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Original Article

The relationship between inadequate response to physical therapy and central sensitization in patients with knee osteoarthritis: A prospective cohort study

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ABSTRACT

Objectives: This study aims to investigate the relationship between physical therapy response and the presence of central sensitization (CS) in patients with painful knee osteoarthritis (OA).

Patients and methods: Between May 2019 and March 2020, a total of 84 patients with knee OA (12 males, 72 females; mean age: 60.7±7.7 years; range 50 to 74 years) and 30 age and sex-matched controls (6 males, 24 females; mean age: 59.2±8.9 years; range 50 to 75 years) were included in this study. Knee pain and functional status were evaluated by Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Structural damage was assessed by knee radiography. The Central Sensitization Inventory (CSI), Beck Depression Inventory (BDI), Insomnia Severity Index (ISI), Pain Catastrophizing Scale (PCS), and PainDETECT Questionnaire (PDQ) were applied at baseline. Pain pressure thresholds (PPTs) of the patients were measured and compared with the control group. All patients underwent a total of 15 sessions of physical therapy program for five sessions/weekly. After treatment, the patients were divided into two groups as responders and non-responders according to the Osteoarthritis Research Society International (OARSI) criteria.

Results: The CSI score of the patients in non-responder group was significantly higher compared to the responder group (p=0.004). Using a cut-off value of ≥40, the proportion of patients with CSI scores of ≥40 was significantly lower in the responder group compared to non-responder group (p=0.021). The PPT measurement values were significantly lower in the non-responder group compared to the responder and control groups (p<0.01). There was a significant difference in the frequency of hyperalgesia between the groups (p=0.021). Central sensitization and depression were the most significant predictors of non-response to physical therapy (p=0.045 and p=0.024, respectively).

Conclusion: Our study results suggest the presence of CS and depression may result in an inadequate response to physical therapy in patients with knee OA. Clinicians should consider the findings of CS and depression in treatment planning.

Keywords: Central sensitization, depression, knee osteoarthritis, neuropathic pain, pain, physiotherapy.

Osteoarthritis (OA) is the most common type of arthritis worldwide. Pain, the disease's primary symptom, is a major determinant of quality of life and disability. Pain in knee OA, in particular, is defined as a transition from intermittent weight-bearing pain to more permanent, chronic pain. Furthermore, pain is considered the major criterion in determining disease activity and assessing the efficacy of potential new treatments.[1]

Pain is caused by a complex interaction of harmful stimuli and peripheral and central nervous system responses. Pain pathophysiology in OA is complicated and was previously thought to be solely nociceptive in nature; however, it is currently thought to be a pain

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with both nociceptive and neuropathic components, as well as be influenced by peripheral and central sensitization (CS) mechanisms.[2] The fact that pain intensity is unrelated to radiological findings and that pain persists after total knee replacement has highlighted the role of CS mechanisms in osteoarthritic pain.[3]

Non-pharmacological and pharmacological modalities, as well as surgery, are currently available treatments for knee OA. Patient education, weight loss, exercise programs (range of motion [ROM] and strengthening exercises, balance and posture training), aquatic therapy, electro-analgesia (transcutaneous electrical nerve stimulation [TENS]), ultrasound therapy (US), and laser therapy are the most commonly used non-pharmacological therapies for knee OA.[4] The TENS and US have been suggested to improve the clinical course of knee OA in several countries.[5,6] However, the evidence supporting a beneficial effect of TENS and US for knee OA pain is mainly based on low-quality trials, and subgroup analysis showing significant heterogeneity.

There is some evidence that CS and related conditions adversely affect treatment outcomes. These include neuropathic pain, pain catastrophizing, depression, and sleep problems.[7-10] Depression has been shown to be associated with pain, physical limitation, and poor treatment outcomes in patients with OA.[11] Widespread pain sensitivity and thermal hyperalgesia have been linked to a poor prognosis in painful musculoskeletal disorders, such as shoulder impingement and lateral epicondylitis.[12,13] The presence of CS prior to total knee replacement in knee OA has been linked to persistent knee pain after surgery.[14] It has been demonstrated that the presence of sensory hypersensitivity and cold hyperalgesia in whiplash injury-related diseases reduces the likelihood of a positive response to physical therapy.

