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How Does Preoperative Central Sensitization Affect Quality of Life Following Total Knee Arthroplasty?

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ABSTRACT

Background: Central sensitization (CS) has been recently identified as a significant risk factor for persistent pain and patient dissatisfaction following total knee arthroplasty (TKA). However, it remains unclear as to whether the preoperative CS persists after the elimination of a nociceptive pain source by TKA, or how CS affects the quality of life after TKA.

Methods: A total of 222 consecutive patients undergoing primary TKA were enrolled in the study. All patients were preoperatively screened for CS using the Central Sensitization Inventory (CSI) and categorized into either a CS (n = 55; CSI ≥ 40) or non-CS group (n = 167; CSI < 40). CSI, pain visual analog scale (VAS), Knee Society Score (KSS), Western Ontario and McMaster Universities Osteoarthritis Index score, and satisfaction were recorded at postoperative 2 years.

Results: Two years after TKA, preoperative CS remained unchanged; there was no difference between preoperative and postoperative CSI scores, and both preoperative and postoperative CSI severity levels were similar ($P > .1$). The CS group showed worse pain VAS, KSS, and Western Ontario and McMaster Universities Osteoarthritis Index scores than did the non-CS group ($P < .01$) and more patients in the CS group were dissatisfied with all activities ($P < .01$). However, a similar percentage of the CS group achieved the previously documented minimal clinically important difference in pain VAS and KSS, compared with the non-CS group. Multivariate regression analysis revealed that preoperative CSI scores were associated with dissatisfaction at postoperative 2 years.

Conclusion: Preoperative CS was persistent at 2 years after TKA. Although CS patients achieved comparable clinical improvement following TKA, CS patients had worse quality of life, functional disability, and dissatisfaction than non-CS patients.

Great advances in pain management protocol and in surgical techniques have improved postoperative recovery after total knee arthroplasty (TKA) [1]. However, despite excellent postoperative analgesia administered during the early postoperative period, prevalence of persistent pain after TKA, in the absence of any satisfactory surgical explanation, has remained consistent over the past decades, ranging from 10% to 34% [2,3]. Recent evidence supports the belief that central sensitization (CS), which can be defined as an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity, is a potent risk factor for persistent pain and patient dissatisfaction after TKA [4–10]. Generally, continuous peripheral nociceptive stimuli and accompanying modulation of these stimuli within the CNS are known to initiate CS, which manifests as neuropathic pain (NP) [11–13]. However, although NP is known to contribute to the pain of knee osteoarthritis (OA) [14,15], the mechanisms remain unclear as to how CS develops in patients with knee OA, and whether elimination of peripheral pain sources by surgical procedures such as TKA affects CS and NP.

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A growing body of evidence suggests that a substantial proportion (20%-40%) of patients with advanced knee OA who are scheduled for TKA are centrally sensitized and experience a component of NP before surgery [8,16,17]. In addition, preoperative CS is reported to be predictive of adverse clinical outcomes after TKA including severe, unpredictable postoperative pain that is resistant to traditional analgesia, higher opioid consumption, and dissatisfaction after TKA [4–7,18]. Preoperative NP is reported to be a predictor for persistent pain within the first postoperative year [5,6,19], although other studies have reported that preoperative NP has limited prognostic value for post-TKA outcomes [20,21]. Multiple previous studies investigated NP as a proxy for CS [5,6,10,19,21,22]; only a few previous studies have assessed CS directly [4,9,23]. As a result, there is a paucity of data regarding the natural history of preoperative CS in advanced knee OA patients, and our knowledge of how CS affects postoperative health status and functional outcomes in patients undergoing TKA remains incomplete.

This study was conducted to determine (1) whether, in knee OA patients who are scheduled for TKA, preoperative CS, as evaluated with the Central Sensitization Inventory (CSI), persists after elimination of the peripheral nociceptive pain source by TKA; and (2) how preoperative CS affects quality of life (QoL) and functional outcomes at postoperative 2 years after TKA.

