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Widespread sensitization in patients with chronic pain after revision total knee arthroplasty

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ABSTRACT

Pain and sensitization are major issues in patients with osteoarthritis both before and after total knee arthroplasty (TKA) and revision TKA (re-TKA). The aim of this study was to assess sensitization in patients with and without chronic pain after re-TKAs. Twenty patients with chronic knee pain and 20 patients without pain after re-TKA participated. Spreading of pain was evaluated as the number of pain sites using a region-divided body chart. The pressure pain threshold (PPT) and pressure pain tolerance (PTT) were assessed by cuff algometry at the lower leg. Temporal summation of pain was assessed by recordings of the pain intensity on a visual analog scale (VAS) during repeated cuff pressure stimulations. Conditioning pain modulation (CPM) was recorded by experimental tonic arm pain by cuff pressure stimulation and assessment of PPTs on the knee, leg, and forearm using handheld pressure algometry. Participants with pain after re-TKA compared to participants without pain demonstrated: (1) significantly more pain sites ($P = .004$), (2) decreased cuff PPTs and PTTs at the lower leg ($P < .001$), (3) facilitated temporal summation ($P < .001$), and (4) impaired CPM ($P < .001$). Additionally, significant correlations between knee pain intensity and cuff PPTs, temporal summation, and CPM and between total duration of knee pain and temporal summation were found ($P < .05$). This study demonstrated widespread sensitization in patients with pain after re-TKA and highlighted the importance of ongoing nociceptive input for the chronification process. This has important implications for future revisions, and precautions should be taken if patients have widespread sensitization.

1. Introduction

The incidence of primary and revision total knee arthroplasty (TKA and re-TKA, ie, when a second surgery is needed to remove, add, or exchange one or more TKA components [13]) has increased since their introduction [18,35], and the numbers are expected to increase in the future as a result of demographic and lifestyle changes [36]. Primary TKA is regarded as an effective and successful treatment for end-stage knee osteoarthritis (OA) [13]. Nevertheless, around 20% of the patients receiving a primary TKA experience small or no improvement in pain or even a worsening of the situation [9] and develop chronic postoperative pain [58]. Pain, aseptic loosening, infection, instability, and stiffness after the primary TKA account for 80% to 90% of all revisions [6,48,55]. However, re-TKA is not as effective as the primary TKA [13], and the risk of repeat revision is 4 to 5 times higher than the risk of revision after the primary TKA [6].

It has been suggested that peripheral and central sensitization in knee OA could be important for the poor pain outcome for some patients after TKA and pharmacological interventions [3,52]. Quantitative sensory testing (QST) has frequently been applied to investigate sensitization in OA, and increased pain sensitivity both locally and distantly from the affected joint has been reported [4,7,26,29,34,38,52,54]. Cuff algometry, a method for investigating deep tissue pain sensitivity and central mechanisms, is less influenced by intertester bias than handheld pressure algometry [45] and has recently been used to assess mechanisms of sensitization in knee OA [26,52].

Temporal summation of pain is the perceptual correlate in humans thought to mimic the initial phase of the windup process in dorsal horn neurons. In chronic musculoskeletal pain such as OA and fibromyalgia, temporal summation to repetitive pressure pain stimulations has been demonstrated to be facilitated compared to healthy controls [4,53] as a result of sensitized central

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mechanisms. In patients with chronic painful knee OA, higher clinical pain intensities and longer pain durations caused relatively more temporal summation of pain compared with patients with shorter duration and less pain [4].

Another important aspect associated with sensitization is the descending inhibitory and facilitatory modulation of the peripheral nociceptive inputs in the dorsal horn neurons [3,57]. Conditioned pain modulation (CPM) is a manifestation of this modulation which can be assessed in patients and is characterized by a changed response to a painful test stimulus when another painful conditioning stimulus is applied [61]. CPM is impaired in chronic pain disorders such as knee and hip OA [4,26,34], temporomandibular joint disorders [33], and fibromyalgia [16,37].

Previous studies have shown that sensitization in knee OA patients is normalized after successful joint replacement [26,34], with no residual pain indicating that the sensitization is maintained by peripheral input [26,34]. However, the state of the nociceptive system after re-TKA with and without pain alleviation is unknown.

The aim of this study was to compare patients with and without pain after re-TKA utilizing a variety of experimental pain techniques for assessing (1) local sensitization, (2) widespread sensitization, (3) temporal summation, and (4) conditioned pain modulation.