In the light these data, we hypothesized that physical therapy would be less beneficial for knee OA patients having CS-related conditions. However, the number of studies investigating the relationship between CS and physical therapy response is very limited.[15] In the present study, we, therefore, aimed to investigate the relationship between physical therapy response and the presence of CS in patients with painful knee OA.

PATIENTS AND METHODS

This single-center, prospective cohort study was conducted at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation between May 2019 and March 2020. Patients with knee pain lasting more than three months and diagnosed with primary knee OA according to the American College of Rheumatology (ACR 2016) criteria were screened. Inclusion criteria were as follows: having a diagnosis of primary knee OA according to the ACR 2016 criteria, age between 50 and 75 years, having pain for more than three months, pain intensity being 5 or more according to the Visual Analog Scale (VAS), and giving consent to participate in the study. In the OA group, active synovitis, patients with cervical or lumbar radiculopathy, systemic inflammatory disease, diabetic neuropathy, sensory loss due to chemotherapy or radiotherapy, fibromyalgia or chronic fatigue syndrome, cognitive impairment or psychiatric illness that prevents cooperation during the evaluation, and patients undergoing physical therapy and/or injection to the knees within the last three months were excluded from the study. Finally, a total of 84 patients (12 males, 72 females; mean age: 60.7±7.7 years; range 50 to 74 years) with knee OA were included.

The control group consisted of 30 age- and sex-matched healthy individuals (6 males, 24 females; mean age: 59.2±8.9 years; range 50 to 75 years) who did not have pain in the knee and forearm, who did not have mechanical, inflammatory, endocrine, degenerative or systemic comorbidities that can affect the joint, and who agreed to participate in the study. They were recruited from the relatives of inpatients and outpatients during the study period. The participants with an uncontrolled systemic disease, cognitive impairment that prevents cooperation, diagnosis of knee OA, chronic painful disease, peripheral neuropathy, and rheumatological disease were not included. The control group essentially served as a source of the normal pain pressure threshold (PPT) values for comparison with those of the patients in the assessment of hyperalgesia.

Intervention

Patients in the OA group underwent a total of 15 sessions of conventional physical therapy program including hot pack, US, TENS and exercise five days a week for a total of three weeks. Hot pack was applied for 10 min, US was applied continuously at 1 MHz, 1.0 W/cm^2 for 10 min, and TENS was applied for 30 min according to the patient's tolerance. The exercise program consisted of active, active-assisted ROM, and isometric quadriceps strength training. At the end of treatment, patients were divided into two groups as responders and non-responders according

to the Osteoarthritis Research Society International (OARSI) responder criteria.[16] Patients were only evaluated before and after treatment, and no follow-up schedule was applied.

Outcomes

Demographic and clinical assessment

At the beginning of the study, age, sex, body mass index (BMI), pain duration of all patients with knee OA were recorded. They were subjected to a physical examination, which included a patellar tap test, temperature increase, and ROM measurements.

Evaluation of pain and functional status

The pain intensity was measured using a VAS (0-100 mm). The health status of patients with knee OA was evaluated by the Turkish version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[17] The 5-point Likert version of the WOMAC was preferred.

Radiographic evaluation

Knee anteroposterior (AP) radiographs taken in the outpatient setting of all participants in the OA group were evaluated by a single researcher and an experienced physical medicine and rehabilitation specialist according to the Kellgren-Lawrence (KL) radiographic grading system. The knee X-rays of the participants in the control group were not taken.

