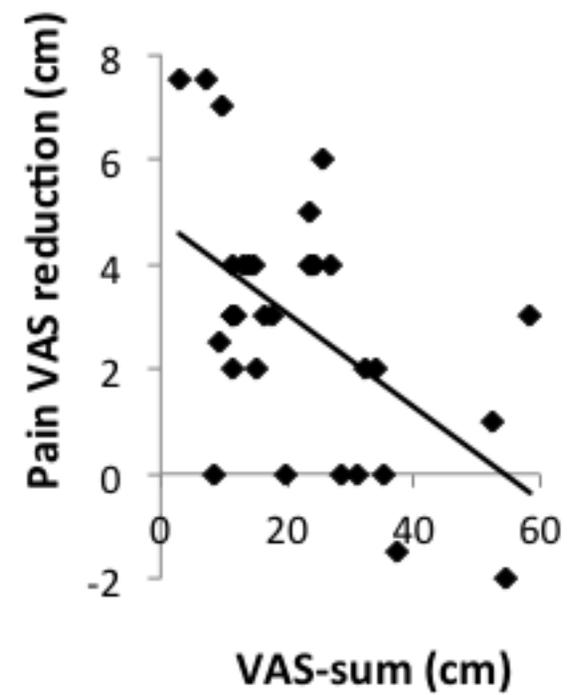
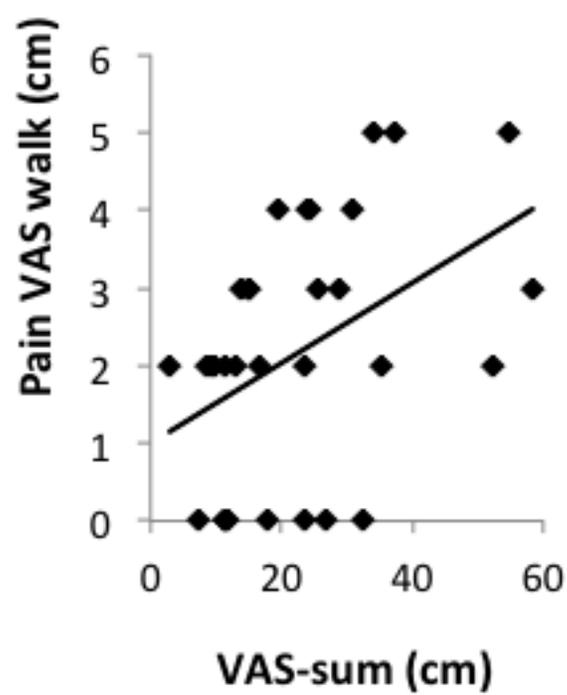
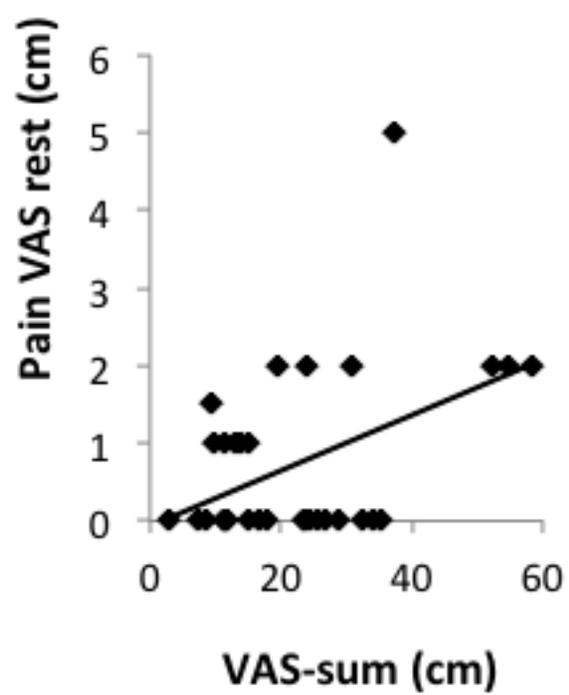


Table 1. Demographic data and pain profiles in hip OA patients compared with control subjects.

Parametric data are presented as mean \pm SD, and non-parametric data as median and interquartile

range [0.25-0.75]. The pain VAS scores at rest and while walking significantly reduced after THA

(*;Wilcoxon: $P < 0.00002$).

Variable	OA patients	Control subjects
Number	40	40
Age, years	68 \pm 9	65 \pm 7
Gender, number (%)		
Male	20 (50)	20 (50)
Female	20 (50)	20 (50)
BMI, kg/m ²	27.4 \pm 4.0	26.1 \pm 5.1
Symptomatic hip, number (%)		
Left	18 (45)	-
Right	22 (55)	-
Pre-op pain duration, months	24 [12-53]	-
Pre-op rest pain VAS, cm	3.8 [2.0-5.0]	-
Pre-op walk pain VAS, cm	6.0 [4.0-8.0]	-
Pre-op McGill pain questionnaire, number (%)		
Shooting	27 (68)	-
Tiring	23 (58)	-
Spreading	21 (53)	-
Pre-op painDETECT	10.8 \pm 5.8	-
Follow-up number (%)	36 (90)	-
Follow-up period, weeks	6.0 [6.0-7.0]	-
Post-op rest pain VAS, cm	0 [0-1.1] *	-
Post-op walk pain VAS, cm	2.0 [1.5-3.0] *	-

Table 2. The frequency (percentages in parenthesis) of pain distribution in preoperative hip OA patients (n=40). Four typical pain distribution patterns were categorized as “hip”, “hip and thigh”, “hip and below thigh”, and “hip and thigh and below thigh”.