2. Methods

2.1. Materials

Patients initially diagnosed with end-stage knee OA who had undergone knee arthroplasty followed by a re-TKA using standard procedures [19] with pain as one of the reasons for the revision surgery were invited to participate in this study. In total, 54 patients were screened and 40 agreed to participate, 20 with pain in the revised knee and 20 without pain in the revised knee. Patients were matched for body mass and reasons for re-TKA (besides pain; loosening, infection, instability, and stiffness). Demographics and clinical characteristics are listed in Table 1. The participants were asked to refrain from using pain medication 24 h before the QST session. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee of the North Denmark Region (N-20100050). Oral and written information were provided to the participants, and written consent was obtained from all participants.

2.2. Protocol and questionnaires

Before the QST, the participants completed a questionnaire on demographics and clinical characteristics including questions on revision knee, reasons for revision other than pain, time between primary arthroplasty and first revision, number of revisions, and total number of surgeries after their primary arthroplasty, duration of pain, and mean pain intensity during daily function in the revised knee before the primary arthroplasty, before the first revision and current knee pain measured on a 100 mm visual analog scale (VAS) with the end point descriptors of "no pain" and "maximal pain," respectively. Furthermore, the participants reported pain sites on a region-divided body chart, completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [8], and the Knee Pain Map to evaluate their knee pain location and pattern [56]. The Knee Pain Map identifies areas of the knee that are painful and characterizes knee pain as localized (patellar, superiomedial, inferiomedial, medial joint line, superiolateral, inferiolateral, lateral joint line, or back of knee), regional (medial, lateral, patellar, or back of the knee), or diffuse, defined as unable to identify pain as localized or regional.

The participants rested in a comfortable recumbent position in a quiet, temperature-controlled room during the QST. The participants were carefully instructed in the QST methods before the experiment was initiated to make them familiar with the procedure. The QST procedure consisted of 3 different psychophysical parameters: (1) cuff algometry at the lower leg, (2) temporal summation of cuff-induced pain, and (3) CPM. The procedure was performed bilaterally, and the sequence was randomized. The data were collected by the same examiner (STS).

2.3. Cuff algometry for assessment of pain sensitivity

Pressure pain thresholds (PPT) and pain tolerance thresholds (PTT) were recorded by a computer-controlled cuff algometer (Aalborg University, Denmark) [46]. A 13-cm-wide tourniquet cuff (VBM, Germany) with an equal-size proximal and distal chamber was wrapped around the lower leg at the level of the heads of the gastrocnemius muscle. The pressure was increased with a rate of 1 kPa/s; the maximal pressure limit was 100 kPa. The participants used an electronic VAS to rate their pressure-induced pain intensity and a pushed button to release the pressure. The electronic VAS was sampled at 10 Hz. Zero and 10 cm extremes on the VAS were defined as "no pain" and as "maximal pain," respectively. The participants were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as pain (PPT) and to press the pressure release button when the pain was intolerable (PTT). The assessments were performed by inflation of the proximal chamber, the distal chamber, and both chambers simultaneously in a randomly generated sequence; each of the 3 conditions was repeated twice, and a mean of the different parameters was applied in the statistical analysis.

Table 1
Demographics and clinical characteristics of 40 study participants.

Demographic variable or clinical characteristic	Pain, mean ± SEM or fractions (n = 20)	No pain, mean ± SEM or fractions (n = 20)	P
Age (y)	61.5 ± 1.8	65.7 ± 1.3	.06
Gender (F/M)	14/6	8/12	.06
Body mass index (kg/m^2)	30.7 ± 1.2	31.5 ± 0.9	.61
Revision knee (right/left)	11/9	6/14	.11
Duration of pain before primary arthroplasty (mo)	66.9 ± 19.0	36.1 ± 9.3	.15
Total duration of knee pain (moths)	167.0 ± 22.6	64.3 ± 11.4	<.001*
Time between primary arthroplasty and first revision (mo)	43.2 ± 11.8	25.4 ± 6.1	.18
Knee pain before primary arthroplasty (mm)	78.3 ± 3.8	81.9 ± 4.2	.53
Knee pain before first revision (mm)	64.6 ± 4.7	55.9 ± 6.8	.30
Current knee pain (mm)	49.7 ± 5.9	0.0 ± 0.0	<.001*
WOMAC total (arbitrary unit)	46.2 ± 4.2	11.2 ± 2.1	<.001*
No. of surgeries after primary arthroplasty (revisions/total)	1.4 ± 0.8/2.9 ± 2.5	1.2 ± 0.7/1.4 ± 1.1	.41/.03*
Total pain sites	5.9 ± 0.6	3.0 ± 0.7	<.001*
Knee pain pattern (localized/regional/diffuse)	2/3/15	0/0/0	.49/.23/<.001*

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
* Statistically significant difference (P < .05).