Evaluation of central sensitization

The PPT measurement and Central Sensitization Inventory (CSI) were used to evaluate CS.[18,19] The PPT was measured on the painful knee in the OA group, on the knee with the most severe pain if both knees were painful, and on a randomly determined knee in the control group, on the same side tibialis anterior (TA) muscle and the opposite side forearm. The knee as measured over the medial joint spacing, TA muscle as measured 5 cm distal to the tuberositas tibia, and the forearm as measured 5 cm distal to the medial epicondyle on the volar side. As the medial tibiofemoral compartment is more commonly affected in knee OA, measurements were taken in the medial joint space. The TA muscle was evaluated to determine the extent of pain's peripheral spread, and the forearm was evaluated to determine the presence of sensitization at a distant point. All points were chosen from areas that could be marked with bone markers so that measurements could be taken from the same points in each participant. Previously, the CSI score revealed the presence of CS with a sensitivity of 81% and a specificity of 75% using a cut-off value of ≥40.[20] Therefore, the cut-off value of CS was set at 40 out of 100.[18]

A digital pressure algometer (JTECH Medical, UT, USA) was used for the measurements. This instrument has a high test-retest correlation and ensures 99% force accuracy by using autocalibration.[21] The hard 1 cm^2 tip of the algometer was placed perpendicular to the skin on the points to be measured, and the pressure was gradually increased until the subject felt pain, at which point the value was recorded. Three measurements were made for each region. During the measurements, the probe was slightly shifted to prevent sensitization of the area and a 30-sec interval was left between each measurement. Initial measurement was evaluated as a trial for learning. The average of the previous two measurements was reported in N/cm^2. It was ensured that participants did not take analgesics in the preceding 24 h, and other medical treatments (antidepressants, pregabalin, etc.) were allowed, if applicable.

Evaluation of clinical disorders associated with OA and CS

The potential clinical disorders related to OA and CS, such as neuropathic pain, pain catastrophizing, depression, and sleep problems, were also investigated. The presence of neuropathic pain was evaluated using the painDETECT Neuropathic Pain Questionnaire (PDQ), pain catastrophizing was evaluated using the Pain Catastrophizing Scale (PCS), depression was evaluated using the Beck Depression Inventory (BDI), and sleep problems were evaluated using the Insomnia Severity Index (ISI).[22-25] The Turkish version of all these scales were used.[26-29]

Evaluation of hyperalgesia

To evaluate the presence of CS in patients individually and to determine the proportion of patients with hyperalgesia, the PPT values from three locations of all participants were compared with the normal PPT values obtained from the healthy control group. The Z transformation was used to make this comparison on a personal level, regardless of the unit. The Z scores were calculated after a logarithmic transformation was performed to ensure the normal distribution of PPT values, as recommended by the German Research Network on Neuropathic Pain (DFNS).[30] The Z scores were computed according to the following formula:

Z score=[Xsubject–Mean (control)]/Standard deviation (control)

The normal distribution of PPT values was achieved after the Z transformation. A mean Z score of 0±1.96 represents 95% of the distribution of the healthy control group's outcomes. Those outside the 95% confidence interval (CI) of the healthy control group outcomes, i.e., those with a Z score of <-1.96 or >1.96, were recognized as abnormal. Negative values represent hyperalgesia, while positive values represent hypoalgesia.

Statistical analysis

Considering an effect size (d) of 0.3145 and a margin of error of 5%, 80 OA patients were needed to be included to reach a power of 80% with a 1 degree of freedom in the chi-square test.

Statistical analysis was performed using the R Statistical Software version 3.6.2 (R Statistical Software, Institute for Statistics and Mathematics, Vienna, Austria). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max or interquartile range [IQR]), while categorical variables were expressed in number and frequency. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of data. The one-way analysis of variance (ANOVA), Student t-test, Mann-Whitney U test, and the Pearson chi-square test were used for inter-group comparisons. The Spearman rank correlation test was used to investigate the relationship between the variables. The correlation coefficient value served as the basis for deciding the linear relationship's strength.[31] A logistic regression model was used to evaluate the relationship between groups that responded to and did not respond to treatment and CS. A p value of <0.05 was considered statistically significant.

