Observational Study

The Role of Pain Catastrophizing and Depression in the Outcomes of Physical Therapy in a Prospective Osteoarthritis Cohort

Aslı Çalıskan Uçkun, MD¹, Burcu Köse Dönmez, MD², Fatma Gül Yurdakul, MD¹, Yesim Garip, MD¹, and Hatice Bodur, MD¹

From: 'Ankara Numune Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey; 'Physical Medicine and Rehabilitation, Duru Medical Center, Ankara, Turkey

Address Correspondence: Aslı Çalıskan Uçkun, MD Ankara Numune Egitim ve Arastırma Hastanesi, Talatpasa Bulvarı No:5 Altındag / Ankara E-mail: draslical@gmail.com

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Free full manuscript: www.painphysicianjournal.com **Background:** Physical modalities have been safely used for decades for pain relief and for reducing physical disability in the conservative treatment of knee osteoarthritis (OA). However, patients' response to treatment is highly variable, which may be related to certain patient-related factors such as pain catastrophizing and depression.

Objectives: This study aimed to evaluate the effects of pain catastrophizing and depression on physical therapy outcomes and to identify the baseline factors predictive of poor outcomes in patients with knee OA.

Study Design: This research used a prospective, cohort, observational study design.

Setting: The research took place in an outpatient physical therapy unit within a tertiary hospital in Ankara, Turkey.

Methods: Eighty-nine patients with knee OA underwent 10 sessions of physical therapy. At baseline, depression and pain catastrophizing were evaluated using the Beck Depression Inventory-II (BDI-II) and the Pain Catastrophizing Scale (PCS). The therapeutic efficacy of physical therapy was assessed based on the level of pain and disability using the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Changes in the VAS score and WOMAC were evaluated at 2 and 6 weeks following physical therapy. A multivariate logistic regression analysis was conducted to identify the predictors of poor outcomes.

Results: Patients with low pain-catastrophizing and low depression scores tended to demonstrate better improvement at weeks 2 and 6. The results of a multivariate logistic regression analysis showed that the significant outcome predictor for both pain and function at week 6 was the baseline PCS score. The baseline depression score was not an independent predictor of a clinically poor outcome.

Limitations: This study is limited owing to the combined use of several physical therapy modalities and short follow-up.

Conclusions: This study suggests that the baseline PCS score is a predictive factor of poor response to physical therapy in patients with knee OA. Considering this factor before therapy and taking the necessary precautions may improve the outcomes of physical therapy.

Key Words: Catastrophization, central nervous system sensitization, depression, disability evaluation, knee osteoarthritis, pain, physical therapy modalities, transcutaneous electric nerve stimulation.

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nee osteoarthritis (OA), the most frequently encountered type of OA, is a leading cause of chronic pain and disability (1). Pain from OA has historically been defined as a nociceptive pain associated with the grade of structural impairment of the affected joint. Nevertheless, differences in the severity of pain in patients with similar characteristics, the inconclusive connection between pain and joint damage, and persistent pain after removal of the peripheral nociceptive structures in patients subjected to knee arthroplasty (KA) have suggested the existence of different mechanisms in OA pain pathogenesis (1-3). Recently, a growing number of investigations have emphasized the importance of central sensitization (CS), described as "enhanced responsiveness of nociceptive neurons to the subthreshold or normal afferent inputs," compared to other peripheral mechanisms in the pathogenesis of OA-related pain (2-6). Therefore, the treatment of patients with OA requires personalized management that focuses on both nociceptive pain and CS (4).

Unfortunately, there is no cure for knee OA; treatment is focused on reducing physical disability and controlling pain (7). For this purpose, for decades, physical modalities have been safely employed in the conservative treatment of knee OA. However, there are inadequate data concerning the impact of these modalities on knee OA. To this point, the available data suggest that physical modalities relieve pain using different peripheral and central mechanisms (8,9). Although there is no consensus on how these agents should be used, they are widely used together with a combination of thermotherapy and electrotherapy procedures in clinical practice (10,11).