2.4. Temporal summation of cuff-induced pressure pain

Temporal summation was assessed by the computer-controlled cuff algometer (Aalborg University, Denmark) [46]. Ten cuff pressure stimuli (1-s duration and 1-s interstimulus interval) were delivered to the lower leg by simultaneous inflation of both cuff chambers at an intensity equivalent to the mean of the PPT and PTT recorded during the assessment of the pain sensitivity. In the period between stimuli, a constant nonpainful pressure of 5 kPa was kept, thus ensuring that the cuff did not move. The participants rated their pain intensity continuously during the sequential stimulation on the electronic VAS without returning it to zero in between the stimulations. The mean VAS score during the 1-s interstimuli interval after each of the 10 stimuli was extracted, normalized by subtraction of the mean VAS scores from the first stimulation. Two series of recordings were completed, and the average was used in the statistical analysis.

2.5. Handheld algometry

Pressure was applied at a rate of 30 kPa/s perpendicular to the skin with a 1 cm^2 probe until the participant estimated the pressure as pain and pressed a button that defined the pressure pain threshold. PPTs were assessed twice, bilaterally, at 8 test sites in the peripatellar region, 1 site at the tibialis anterior muscle (TA; 5 cm distal to the tibial tuberosity), and 1 site at the extensor carpi radialis longus muscle (forearm; 5 cm distal to the lateral epicondyle of humerus) using a handheld pressure algometer (Algometer Type II, Somedic AB, Sweden). The sites in the peripatellar regions were: 2 cm distal to the inferior medial edge of patella (site 1); 2 cm distal to the inferior lateral edge of patella (site 2): 3 cm lateral to the midpoint on the lateral edge of patella (site 3); 2 cm proximal to the superior lateral edge of patella (site 4); 2 cm proximal to the superior edge of patella (site 5); 2 cm proximal to the superior medial edge of patella (site 6); 3 cm medial to the midpoint on the medial edge of patella (site 7); and at the center of patella (site 8) [4]. The average of 2 PPT measurements from all 8 sites for the peripatellar region, the tibialis anterior muscle, and the forearm was applied in the analysis of CPM [4].

2.6. Conditioned pain modulation

Experimental tonic pain was induced in the left arm by cuff-induced pain (conditioning stimulation), and assessment of pressure pain thresholds (test stimulus) was performed before, during, and 5 min after the conditioning stimulation using handheld pressure algometry.

The conditioning stimulation was induced by constant cuff stimulation. A 7.5-cm-wide tourniquet cuff (VBM, Germany) was wrapped around the left arm with the lower rim of the cuff placed 3 cm proximal to the cubital fossa. The computer-controlled cuff algometer (Aalborg University, Denmark) maintained a constant pressure corresponding to a pain of 4 cm at the electronic VAS rated by the individual participant. If the cuff-induced pain did not reach 4 cm on the VAS scale, the participants were asked to do handgrip exercise until the pain intensity target was achieved.

2.7. Statistical analysis

Data were assumed to be normally distributed, which was confirmed by visual inspection of Q-Q plots. To compare demographics and clinical characteristics between the 2 groups, Pearson's chi-square test was used for gender and revision knee, Fisher's exact test for knee pain pattern, Mann-Whitney *U* test for total pain sites, and independent samples *t* test for the other characteristics. A 3-way analysis of variance (ANOVA) was used to evaluate cuff algometry and temporal summation data with factors Group (pain, no pain), Side (revised, contralateral) and Chamber (proximal, distal, both) or Stimulation Number (1–10). A repeated measures (RM) ANOVA was used to evaluate CPM with Time (before, during, after conditioning stimulation) as the within-subject factor and Side (revised, contralateral) and Pressure Site (peripatellar, TA, forearm) as the between-subject factors for both the pain group and the no-pain group. Tukey's HSD test (for 3-way ANOVA) or Bonferroni (repeated measures ANOVA) was used as post hoc tests in cases of significant ANOVA factors or interactions. Gender and age were set as covariates in the between-group ANOVA analyses to control for potential effects of these variables. Pearson's product moment correlations were applied to assess the association between current knee pain intensity and total duration of knee pain and the QST parameters. In the correlation analysis, the accumulated VAS score from the 10 stimuli by the cuff algometer (each VAS score normalized by subtraction of the first stimulation from the mean VAS score) was used as a measure of temporal summation, and CPM was evaluated as PPT (assessed using handheld algometry) during the painful conditioning stimulation as a percentage of the PPT before the conditioning stimulation.