RESULTS

According to the OARSI responder criteria, patients who completed the conventional physical therapy were divided into two groups. While 50 patients responded favorably to the treatment, 34 did not receive any benefit. The demographic and clinical characteristics of the patients are shown in Table 1.

Before treatment, there was a significant difference between the two groups in terms of pain intensity as measured by the VAS and WOMAC scores (Tables 1 and 2). The initial VAS scores were significantly greater in the non-responder group compared to the responder group (p=0.035). The post-treatment VAS score was significantly lower in the responder group (p<0.001). The responder group had significantly lower initial WOMAC scores (pain, stiffness, physical and total score) than the non-responder group (p=0.003).

TABLE 1
Baseline demographic and clinical characteristics of responder and non-responder groups

	Responder group (n=50)			Non-responder group (n=34)			
	n	%	Mean±SD	n	%	Mean±SD	p*
Age (year)			59.5±8.1			61.7±8.1	0.23
Sex							0.75
Male	8	16		4	11.8		
Female	42	84		30	88.2		
KL grade							0.86
Grade 1	11	22		6	17.6		
Grade 2	24	48		15	44.1		
Grade 3	12	24		11	32.3		
Grade 4	3	6		2	5.8		
Body mass index (kg/m²)			27.7±3.4			28.5±4.0	0.36
Pain duration (month)			12.4±9.9			16.7±12.6	0.09
WOMAC pain			11.2±2.9			13.1±2.6	**0.03**
WOMAC stiffness			1.8±1.3			2.8±1.6	**0.004**
WOMAC physical function			43.8±9.4			49.4±9.6	**0.01**
WOMAC total			56.9±11.9			65.3±11.4	**0.002**

SD: Standard deviation; KL: Kellgren-Lawrence; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; * Student t-test.

TABLE 2
Central sensitization and related variables of responder and non-responder groups

	Responder group (n=50)				Non-responder group (n=34)				
	Mean±SD	Median	Min-Max	IQR	Mean±SD	Median	Min-Max	IQR	*p**
Pre-treatment VAS	65.4±10.5	63.5	50-95	14	69.8±10	70	50-91	13	0.04
Post-treatment VAS	26.7±9.5	25	9-60	11	54.12±9.5	54.5	31-69	13	<0.001
CSI	23.8±16.7	16	5-63	29	35.3±16.8	42	9-67	30	0.004
BDI	11.1±5.2	10	3-26	7	14.5±6.3	12.5	5-27	11	0.02
ISI	10.7±5.2	11	1-21	9	13.5±5.5	14	4-23	11	0.03
PCS	17.2±9.5	14	5-39	15	22.03±10.3	19	6-42	19	0.02
PDQ	13.1±5.8	12.5	3-24	9	17.1±7.04	17	5-32	9	0.01

SD: Standard deviation; IQR: Interquartile range; VAS: Visual Analog Scale; CSI: Central Sensitization Inventory; BDI: Beck Depression Inventory; ISI: Insomnia Severity Index; PCS: Pain Catastrophizing Scale; PDQ: PainDETECT Questionnaire; * Mann-Whitney U test.

TABLE 3
Comparison of pain pressure thresholds

	Responder group (n=50)	Non-responder group (n=34)	Control group (n=30)	
	Mean±SD	Mean±SD	Mean±SD	*p**
PPT knee (N/cm²)	15.08±4.50	10.7±3.50	20.9±6.60	<0.001
PPT TA (N/cm²)	18.7±4.40	16.6±3.80	23.2±6.30	<0.001
PPT forearm (N/cm²)	28.8±6.10	24.9±7.90	31.2±6.80	0.002

SD: Standard deviation; PPT: Pain pressure threshold; TA: Tibialis anterior; * One-way ANOVA test.