Materials and Methods

We retrospectively reviewed 250 consecutive primary TKAs performed between 2015 and 2016 at a single institute. After approval was granted by our institutional review board (KC19RESI0127), we included only those patients who underwent TKA for primary OA, had known clinical outcomes, and had a minimum follow-up period of 2 years. To investigate the effect of TKA on postoperative CS in advanced knee OA patients, we excluded those with postoperative complications requiring reoperation; those with an American Society of Anesthesiologists classification system score (for assessing preoperative comorbidities) of 3 or higher; those with a history of central sensitivity syndrome such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and chronic low back pain [24]; and those with a history of use of a centrally acting agent or with a known psychiatric disorder that could potentially affect postoperative CS. Thus, 28 of 250 TKAs were excluded for a range of reasons such as rheumatoid arthritis or secondary OA (4 patients); no available clinical outcomes for postoperative 2 years (3 patients); periprosthetic joint infection requiring open debridement (2 patients); American Society of Anesthesiologists score $\geq$ 3 (8 patients); history of central sensitivity syndrome (fibromyalgia in 1 patient, irritable bowel syndrome in 1 patient); and history of centrally acting agents or psychiatric disorder (9 patients). Consequently, 222 TKAs were finally included in this study. Of these 222 patients, 201 (91%) were female and 21 were male. Mean age was 70 years (range, 57-83 years), and the average body mass index (BMI) was 26.4 kg/m^2 (range, 17.8-38.1 kg/m^2).

Preoperatively, in all patients, the severity of CS was routinely assessed using the Central Sensitization Inventory (CSI) questionnaire administered by a clinical investigator (M.S.K.) (Table 1). CSI severity levels were categorized into 4 groups: subclinical = 0 to 29; mild = 30 to 39; moderate = 40 to 49; severe to extreme = 50 to 100 [25]. Patients were classified into either the CS group or the non-CS group, with CS defined as a score of $\geq$40 [26]. Of the 222 patients, 55 patients were centrally sensitized and 167 were not. All patients and research assistants (K.Y.C. and S.S.) who collected the clinical data were kept unaware of preoperative CSI score until the final data analyses were completed. The mean age of the CS group was older than that of non-CS group, and those in the CS group had a lower mean BMI and more severe preoperative pain (Table 2).

All patients received 200 mg of celecoxib and 150 mg of pregabalin 2 hours preoperatively for preemptive pain control. All operations were performed by a single surgeon (Y.I.) under general anesthesia using standard procedures. A currently available, conventional, cemented-type, posterior-stabilized knee system (Lospa; Corentec Co, Ltd, Seoul, Korea) was used in all patients. A pneumatic tourniquet that inflated to 300 mmHg was applied for the

Table 1
Central Sensitization Inventory [25,40].

Symptom	Response				
(1) I feel tired and unrefreshed when I wake from sleeping.	Never	Rarely	Sometimes	Often	Always
(2) My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
(3) I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
(4) I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
(5) I have problems with diarrhea and/or constipation.	Never	Rarely	Sometimes	Often	Always
(6) I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
(7) I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
(8) I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
(9) I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
(10) I have headaches.	Never	Rarely	Sometimes	Often	Always
(11) I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Sometimes	Often	Always
(12) I do not sleep well.	Never	Rarely	Sometimes	Often	Always
(13) I have difficulty concentrating.	Never	Rarely	Sometimes	Often	Always
(14) I have skin problems such as dryness, itchiness, or rashes.	Never	Rarely	Sometimes	Often	Always
(15) Stress makes my physical symptoms get worse.	Never	Rarely	Sometimes	Often	Always
(16) I feel sad or depressed.	Never	Rarely	Sometimes	Often	Always
(17) I have low energy.	Never	Rarely	Sometimes	Often	Always
(18) I have muscle tension in my neck and shoulders.	Never	Rarely	Sometimes	Often	Always
(19) I have pain in my jaw.	Never	Rarely	Sometimes	Often	Always
(20) Certain smells, such as perfumes, make me feel dizzy and nauseated.	Never	Rarely	Sometimes	Often	Always
(21) I have to urinate frequently.	Never	Rarely	Sometimes	Often	Always
(22) My legs feel uncomfortable and restless when I am trying to go to sleep at night.	Never	Rarely	Sometimes	Often	Always
(23) I have difficulty remembering things.	Never	Rarely	Sometimes	Often	Always
(24) I suffered trauma as a child.	Never	Rarely	Sometimes	Often	Always
(25) I have pain in my pelvic area.	Never	Rarely	Sometimes	Often	Always

Each item was graded on a 5-point Likert scale ranging from 0 to 4 points (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always).
Subclinical <29; mild CS = 30~39; moderate CS = 40~49; severe to extreme >50.
CS, central sensitization.