P values of less than .05 were considered significant. Data are presented as mean values and standard error of the mean (SEM) or fractions. All analyses were performed by IBM SPSS Statistics software (version 19).

3. Results

The pain group had a significantly longer total duration of knee pain ($P < .001$), higher current knee pain intensity ($P < .001$), higher total WOMAC score ($P < .001$), higher number of repeated surgeries after TKA ($P = .02$), and more pain sites than the no-pain group ($P < .001$; Table 1, Fig. 1). In the pain group, 15 identified their knee pain as diffuse, 3 as regional, and 2 as localized.

3.1. Cuff algometry

Cuff PPTs and PTTs were significantly lower in the group with pain after the re-TKA compared to the group without pain after re-TKA (ANOVA: $F(1,220) > 15.6$, $P < .001$; Figs. 2 and 3). In both groups, the PTT obtained from the proximal chamber was significantly higher compared to the distal chamber and both chambers at the same time (ANOVA: $F(2,220) = 6.69$, $P < .002$; Tukey: $P < .05$; Fig. 3). Age and gender were both significant covariates (ANOVA: $F(1,220) > 7.41$, $P < .01$).

3.2. Temporal summation of cuff-induced pain

An interaction between group and stimulation number showed that the normalized VAS scores to sequential stimulation were significantly higher in the pain group compared to the no-pain group for stimulation 4 to 10 (ANOVA: $F(9,738) = 6.13$, $P < .001$; Tukey: $P < .05$; Fig. 4). For both groups, the VAS scores showed a progressive increase during the cuff stimulations, with the last 9 VAS scores being higher than the VAS score from the first stimulation (Tukey: $P < .001$). Age and gender were both significant covariates (ANOVA: $F(1,738) > 29.8$, $P < .001$).

3.3. Conditioned pain modulation

Three participants (2 in the no-pain group and 1 in the pain group) acquired handgrip exercise to reach 4 cm on the VAS scale. In the pain group handheld algometry PPTs from the peripatellar region, the TA, and the forearm were significantly reduced from baseline during the painful conditioning stimulation (ANOVA: $F(1.446, 164.830) = 8.248$, $P = .001$; Bonferroni: $P < .001$; Fig. 5A).