The CSI score of the patients in the non-responder group was significantly higher than the CSI score of the responder group (p=0.004) (Table 2). According to the cut-off value used to determine CS, the proportion of patients with CSI scores equal or greater than 40 was 26% (n=13) in the responder group and 52.9% (n=18) in the non-responder group (p=0.021). The PPT measurement values from all three regions (painful knee, same-side TA, and opposite side forearm) were significantly lower in the non-responder group (p=0.001, p=0.001, and p=0.002, respectively) compared to the responder and control groups (Table 3).

There was a weak (r=-0.21) (p=0.05) negative correlation between the painful knee PPT and CSI scores, and a low-to-moderate negative correlation (r=-0.34 and r=-0.42, respectively) between the same side TA and the opposite side forearm PPT and CSI scores (p=0.002 and p<0.001, respectively) (Table 4). The frequency of pressure hyperalgesia in the knee and forearm was significantly higher in the non-responder group compared to the responder group (17.6% and 4%, respectively) (p=0.021).

TABLE 4
Correlations of PPT and outcome measures of the patients with osteoarthritis

	CSI	Knee PPT	TA PPT	Forearm PPT
CSI				
r		-0.21	-0.34	-0.42
p		**0.05**	**0.002**	**<0.001**
PDQ				
r	0.57	-0.200	-0.224	-0.37
p	**<0.001**	0.06	0.04	**<0.001**
PCS				
r	0.642	-0.11	-0.194	0.356
p	**<0.001**	0.32	0.08	**<0.001**
ISI				
r	0.41	-0.132	-0.234	-0.327
p	**<0.001**	0.23	0.03	**0.002**
BDI				
r	0.15	-0.18	-0.09	-0.25
p	0.17	0.09	0.40	**0.02**

PPT: Pain pressure threshold; CSI: Central Sensitization Inventory; TA: Tibialis anterior; PDQ: PainDETECT Questionnaire; PCS: Pain Catastrophizing Scale; ISI: Insomnia Severity Index; BDI: Beck Depression Inventory; r: Correlation coefficient.

TABLE 5
Simple linear regression analysis demonstrating the effect of variables on the risk of poor response to conventional physical therapy

	OR	95% CI	*p*
Pre-treatment VAS	1.041	0.997-1.088	0.07
BMI	1.057	0.938*-1.191	0.26
KL grade	1.202	0.707-2.044	0.50
Hyperalgesia (forearm)	5.143	0.971-27.232	**0.04**
Hyperalgesia (knee)	5.143	0.971-27.232	**0.04**
Hyperalgesia (TA)	1.375	0.120-15.792	0.07
CSI	3.202	1.272-8.063	**0.01**
BDI	4.000	1.324-12.084	**0.01**
PCS	3.351	1.156-9.713	**0.03**
PDQ	2.799	1.081-7.251	**0.03**
ISI	1.633	0.656-4.067	0.29

OR: Odds ratio; CI: Confidence interval; VAS: Visual Analog Scale; BMI: Body mass index; KL: Kellgren-Lawrence; TA: Tibialis anterior; CSI: Central Sensitization Inventory; BDI: Beck Depression Inventory; PCS: Pain Catastrophizing Scale; PDQ: PainDETECT Questionnaire; ISI: Insomnia Severity Index.

TABLE 6
Multivariate logistic regression analysis to predict the likelihood of a poor response to conventional physical therapy

	B	OR	95% CI	*p*
Age	0.025	1.025	0.966-1.088	0.41
Sex	0.385	1.469	0.354-6.094	0.59
CSI	0.855	2.351	**0.665-8.316**	**0.04**
BDI	1.362	3.390	**1.197-12.717**	**0.02**
PCS	0.449	1.567	0.372-6.596	0.54

B: Regression coefficient; OR: Odds ratio; CI: Confidence interval; CSI: Central Sensitization Inventory; BDI: Beck Depression Inventory; PCS: Pain Catastrophizing Scale.