Table 2
Preoperative Characteristics in the Non-CS and CS Groups.[a]

Variables	Non-CS (N = 167)	CS (N = 55)	Significance
Demographic factor			
Age	69.0	71.2	.017
Gender, ♀ (%)[b]	151 (90)	50 (91)	.914
BMI (kg/m^2)	26.7	25.4	.014
ASA status (%)[b]			
1	21 (13)	3 (5)	.209
2	146 (87)	52 (95)	
ROM (°)			
Flexion contracture	6.9	7.0	.882
Further flexion	124.8	126.8	.158
CSI score	21.3	53.1	<.01
Pain VAS	5.2	5.8	.012
Knee Society score	111.2	109.8	.772
WOMAC score	56.7	54.5	.555

CS, central sensitization; BMI, body mass index; ASA, American Society of Anesthesiologists; ROM, range of motion; CSI, Central Sensitization Inventory; VAS, visual analog scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index Scale.
[a] Data are presented as mean.
[b] Data are presented as number of patients (percentage).

entire procedure. An intramedullary alignment system was used for the femoral cuts and an extramedullary system was used for the tibial cut. Patellar resurfacing was performed for all patients. Meticulous bleeding control was performed after deflation of the tourniquet. Starting the day after surgery, the patients were allowed to walk using a walker and began gradually increasing range of motion (ROM) exercises in bed.

All clinical information was collected by research assistants (K.Y.C. and S.S.) using a predesigned case report form. The clinical information included demographic data and postoperative clinical outcomes evaluated at 3, 6, 12, and 24 months. The postoperative clinical outcomes included CSI [25], pain visual analog scale (VAS) [27], the ROM of the knee, the knee and function scores according to the American Knee Society [28], the Western Ontario and McMaster University Osteoarthritis Index scale (WOMAC) [29], and patients satisfaction [30]. Pain levels were estimated using a VAS that ranged from 0 (no pain) to 10 (worst imaginable pain). Persistent pain is defined as pain VAS >3 within the last 24 hours at postoperative 2 years after TKA [6,31]. The ROM of the knee, which was measured in flexion contracture and maximum flexion to the nearest 5° using a standard 38-cm goniometer, was performed with the patient in the supine position. Patient satisfaction was assessed according to the New Knee Society Scoring System, which consists of 5 questions regarding satisfaction according to different physical activities [30]. Patient satisfaction was classified into either satisfied (21–40 points) or dissatisfied (0–20 points) based on total satisfaction points [9,32]. In addition, we searched the minimum clinically important difference (MCID) value of pain VAS [8,27], KSS [28], and WOMAC [29] after TKA and adapted these values to this study for assessment of improvement.

Statistical Methods

To determine whether preoperative CS would persist postoperatively, the paired *t*-test was used to compare the preoperative and postoperative CSI and correlation analysis was also performed. In addition, changes in the percentage of CSI severity level were calculated. To evaluate the effect of preoperative CS on outcomes after TKA, we compared CSI, pain VAS, percentage of persistent pain, ROM, KSS, WOMAC, and satisfaction at 2 years after TKA between the CS and non-CS groups. In addition, the MCID of each outcome variable, the postoperative improvement from preoperative status, and the proportion of patients who achieved MCID were compared between the 2 groups. Chi-square tests were used to determine the statistical significance between differences for each categorical variable, and the Student *t*-test or Wilcoxon signed-rank test was used to evaluate the significance of differences between continuous variables. Finally, to identify risk factors for patient dissatisfaction, multivariate regression analysis was performed and 95% confidence intervals were calculated for dissatisfaction. A power analysis showed that this study had 82% power to detect a 2-point VAS difference in the pain level, 80% power to detect a 10% difference from the baseline score for the WOMAC score, and 80% power to detect a 2-point difference in satisfaction using a 2-sided hypothesis test at an alpha level of 0.05. The statistical analyses were performed using SPSS for Windows software (version 26.0; IBM Corp, Armonk, NY).