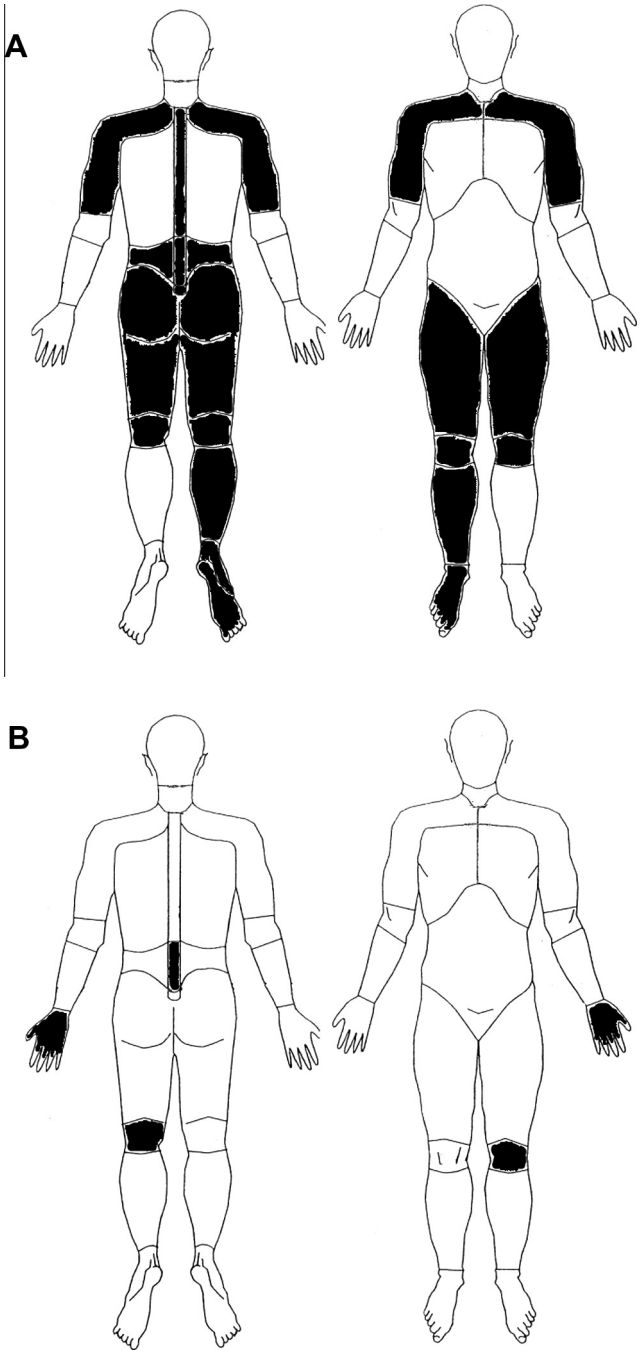

Fig. 1. Pain sites. Sites of the body where at least 25% ($n = 5$) of the patients with pain (A) and without pain (B) after revision total knee arthroplasty (re-TKA) reported pain. The right side of the body has been set as the side with re-TKA.

In contrast, in the no-pain group PPTs from all sites increased significantly from baseline during the painful conditioning stimulation (ANOVA: $F(1.575, 170.071) = 33.1$, $P < .001$; Bonferroni: $P < .001$; Fig. 5B).

3.4. Correlations

The correlation coefficients are presented in Table 2. Significant correlations were found between knee pain intensity and cuff PPTs, temporal summation and CPM, and total duration of knee pain and temporal summation ($P < .05$).

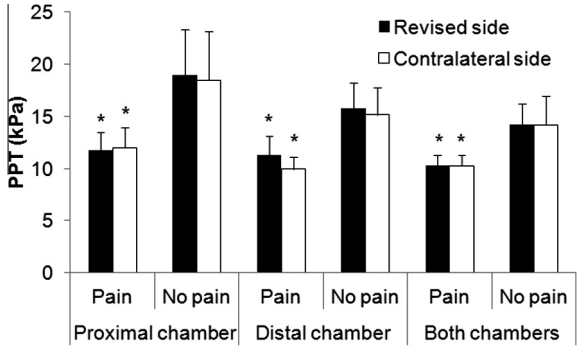

Fig. 2. Cuff pressure pain thresholds. Mean (±SEM, $n = 20$) cuff pressure pain thresholds (PPT) in patients with (solid symbols) and without pain (open symbols) after revision total knee arthroplasty (re-TKA). PPTs were assessed for proximal, distal, and both chambers with a cuff mounted at the lower leg of the leg with re-TKA and contralaterally. Significantly lower PPTs were found in the pain group than in the pain-free group ($^{*}P < .001$).

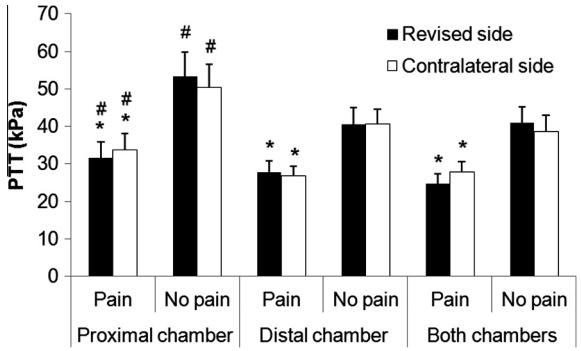

Fig. 3. Cuff pressure pain tolerances. Mean (±SEM, $n = 20$) cuff pressure pain tolerances (PTT) in patients with (solid symbols) and without pain (open symbols) after revision total knee arthroplasty (re-TKA). PTTs were assessed for proximal, distal, and both chambers with a cuff mounted at the lower leg of the leg with re-TKA and contralaterally. Significantly lower PTTs were found in the pain group than in the pain-free group ($^{*}P < .001$). Furthermore, significantly higher PTTs were found for the proximal chamber compared to both the distal and both chambers ($^{\#}P < .05$).