The most frequently used physical modalities are local heat applications, transcutaneous electrical nerve stimulation (TENS), which transmits pulsed electrical currents through electrodes across the intact surface of the skin, and ultrasound (US) therapy, which uses high frequency vibrations to generate heat (12-14).

Several factors predictive of both nonsurgical and surgical treatment outcomes in knee OA have already been described (15-17). Most physicians dealing with musculoskeletal pain have postulated physical examination findings rather than psychosocial features as important outcome predictors, but previous literature suggests that the most significant predictors of poor outcomes are psychosocial. Pain catastrophizing (PC) and depression have emerged as 2 of the most important psychological predictors of poor outcomes. Depression and catastrophizing, which is the tendency to define a pain experience in more exaggerated terms than the average individual, usually – but not always – can be found together (2,18). These can lead to impairment of endogenous pain pathways and loss of inhibitor control, and have been considered as indicators of CS (2,19). As such, it might not be surprising that individuals with these features are likely to have greater pain and disability (20) and poor outcomes after knee operation (15,21,22) due to increased CS.

However, the effect of these features on the outcomes of physical therapy (PT) has not been adequately investigated. Considering the prevalence of patients receiving PT for knee OA, screening for these risk factors and carrying out necessary interventions could have a significant impact on the outcomes of PT (23). Therefore, the aim of the current investigation was to evaluate the effect of PC and depression on PT outcomes in knee OA patients. We also aimed to investigate patients' baseline factors that might predict the outcomes of PT. Based on limited data, we hypothesized that higher PC and depression scores would be predictors of lower improvement in the outcomes of PT (18,24).

METHODS

Patients

The patient population was comprised of patients with knee OA who were scheduled for a combined PT program at our outpatient PT unit between September 2017 and February 2018. All patients received standard PT with the same intensity and duration that is routinely used. Patients received no additional intervention. All patients gave written informed consent to participate and all procedures were approved by the local ethics committee (E 17-1517). The study was conducted in accordance with the Declaration of Helsinki. The inclusion criteria for the current study were as follows: the patients (1) fulfilled the American College of Rheumatology classification criteria for knee OA (25), (2) were aged between 40 and 75 years, (3) had radiological stage 2 or 3 bilateral knee OA by the Kellgren-Lawrence (KL) Grading Scale (26), and (4) had the capacity to walk at least 100 meters on a flat floor. The exclusion criteria included a history of previous knee operation, limitation of motion of the knee, impaired quadriceps muscle strength, presence of effusion on physical examination, having received intraarticular hyaluronate or corticosteroid injection within the last 6 months; previously diagnosed with inflammatory joint diseases, polyneuropathy, fibromyalgia, neurological or psychiatric diseases; and use of anticonvulsant, antidepressant, or opioid drugs.

Treatment Protocol

Ten sessions of PT including hot-pack, TENS, and US were applied to all patients as in our routine clinical practice. Every session included 20 minutes of hot-pack, 20 minutes of TENS, and 5 minutes of continuous US administration to both knees.

The hydrocollator hot-packs (at a surface temperature of almost 42°C) (Chattanooga Medical Supply Inc., Chattanooga, TN) were applied on knees while patients were in sitting position with the knees extended.

Conventional TENS (TENScare, Surrey, United Kingdom) was used with a 4-channel transcutaneous electrical stimulator device [pulse duration of 50 to 80 µs; pulse frequency of 50 to 100 Hz; low-intensity (paraesthesia, not painful)]. Electrodes were placed around painful regions as patients were in the sitting position with the knees extended.

All patients received continuous US (Eletronica Pagani, Paderno Dugnano, Italy) at a one-MHz frequency and an intensity of one W/cm² using an applicator with a 5-cm diameter. The US was applied to the medial tibiofemoral compartment of the knee with an acoustic gel containing no pharmacological agent with a circular movement of the probe at proper angles.