A simple linear regression analysis was performed for each assessment parameter to predict the risk of non-response to conventional physical therapy. The results are given in Table 5. Accordingly, the presence of hyperalgesia in the knee and forearm, CS, depression, pain catastrophizing, and neuropathic pain could successfully predict the risk of treatment non-response. A multiple logistic regression model was created by adding age and sex variables to the three parameters with the lowest p values (CSI, BDI, and PCS) in the simple linear regression analysis (Table 6). Accordingly, CS and depression were the most significant predictors of non-response to the conventional physical therapy (p=0.045 and p=0.024, respectively).

DISCUSSION

In the present study, we investigated the relationship between physical therapy response and the presence of CS in patients with painful knee OA. Our study results showed a link between the response to conventional physical therapy and CS in patients with painful knee OA. Accordingly, the evaluation of CS and depression before deciding on a physical therapy program can affect the treatment success.

The primary goals of OA treatment are to alleviate pain and improve function. It is well understood that CS plays a role in the pain mechanisms associated with OA.[32] It is thought that, in case of CS, where various changes in somatosensory input processing mechanisms and central nervous system neurons become overstimulated, the response to pain treatment can be more difficult. In the literature, there is only one study examining the effect of CS on physical therapy response.[15] O'Leary et al.,[15] for the first time, investigated the effect of pain sensitization on physical therapy response in patients with knee OA and found that the CSI score was higher in the non-responder group. Similarly, in our study, the CSI score of the non-responder group was significantly higher than that of the responder group. Using a cut-off value of 40 for CSI, the incidence of CS was higher in the non-responder group than in the responder group. However, there are several studies evaluating the effect of CS after knee arthroplasty showing that when the CSI score is above 40, the risk of persistent pain increases.[33,34]

The PPT measurement is another objective method of measuring central and peripheral sensitization.[35] Theoretically, patients with low PPT values are expected to respond poorly to treatment due to sensitized pain mechanisms. O'Leary et al.[15] reported that the values of the painful knee, same side TA, and opposite side forearm in the non-responder group were significantly lower than the values in the responder group. These findings are consistent with our study findings. Wylde et al.[36] found that patients with low forearm PPT values prior to knee arthroplasty had higher postoperative first-year WOMAC pain scores. Similarly, in our study, the PPT values were obtained from three regions, and the non-responder group had lower PPT values than the responder and healthy control groups.

Primary hyperalgesia, defined as an increase in pain sensitivity in the area of tissue damage or inflammation, is recognized as a protective and adaptive response during the acute period and is

referred to as peripheral sensitization.[37] However, with the formation of central nervous system changes and the transformation of acute pain to chronic pain, this situation ceases to be a protective response and becomes a maladaptive process in the chronic period.[37] This process results in the development of CS, its persistence and, eventually, an increase in peripheral pain sensitivity. Secondary hyperalgesia, defined as an increase in pain sensitivity outside the site of tissue damage, was described as a finding of CS by Woolf.[38] In our study, non-responders (17.6%) had significantly more pressure hyperalgesia in the painful knee and forearm than responders (4%). This finding suggests that peripheral and CS may have a negative impact on physical therapy response.