4. Discussion

To our knowledge, this is the first study to demonstrate widespread sensitization in patients with chronic pain after re-TKA. Participants with chronic pain after re-TKA had significantly more pain sites and pressure pain hyperalgesia at the lower leg and forearm (widespread sensitization) compared to the participants without pain after re-TKA. Furthermore, the chronic pain group demonstrated facilitated temporal summation of pain and impaired descending pain modulation which highlight the importance of central components in the process of spreading pain sensitization.

4.1. Widespread pain sensitization after revision TKA

In chronic knee OA, localized pain and peripheral sensitization together with diffuse pain and widespread hyperalgesia (central sensitization) are predominant factors [20,25,29,41,49,50]. The present study showed that similar factors are also important in patients with maintained chronic pain after re-TKA. As the TKA and subsequent revision(s) change the environment from where nociception can occur, it seems that there is still adequate peripheral drive to maintain the pain and sensitization. A recent systematic review and meta-analysis concluded that compared to healthy participants, people with OA had lower PPTs in both the affected joint and

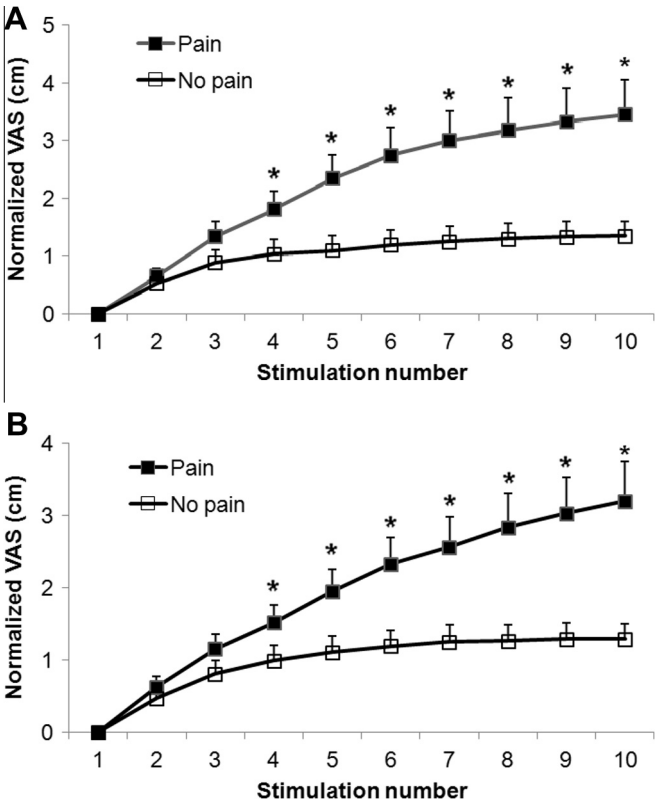

Fig. 4. Temporal summation. Mean (±SEM, $n = 20$) visual analog scale (VAS) scores after 10 cuff pressure pain stimulations (temporal summation) in patients with (solid symbols) and without pain (open symbols) after revision total knee arthroplasty (re-TKA). VAS scores were normalized by subtraction of the VAS scores from the first stimulation and presented for the leg with re-TKA (A) and contralaterally (B). The pain group had significantly higher VAS scores than the pain-free group for stimulations 4 to 10 ($^*P < .05$).