Measures

All patients were evaluated by the same physiatrist on 3 occasions: baseline, after therapy completion (2 weeks after baseline), and at 6 weeks after baseline. Socio-demographic and clinical data were initially recorded and included age (years), gender, body mass index (kg/m²), employment status, duration of symptoms (months), level of education, and preexisiting comorbidities. At baseline, depression and PC were evaluated with the Beck Depression Inventory-II (BDI-II) and Pain Catastrophizing Scale (PCS), respectively. The therapeutic efficacy of the PT was evaluated based on the level of pain, evaluated using the Visual Analog Scale (VAS), and disability, evaluated using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The VAS and WOMAC were administered 3 times as follows: just before the program (baseline), after therapy completion (second week), and 6 weeks after the baseline (sixth week).

The BDI-II is formed of 21 questions defining dif-

ferent signs of depression. A cut-off score of 13 was determined to detect patients with clinical symptoms of depression (27,28).

The PCS consists of 13 questions in 3 subscales (rumination, helplessness, and magnification) and defines specific beliefs and catastrophic thinking related to pain. Each question is evaluated on a 5-point scale (0-4). A higher final score indicates a higher grade of PC. It has been indicated that a total PCS score of > 30 reflects a clinically relevant level of catastrophizing (29-31). In the present investigation, patients who scored > 30 points were considered to have high PC and those with lower scores to have low PC.

The severity of knee pain was evaluated using the VAS, which scored between 0 (no pain) and 10 (the worst imaginable pain), after patients had walked for 5 minutes on a flat surface (32).

The WOMAC was applied to evaluate functional disability in the patients with knee OA. It is a typical questionnaire for the assessment of stiffness (2 questions), pain (5 questions), and physical function (17 questions) in patients with hip and knee OA. The total score varies from 0 to 96 points and a higher score indicates more severe impairment (33).

Statistical Analysis

A power analysis was performed using G*Power Version 3.0.10 (Franz Faul, Kiel, Germany); to achieve a power of .80 with α = .05 and β = .20 required a sample size \geq 88 patients. SPSS Version 17 (SPSS Inc., Chicago, IL) was used for statistical analyses. The Shapiro-Wilk test was used to test normality. General descriptive statistics are summarized as mean ± standard deviation and median (minimum-maximum) for continuous variables. Categorical data are summarized using a number and percentage. The chi-square test was used for comparison of nominal variables between groups. Continuous variables were compared using the Mann-Whitney test or the independent-samples t test. Outcomes were evaluated by repeated-measures analysis of variance (ANOVA). Multivariate logistic regression modeling was used to identfy the baseline predictive factors for poor outcome following PT. For these analyses, 2 groups were constituted according to the changes in both VAS and WOMAC global scores at the 6-week evaluation compared to baseline scores. For the VAS score analysis, patients were classified into a "good outcome" group (50% or greater decrease in the 6-week VAS compared to the initial VAS) and a "poor outcome" group (negative or no change in the 6-week VAS, or < 50% improve-

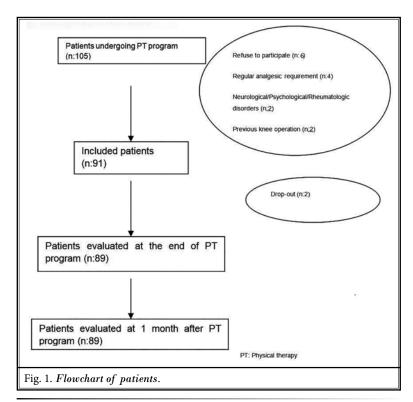


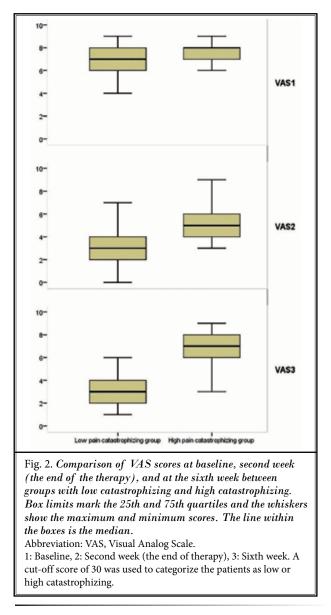
Table 1. Demographic data for all patients.