Results

Preoperative CS was persistent even after the elimination of the peripheral nociceptive pain source by TKA. There was no difference in the preoperative and postoperative 2-year CSI scores (29.2 in preoperative vs 29.9 in postoperative 2 years, $P = .192$), and both preoperative and postoperative CSI were highly correlated (Pearson coefficient = 0.909, $P < .01$). In addition, the preoperative CSI severity level was similar to that at postoperative 2 years ($P = .771$). Moreover, both resolution of preoperative CS and new development of postoperative CS occurred only rarely (2% and 5%, respectively) (Fig. 1).

Preoperative CS patients showed limited benefit at postoperative 2 years following TKA when compared with non-CS patients. The CS group had a higher mean CSI score, and pain VAS, KSS, and WOMAC scores than did the non-CS group ($P < .01$ in all metrics). In addition, more patients in the CS group experienced persistent CS and pain ($P < .01$ in all variables). However, more than 80% of the CS group achieved postoperative improvement (more than the previously documented MCID) in pain VAS (86%), KSS (89%), and WOMAC score (80%). The proportions of MCID achievement were comparable between groups, with the exception of the WOMAC score (Table 3).

More patients in the CS group experienced dissatisfaction with all kinds of daily activities than did the non-CS group ($P < .01$ in all variables) (Fig. 2). Multivariate regression analyses revealed that preoperative CSI score, postoperative pain VAS, and WOMAC score were risk factors for dissatisfaction following TKA ($P < .01$ in all

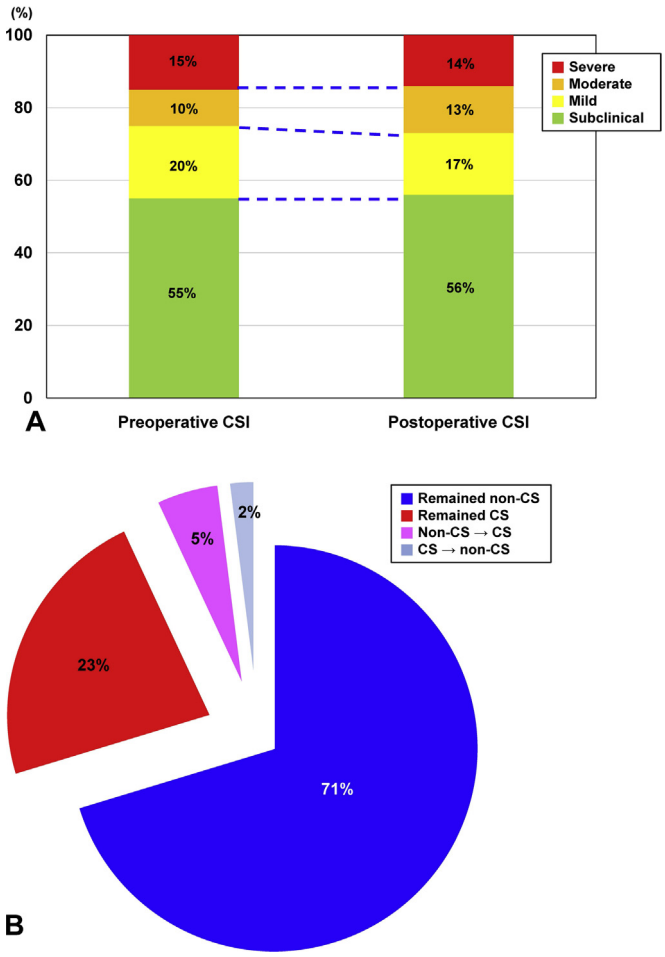

Fig. 1. Changes in percentage of CSI grade at preoperative and postoperative 2 years. (A) Changes in percentage of CSI severity level at preoperative and postoperative 2 years. (Subclinical <29; mild CS = 30–39; moderate CS = 40–49; severe to extreme >50). (B) Changes in percentage of CS (non-CS < 40; CS ≥ 40). CS, central sensitization; CSI, Central Sensitization Inventory.

predictors). The R^2 value for the multivariate regression model, using these 3 variables, was 0.692, indicating that 69.2% of the variation in the outcome could be explained by these 3 variables (Table 4).