Location	Number (%)			
Locations				
Groin	31 (78)	Hip 7 (17.5)	Hip & Thigh 13 (32.5)	Hip &
Greater Trochanter	30 (75)			Hip &
Buttock	22 (55)			
Anterior Thigh	17 (43)			Thigh & Below thigh 9 (22.5)
Posterior Thigh	7 (18)			
Lateral Thigh	10 (25)			
Medial Thigh	6 (15)			
Knee	15 (38)			Below thigh 9 (22.5)
Lower Leg	7 (18)			Below thigh 9 (22.5)
Foot	1 (3)			
Lumbar	2 (5)			

SUPPLEMENTARY TABLES

Supplementary table 1. Mean (\pm SEM) spatial summation ratio (thresholds from the double-chamber cuff divided by the thresholds from single-chamber cuff) calculated from cPPT, PVAS6, and cPTT on the affected and contralateral leg. Lower ratio indicates a higher degree of spatial summation.

	Spatial summation ratio		
	cPPT	PVAS6	cPTT
Affected side			
OA before THA	0.82 \pm 0.02	0.81 \pm 0.03	0.75 \pm 0.02
OA after THA	0.79 \pm 0.03	0.77 \pm 0.03	0.76 \pm 0.02
Control	0.78 \pm 0.04	0.76 \pm 0.04	0.74 \pm 0.04
Contralateral side			
OA before THA	0.74 \pm 0.03	0.76 \pm 0.02	0.76 \pm 0.02
OA after THA	0.83 \pm 0.03	0.82 \pm 0.03	0.75 \pm 0.02
Control	0.78 \pm 0.03	0.75 \pm 0.02	0.73 \pm 0.02

Supplementary table 2. Mean (\pm SEM) CPM-difference evaluated by cuff algometry (cPPT, PVAS6, cPTT) and pressure algometry (PPT Hip-2 and Hip-4) on the affected leg.

CPM-difference	Cuff algometry			Pressure algometry	
	cPPT (kPa)	PVAS6 (kPa)	cPTT (kPa)	PPT Hip-2 (kPa)	PPT Hip-4 (kPa)
OA before THA	9.1 \pm 2.7	10.1 \pm 2.8	9.2 \pm 2.4	149 \pm 45	166 \pm 37
OA after THA	10.1 \pm 2.3	11.0 \pm 2.1	9.5 \pm 2.1	156 \pm 27	169 \pm 26
Control	11.0 \pm 1.8	8.4 \pm 2.1	9.1 \pm 1.8	157 \pm 28	201 \pm 32

Supplementary table 3. Median and interquartile range [0.25-0.75] of VAS scores to pinprick stimulation and mean (\pm SEM) thermal thresholds (CDT: cold detection threshold, WDT: warm detection threshold; CPT: cold pain threshold, HPT: heat pain threshold) on the affected and contralateral leg in OA patients and healthy subjects. For CPT, only 5 patients reported pain during cold stimulation so that the data were not statistically analyzed. Significantly increased compared with control subjects (*, $P < 0.05$). Significantly decreased compared with before THA (#, $P < 0.05$).

	Pin-prick VAS (cm)		Thermal thresholds			
	26 g	51 g	CDT ($^{\circ}$ C)	WDT ($^{\circ}$ C)	CPT ($^{\circ}$ C)	HPT ($^{\circ}$ C)
Affected side						
OA before THA	1.3 [1.0-2.3]*	2.2 [1.2-3.4]*	25.8 \pm 0.5	37.9 \pm 0.5*	12.0 \pm 2.7	46.7 \pm 0.5
OA after THA	1.0 [1.0-1.3]#	1.3 [1.0-2.0]#	27.3 \pm 0.4	38.1 \pm 0.6	14.9 \pm 4.7	46.9 \pm 0.6
Control	1.0 [1.0-1.7]	1.7 [1.0-2.1]	26.1 \pm 0.6	36.9 \pm 0.5	11.3 \pm 2.5	47.1 \pm 0.4
Contralateral side						
OA before THA	1.3 [1.0-2.1]*	2.3 [1.2-3.7]*	25.8 \pm 0.5	37.3 \pm 0.4*	17.6 \pm 0.8	46.6 \pm 0.5
OA after THA	1.0 [1.0-1.7]#	2.0 [1.0-2.0]#	26.0 \pm 0.7	37.1 \pm 0.4	18.7 \pm 1.7	46.4 \pm 0.6
Control	1.0 [1.0-1.7]	1.5 [1.0-2.4]	26.6 \pm 0.4	36.6 \pm 0.3	14.6 \pm 2.9	46.5 \pm 0.4