	Low High Catastrophizing (n = 47) (n = 42)		Total (n = 89)	P Value
Age, mean ± SD (yrs)	58.9 ± 9.6	62.0 ± 8.5	60.3 ± 0.9	.119
Gender n (%) Female Male	37 (78.7) 10 (21.3)	36 (85.7) 6 (14.3)	73 (82.0) 16 (18.0)	.391
BMI, mean ± SD	29.1 ± 3.6	29.5 ± 3.7	29.3 ± 0.3	.672
Employment Status n (%) Not working Laborers Retail trading Retired Government employee	21 (44.7) 3 (6.4) 6 (12.8) 13 (27.7) 4 (8.5)	31 (73.8) 1 (2.4) 3 (7.1) 5 (11.9) 2 (4.8)	52 (58.4) 4 (4.5) 9 (10.1) 18 (20.2) 6 (6.7)	.091
Duration of Symptoms, mean ± SD (mos)	21.0 ± 11.1	18.2 ± 10.5	19.7 ± 10.8	.226
Educational Level n (%) No education Elementary school High school University	3 (6.4) 22 (46.8) 17 (36.2) 5 (10.6)	2 (4.8) 30 (71.4) 8 (19) 2 (4.8)	5 (5.6) 52 (58.4) 25 (28.1) 7 (7.9)	.128
BDI-II, mean ± SD	9.1 ± 5.6	16.3 ± 8.4	12.5 ± 7.9	<.001*
Initial VAS, mean ± SD	6.9 ± 1.0	7.8 ± 0.9	7.3 ± 1.0	<.001*
Initial WOMAC, mean ± SD	31.6 ± 15.0	55.7 ± 15.6	43.0 ± 19.4	<.001*

Abbreviations: BDI-II, Beck Depression Inventory-II; BMI, body mass index; SD, standard deviation; VAS: Visual Analog Scale; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index. A cut-off score of 30 was used to categorize the patients as low or high catastrophizing. * Statistically significant value (P < .05) ment in the 6-week VAS compared to the initial VAS). For the WOMAC score analysis, patients were classified into a "good outcome" group (a relative change greater than or equal to 18% [100 × change of score/initial score] and an absolute change equal to a 9-point improvement in WOMAC global scores at the 6-week evaluation compared to the initial score) and a "poor outcome" group (who did not meet the above-mentioned changes) (34). The selection of the independent variables started with univariate analysis, and at least moderately significant variables (age, PCS, BDI-II, and baseline VAS and WOMAC scores) were selected for the multivariate logistic regression analysis. Analyses were performed using SPSS Version 21.0 (IBM Corporation, Armonk, NY). All results were reported with a confidence interval of 95%, and statistical significance was set at P < .05.

RESULTS

A total of 105 patients were initially screened, and 91 patients were selected for this prospective cohort investigation. Two patients discontinued treatment without specifying a reason at the first week. Eighty-nine patients (16 men, 73 women; mean age 60.38 ± 0.97 years) were able to complete the study (Fig. 1). None of the 89 patients reported any complications due to the PT given. These patients also reported that they did not receive any analgesic therapy, except paracetamol, during follow-up. The rate of patients with no comorbidities was 37.1%. The most prevalent comorbidity was hypertension (40.4%). More than half (58.4%) of the patients were not working, and 82% were women. The initial mean VAS and WOMAC scores were 7.39 ± 1.07 and 43.03 ± 19.47, respectively. The mean PCS score was 20.77 ± 16.17 . A clinically relevant level of catastrophizing (PCS > 30 points) was found in 47.2% of the patients. Depressive symptoms were determined in 36% of the patients. The clinical and demographic data, except for baseline VAS, WOMAC, and BDI-II scores,



were not different among the catastrophizing groups (Table 1). The patients with high PCS scores compared to those with low PCS scores had significantly higher VAS, WOMAC, and BDI-II scores (all P < .01).