Discussion

A growing body of evidence suggests that CS may contribute to chronic pain in a subset of advanced knee OA patients, and a substantial proportion of patients who are scheduled for TKA experience both nociceptive and neuropathic pain [8,16,17,22,33,34]. In addition, recent evidence supports the idea that preoperative CS is predictive of several adverse clinical outcomes including more severe, persistent pain, higher opioid consumption, and worse functional disability following TKA [4–9,18]. However, it remains unclear as to whether preoperative CS is persistent and how detrimental CS is to post-TKA QoL and functional outcomes at 2 years following TKA.

This study demonstrated that preoperative CS in advanced knee OA patients is persistent even after successful TKA. We found in this study that preoperative CSI score and CSI severity levels were similar to those of postoperative 2 years. It is difficult to compare our study with previous studies investigating postoperative NP after TKA, but our findings are at odds with previous reports that the development of post-TKA NP is unpredictable [20,21]. Despite these inconsistencies, our findings, together with those of previous studies, suggest that the elimination of peripheral nociceptive stimuli by TKA alone may be insufficient to restore preoperatively developed hyperexcitability in the CNS. Further studies are needed to determine the effect of the preoperative screening of CS patient and selective desensitization treatment, including administration of centrally acting agents, on postoperative CS and outcomes in centrally sensitized patients following TKA.

In summary, we found that preoperative CS patients showed limited benefit following TKA when compared with non-CS patients. In this study, CS patients experienced worse QoL, functional disability, and satisfaction than non-CS patients and the proportion of MCID in the WOMAC score was lower in CS patients. However, a similar proportion of patients achieved clinical improvement, more

Table 3
Central Sensitization and Clinical Outcomes at Postoperative 2 Years in the Non-CS and CS Groups.[a]

Clinical Outcomes	Non-CS (N = 167)	CS (N = 55)	Significance
CSI score	22.1	53.5	<.01
Proportion of CS[b] (%)	11 (5)	50 (91)	<.01
Pain VAS	1.0	2.3	.012
Changes from preoperative status	4.2	3.5	.06
Proportion of MCID[c] (%)	154 (92)	47 (86)	.181
Proportion of persistent pain[b] (%)	19 (11)	21 (38)	<.01
ROM (°)			
Flexion contracture	0.1	0.3	.111
Further flexion	128.1	128.7	.544
Hip-knee-ankle axis	0.8	0.7	.688
Knee Society score	177.6	165.3	<.01
Changes from preoperative status	65.2	58.6	.223
Proportion of MCID[d] (%)	157 (94)	45 (89)	.085
WOMAC score	15.4	25.2	<.01
Changes from preoperative status	42.1	29.5	.014
Proportion of MCID[e] (%)	150 (90)	44 (80)	.015

CS, central sensitization; CSI, Central Sensitization Inventory; VAS, visual analog scale; MCID, minimum clinically important difference; ROM, range of motion; WOMAC, Western Ontario and McMaster University Osteoarthritis Index Scale.

[a] Data are presented as mean.
[b] Data are presented as number of patients (percentage).
[c] Proportion of patients whose pain VAS score improved more than 2 [27].
[d] Proportion of patients whose Knee Society score improved more than 19 points [28].
[e] Proportion of patients whose WOMAC score improved more than 10 points [29].