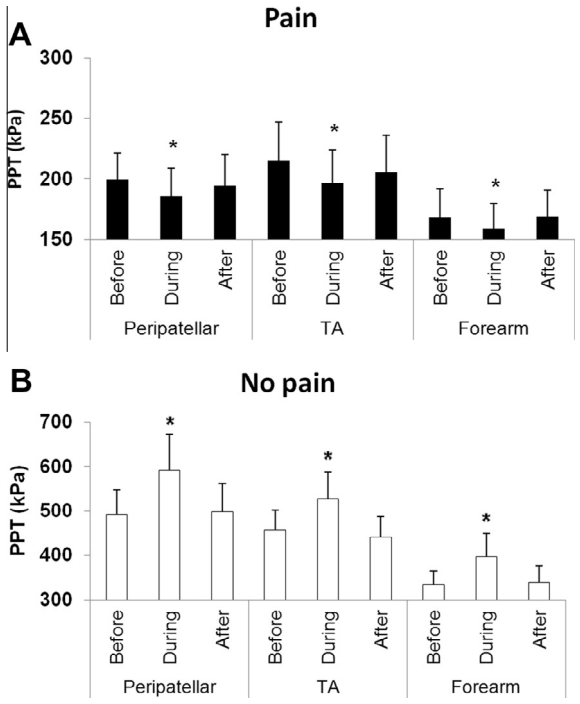

Fig. 5. Conditioned pain modulation. Mean (±SEM, $n = 20$) pressure pain thresholds (PPT) manually assessed in patients with (solid symbols; A) and without pain (open symbols; B) after revision total knee arthroplasty (re-TKA). The PPTs were recorded before, during, and after conditioned pain modulation by tonic arm pain in the peripatellar region (peripatellar), at the tibialis anterior muscle (TA), and at the extensor carpi radialis muscle (forearm). The assessments were averaged between the leg with re-TKA and contralaterally. PPTs were significantly different during compared to before the painful conditioning stimulation ($^*P < .05$).

at remote sites as an indicator for spreading sensitization [54]. The present study extends this finding to people with pain after re-TKA having a diffuse pain pattern in the revised knee and pressure hyperalgesia at the lower leg of both the revised and the contralateral side. The significant negative association between cuff pressure pain thresholds and knee pain intensity supports previous findings in knee OA patients [4,26,29,52]. A recent study showed that interleukin 6 levels increased after a painful stimuli, that high C-reactive protein was related to low PPTs, and that high interleukin 6 levels were related to high heat pain ratings in knee OA patients [38]. Inflammation results in increased pain sensitivity and intensity which may facilitate central pain mechanisms [38]. If such factors are important after TKA and re-TKA is not known. Furthermore, it seems that the pain was bilateral in the pain group in the present study, which also indicates widespread pain due to chronic pain in the revision knee. Nonetheless, it cannot be excluded that pain also originates from the contralateral knee although not recognized as the most severe problem for the patients.

The role of pain sensitization in knee OA and after re-TKAs emphasizes the significance of targeting this mechanism pharmacologically or by other means.

The present human data translate findings from animal studies showing enhanced responses to stimuli applied to sites adjacent and distant to a joint with ongoing nociceptive activity [51]. In rats with unilateral arthritis [27] and chronic polyarthritis [42], spinal cord neurons with input from the joint are more sensitive and have expanded receptive fields. Secondary hyperalgesia due to joint nociception can last for several weeks, and this hypersensitivity is related to increased responses of spinal cord neurons to input from A- and C-fibers [41].

4.2. Temporal summation

Although handheld pressure algometry is the most frequently applied mechanical method applied in QST [24] and has shown good test–retest reliability in knee OA [60], the method could be affected by problems such as intertester bias and difficulties maintaining a constant pressure rate [1,11,22]. Consistent with previous studies in whiplash associated disorder [39], fibromyalgia [31], lateral epicondylalgia [30], and knee OA [26,52] cuff algometry is feasible to investigate sensitization also in re-TKA. Cuff algometry overcomes some of the issues related to handheld pressure algometry because it allows exclusion of manual involvement during the QST [46]. However, the cuff can only activate larger areas, and as such, handheld algometry can still be used for pain mapping of, eg, the knee [4].

The present study is to our knowledge the first demonstrating an enhanced temporal summation using cuff algometry in patients with chronic OA-related pain. Combined with the fact that both the revised and the contralateral side show enhanced temporal summation (mimicking the first part of the windup process), the findings of the present study indicate that patients with pain after re-TKA have central sensitization [2].

4.3. Descending control of the pain sensitivity

A dysfunctional CPM has been suggested to be important for the clinical manifestations of chronic pain concurrently making the entire neuroaxis more vulnerable to pain [5]. The present study showed an impaired CPM as previously demonstrated in OA patients [4,26,34]. Interestingly, a reduction was found in handheld algometry PPT at all sites during the conditioning stimulation in

Table 2
Correlation coefficients in the pain group (Pearson's product moment correlations).[a]

Pain assessment parameter	Mean ± SEM	Correlation	Current knee pain	Total duration of knee pain
Cuff PPT (kPa)	10.3 ± 1.0	*R*	−0.39	−0.22
		P value	.01	.17
VAS sum (cm)	20.5 ± 3.4	*R*	0.40	0.41
		P value	.01	.01
Mean of CPM knee, CPM TA and CPM forearm (% of baseline)	92.0 ± 3.3	*R*	−0.36	−0.19
		P value	.02	.24