Significant improvements in the VAS and WOMAC scores were observed in both the low- and high-catastrophizing groups. However, patients with low PC tended to show better improvement following the therapies (all P < .01) (Figs. 2,3).

A significant benefit of PT was observed among all patients with and without depression. Patients with depressive symptoms were prone to have less improvement in the VAS and WOMAC scores (all P < .01) (Figs.

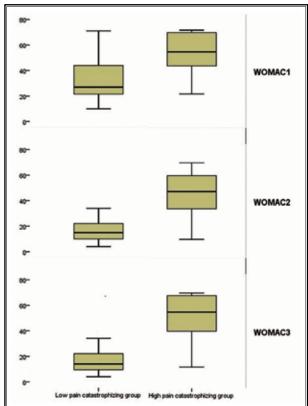


Fig. 3. Comparison of WOMAC scores at baseline, second week (the end of the therapy), and at the sixth week between groups with low catastrophizing and high catastrophizing. Box limits mark the 25th and 75th quartiles and the whiskers show the maximum and minimum scores. The line within the boxes is the median.

Abbreviation: WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index.

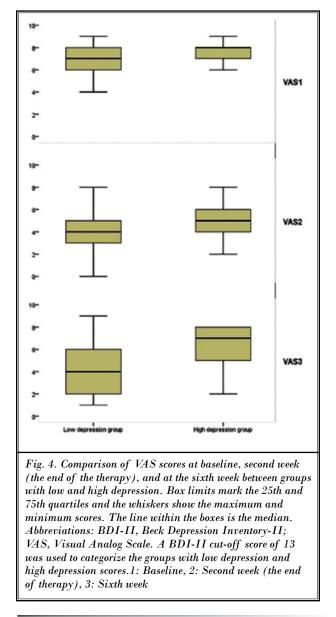
1: Baseline, 2: Second week (the end of therapy), 3: Sixth week. A cut-off score of 30 was used to categorize the patients as low or high catastrophizing.

4,5).

At the sixth week, 33 patients (37%) showed a "good outcome" on the VAS, while 56 (63%) showed a "poor outcome"; 36 patients (40%) showed a "good outcome" on the WOMAC, while 53 (60%) showed a "poor outcome." The results of the multivariate logistic regression analysis are shown in Table 2 for changes in pain and function. Multivariate analyses revealed that the baseline PCS was the only significant determinant of a poor response on both the VAS and the WOMAC.

DISCUSSION

The first objective of this investigation was to compare the outcomes of patients following PT, which was



determined by classifying patients into groups according to their PCS and BDI-II scores. Compared to patients with lower levels, we found that patients with higher PC and depression scores received less benefit from PT. The second aim of this study was to investigate patients' baseline factors that were associated with poor outcomes following PT. Using a multivariate logistic regression analysis, we found that only baseline PCS score was associated with an improvement in both pain and functionality. Patients who achieved higher PCS scores were more likely to have poor outcomes. These results demonstrated the importance of baseline PCS scores in

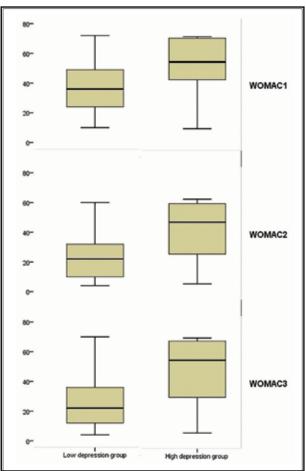


Fig. 5. Comparison of WOMAC scores at baseline, second week (the end of the therapy), and at the sixth week between groups with low and high depression. Box limits mark the 25th and 75th quartiles and the whiskers show the maximum and minimum scores. The line within the boxes is the median.

Abbreviations: BDI-II, Beck Depression Inventory-II; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index. A BDI-II cut-off score of 13 was used to categorize the groups with low depression and high depression scores.1: Baseline, 2: Second week (the end of therapy), 3: Sixth week

predicting the likelihood of the efficacy of PT.