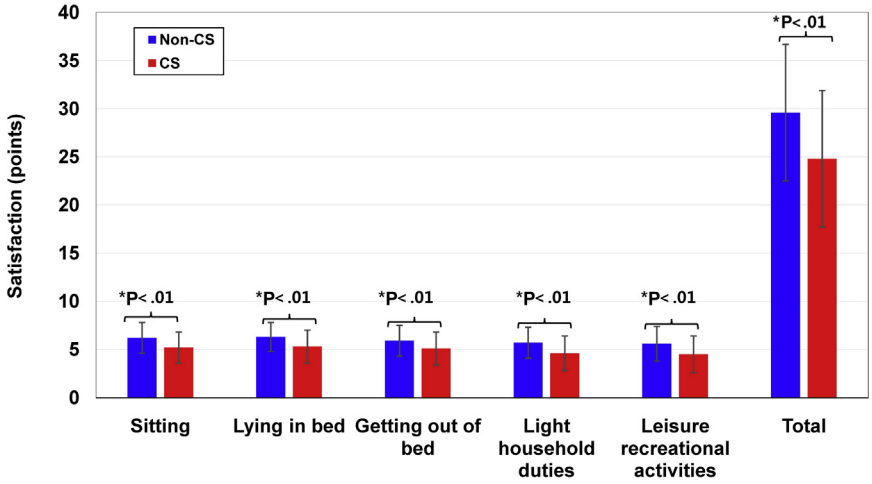

Fig. 2. Comparison of patient satisfaction at postoperative 2 years. Non-CS patients were more satisfied with all kinds of activities than CS patients. CS, central sensitization.

than the previously documented MCID, in terms of pain VAS (86%), KSS (889%), and WOMAC (80%). Our findings are in agreement with previous studies that reported worse clinical outcomes in preoperative CS patients after TKA [5–7,9,10]. The reasons why CS patients showed such limited improvement are unclear, but it may be partly due to the fact that TKA relieves only nociceptive pain caused by knee OA but NP of CS patient remains persistent even after TKA. The results of this study, together with those of previous studies, suggest that surgeons should rule out CS if patients have severe, persistent pain that is resistant to traditional analgesia after TKA, and instead consider more aggressive, tailored multimodal treatment options for CS including cognitive-behavioral therapy, physiotherapy stress management and neurofeedback training, and pharmacological agents.

Our results indicate that the preoperative CS is one of the risk factors for patient dissatisfaction after TKA. In our study, more patients in the CS group were dissatisfied with all kinds of daily activities after TKA. In addition, multivariate regression analysis identified preoperative CS, postoperative severe pain VAS, and worse WOMAC as predictors for dissatisfaction at postoperative 2 years after TKA. These findings concur with previous studies that reported that preoperative CS is a risk factor for persistent pain and dissatisfaction after TKA [4,9,10]. Our findings, taken together with those of previous studies, indicate that surgeons should consider routine assessment of CS before TKA and they should preoperatively advise centrally sensitized patients of the high possibility of dissatisfaction, so as to ensure realistic expectations of outcomes after TKA.

Our study had several limitations. Firstly, because we evaluated only Korean patients, the demographic features of TKA in Korea, such as the predominance of elderly and female patients undergoing the procedure, should be noted before extrapolating our findings to other populations [35–39]. Secondly, as the present study is retrospective, this study was possibly underpowered and subject to type-II error with respect to detecting all relevant outcomes. Thirdly, as the severity of NP or CS is assessed by several questionnaires [20,22,40], evaluation of NP or CS might be affected by the particular assessment tool. However, there is no gold standard assessment method to investigate CS, and assessment validation in knee OA patients following TKA remains uncertain. CSI was used for the assessment of CS in this study and this should be considered before extrapolating our findings to other studies. Finally, we used previously documented MCID for evaluating the level of improvement in terms of pain VAS as 2 points [27], KSS as 19 points [28], and WOMAC as 10 points [29]. It is well documented that MCID is associated with numerous factors and we agree that those differences were clinically important in our TKA practice. Despite these limitations, we believe that this study provides valuable information on preoperative CS and its effect on postoperative outcomes following TKA.

In conclusion, this study demonstrates that preoperative CS remains unchanged at 2 years following TKA. Although CS patients experienced comparable clinical improvement, CS patients had worse QoL, functional disability, and dissatisfaction than non-CS patients after TKA. Surgeons should take into account the preoperative screening of CS and the selective application of tailored multimodal options addressing CS and advise CS patients preoperatively to ensure their realistic expectations of outcomes.

Table 4
Multivariate Linear Regression Analysis for Predictor for Satisfaction.

Predictors	B	Significance	95% CI		R^2
Preoperative CSI	−0.132	<.01	−0.192	−0.073	0.692
Postoperative 2-y pain VAS	−1.147	<.01	−1.893	−0.401	
Postoperative 2-y WOMAC	−0.272	<.01	−0.341	−0.203	

A negative B value means that higher satisfaction was associated with lower preoperative CSI, postoperative pain VAS, and WOMAC score.
CI, confidence interval; CSI, Central Sensitization Inventory; VAS, visual analog scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index Scale.

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