[a] Current knee pain, measured on a 100 mm visual analog scale; cuff PPT, pressure pain thresholds measured using both chambers of a cuff algometer; VAS sum, accumulated VAS score from 10 stimuli from the cuff algometer (each VAS score normalized by subtraction of the first stimulation from the mean VAS score) as a measure of temporal summation; CPM, conditioning pain modulation evaluated as PPT during the painful conditioning stimulation as a percentage of the PPT before the conditioning stimulation in the peripatellar region (knee), at the tibialis anterior muscle (TA), and the extensor carpi radialis muscle (forearm), with a higher number indicating a more potent CPM.

the participants with pain. This is consistent with previous findings in painful knee OA [26] further emphasizing the importance of CPM as a complex interaction between facilitatory and inhibitory mechanisms [26]. Whether the continuous noxious stimuli from a painful joint lead to an increase in facilitatory and/or decrease in inhibitory mechanisms remains to be explored. It is, however, interesting that the group of patients with pain after re-TKA demonstrated increased pain sensitivity during the tonic arm pain suggesting that the descending control acted as a promoting factor.

4.4. Pain generator in widespread sensitization

Two previous studies found a normalization of the sensitized nociceptive system in patients with OA after pain-relieving joint replacement [26,34] with no residual pain, suggesting that the sensitization arises and is maintained by peripheral input [26,34]. The nociceptive input could originate from inflammation of the synovium, stretching of the joint capsule, raised intraosseous pressure in the subchondral bone, and elevation of periosteum by osteophyte growth and/or periarticular tissues [17]. Knee arthroplasty involves replacing the most affected parts of the joint (partial knee replacement) or the entire joint (total knee replacement) [13,40]. Hence, the sources of pain after primary TKA and re-TKA cannot be the same joint-related structures as before surgery. This implies that the retention of the ongoing pain and the sensitization found in the present study could be related to peripheral input from non-surgically removed periarticular tissue such as adjacent muscles, connective tissue, and/or adipose tissue. The finding of lower PTTs from the distal chamber compared to the proximal chamber supports this because the pressure is applied to these nonremoved structures. Additionally, central mechanisms could be involved in the maintenance of the sensitization. This has implications for the pain management strategies as they may be distinctly different from managing OA pain.

Previous studies have shown that having pain elsewhere is significantly associated with persistent pain after joint replacement [43,47,59] and other surgical procedures [10,14,23,44]. Furthermore, the likelihood of having pain elsewhere is associated with already having one pain condition [15]. This is substantiated by the significant findings in this study of more pain sites in participants with pain after re-TKA compared to participants without pain. It has been suggested that this spread of pain is due to a generalized vulnerability to chronic pain [15], possibly because of sensitization following the chronic noxious input from the original painful site [59]. In fact, both pain intensity [28] and duration [21] are known to determine the extent of widespread muscle hyperalgesia and the total pain sites of the patient. Additionally, 2 recent large-scale cross-sectional studies found a strong association between pain intensity and hyperalgesia in persistent postsurgical pain [32] and among pain intensity, hyperalgesia, and allodynia in patients with chronic, self-reported neuropathic pain [12], both indicating sensitization as an important underlying factor in chronic pain. This is supported by the significant correlations between knee pain intensity and cuff PPTs, temporal summation, and CPM, and between total duration of knee pain and temporal summation.

One possible limitation of our study is the difference in gender and age distribution between groups. Nevertheless, the difference in distribution was nonsignificant, and both variables were controlled for, as they were included as covariates in the analyses.

Another limitation could be the application of PPTs in both the analysis of temporal summation and CPM because the differences between groups could be explained by differences in the intensity of the stimulation (PPT). However, one would assume that higher PPTs would result in higher temporal summation, but this study showed the opposite: that the pain group had lower PPTs and at the same time higher temporal summation. Furthermore, because the analysis of CPM was a within-group analysis of changes in PPTs, differences in baseline PPTs would not affect the results.

4.5. Conclusion

This study demonstrated widespread sensitization in patients with chronic pain after re-TKA, suggesting involvement of similar peripheral and central sensitization mechanisms as found in chronic knee OA pain, although some of the peripheral nociceptive drivers are obviously different. This may suggest precautions for future surgical knee interventions.

Conflict of interest statement

The authors report no conflict of interest.

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