It is recognized that radiographic changes and symptoms are not always correlated in patients with knee OA. This is one of the findings that suggests CS may be involved in the pathogenesis of OA pain. There is currently no evidence of a link between the KL stage and PPT levels in patients with knee OA.[39,40] Similarly, no significant relationship was found between the KL stage and PPT measurements in our study. This finding implies that CS may be independent of structural damage severity, and that structural damage may initiate and sustain CS, *albeit* at a low level. In several studies, the relationship between clinical conditions such as depression, pain catastrophizing, sleep disturbance, and neuropathic pain seen in patients with knee OA and their response to physical therapy and pain sensitization has been investigated.[7-10] However, there is only one study investigating the association between PCS and physical therapy response.[7] In this study, the PCS score alone was found to be a significant predictor of responsiveness to physical therapy in patients with knee OA, and individuals with low PCS scores had reduced pain scores following physical therapy.[7] Similarly, the PCS scores of patients in the non-responder group in our study were higher than those of patients in the responder group. There was no correlation between PCS and local and distant PPT in studies evaluating the relationship between PCS and PPT in patients with knee OA.[41] In our study, the PCS score was related to the forearm PPT and CSI scores in a similar way. It is well known that CS and neuropathic pain are frequently seen together in chronic pain patients, and that they frequently trigger each other through similar mechanisms.[42,43] The relationship between these two phenomena has been studied in the literature.

Hochman et al.[42] reported that a high PDQ score was directly related to the frequency of Quantitative Sensory Testing (QST)-assessed CS findings in patients with knee OA. Kurien et al.[43] also found that, among patients with knee OA who underwent arthroplasty, those with high PDQ scores had lower distant PPT values and higher VAS values in the sixth postoperative month compared to patients with low PDQ scores and healthy controls. In line with these findings, we found a moderate positive correlation between the PDQ score and the CSI score, and a moderate negative correlation between the PDQ score and forearm PPT in our study.

Furthermore, the PDQ score of the patients in the non-responder group was higher than that of the responder group. These findings suggest that similar neuroanatomical pathways are affected in CS of pain and neuropathic pain in diseases accompanied by chronic pain. There have been few studies investigating the relationship between pain catastrophizing and neuropathic pain in patients with knee OA.[44] In a cross-sectional study involving symptomatic OA patients, Tanaka and Hirohama[44] found that patients with a high PDQ score had a significantly higher PCS score. Similarly, we found a moderate correlation between PDQ and PCS scores in our study.

The presence of CS and depression were revealed to be significant predictors of non-response to physical therapy, when age and sex were included in the analysis. O'Leary et al.[15] reported that CS as measured by PPT and temporal summation was a significant predictor of a negative response to treatment, whereas depression had no predictive value. In contrast to our study, Uckun et al.[7] investigated the effect of PCS and BDI scores on predicting response to physical therapy and showed that only the PCS score was significant. Of note, this discrepancy can be attributed to the different scales used to assess depression.

Nonetheless, there are some limitations to the current study. First, the small number of male patients in the sample population makes generalizing the findings to the entire OA population difficult. Second, the sample was divided into two groups based on their response to therapy not by randomization. Therefore, the responder and non-responder groups were not guaranteed to be distributed homogeneously with respect to clinical parameters including pain intensity and the WOMAC subscales at the beginning of study. Third, patients were only able to be evaluated before and after treatment, with no mid- or long-term clinical follow-up data. On the other hand, the main strength of the study is that it includes a healthy control group to obtain the normal PPT values; apart from the comparison at the group level, pressure hyperalgesia

was also evaluated individually; and the sample size was calculated using power analysis. Furthermore, to the best of our knowledge, this is the second study in the literature to assess the effect of CS-related conditions on physical therapy response in patients with knee OA.

In conclusion, our study results suggest that physical therapy may not be as effective for treating knee OA, if CS and depression are present. Based on these findings, clinicians should consider CS and depression findings while planning treatment. Further large-scale, prospective, randomized-controlled studies are needed to determine whether the inclusion of CS and depression-oriented therapies to a conventional physical therapy program would result in further benefits for knee OA patients.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (date: 27.05.2019, no: 10-795-19). The study was registered retrospectively on ClinicalTrials.gov as NCT05518097. The trial protocol is available at public site: https://clinicaltrials.gov/ ct2/show/ NCT05518097. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, analysis and/or interpretation, writing manuscript, critical review: S.B.Y., Ş.K., H.G.; Control/supervision: Ş.K., H.G.; Data collection and/or processing: S.B.Y.; Literature search, materials, resources: S.B.Y.

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