Consistent with the existing literature (2,34,35), the present study demonstrated that patients with higher PCS scores had higher depression scores, increased pain severity, and disability. The results of the present study also indicated that the prevalence of clinically relevant levels of catastrophizing was as high as 47%, and the mean PCS scores were 20.77 \pm 16.17, which were higher than those reported in other studies on patients with

		В	SE	P Value	95% CI					
Good outcome for VAS score*										
	Constant	1.872	0.463	< .001						
	PCS	-0.163	0.037	< .001	0.791	0.913				
	Baseline VAS	-0.420	0.368	.254	0.320	1.352				
	BDI-II	-0.580	0.599	.333	0.173	1.811				
Good outcome for WOMAC score**										
	Constant	1,870	0.445	< .0001						
	Age	0.002	0.035	.964	0.933	1.069				
	PCS	-0.134	0.026	< .001	1.087	1.202				
	BDI-II	-0.632	0.500	.206	0.706	3.014				
	Baseline VAS	0.016	0.422	.860	0.970	0.984				
	Baseline WOMAC	0.028	0.024	.245	0.928	1.019				

Table 2. Multivariate logistic regression analysis showing predictors of outcome in VAS and WOMAC scores

Abbreviations: BDI-II, Beck Depression Inventory-II; CI, confidence interval; PCS, Pain Catastrophizing Scale; SE, standard error; VAS, Visual Analog Scale; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index.

* The reference category is: 1.00 (50% or more decrease in 6th-week VAS compared to initial VAS)

** The reference category is: 1.00 (a relative change greater than or equal to 18% (100 × change of score/initial score) and an absolute change of 9 points improvement in WOMAC global scores at the 6-week evaluation compared to initial score)

knee OA (35,36). This discrepancy in PCS scores may be attributed to the different inclusion criteria used in the studies. Patients in the present study had less structural knee damage owing to the use of narrow inclusion criteria (e.g., normal range of motion, only KL 2-3); however, Gandhi et al (36) reported that patients with end-stage knee OA had lower PCS scores (17.3 \pm 13.3). The levels of psychological problems were higher in patients with more pain, despite less joint damage, compared to those with more joint damage (3). Based on this important finding, the source of pain in our patients may result from central sensitization rather than nociception.

TENS stimulates the inhibitory pathways descending from the brain stem and midbrain to inhibit the excitability of nociceptive neurons in the spinal cord; thus, it is a nonpharmacological treatment option that is recommended for CS. Moreover, previous studies have demonstrated that thermotherapy and US may have similar positive effects on CS (4,8,37). According to these suggestions, it may be conceivable to postulate that patients with knee OA and predominant CS findings may benefit from PT as much as, or even more than, those with fewer CS findings. Contrary to this perspective, the current study demonstrated that all patients benefited from the PT program with regard to their pain and functionality; however, this benefit was observed to a less extent in patients with high catastrophizing levels and depressive symptoms. This result is

consistent with a limited number of studies, but there are important differences with regard to methods (18,24). While our study included only a combination of thermotherapy and electrotherapy procedures for patients with knee OA in a single center, the others were multicenter studies that included patients with various musculoskeletal problems and in which types of PT interventions were not clearly defined; for example, it is unclear whether the patients had received any electrotherapy or thermotherapy procedures as in our study. Identifying patients for PC and depression is not routine practice before considering PT in our clinic; however, our findings demonstrate the importance of screening for these prior to the implementation of PT. If these factors can be reduced before treatment by psychological interventions, such as cognitive behavioral therapy (CBT), improved outcomes may be achieved thereby reducing patient risk for chronic pain and disability (23).

We also performed a multivariate logistic regression analysis to clarify the factors associated with the outcomes of PT. Although we hypothesized that both high PC and depression negatively affect the outcomes of PT, the presence of high PCS scores at baseline was the only factor predictive of poor outcomes regarding both pain and functionality following PT. Several studies investigating the effects of PC and depression on rehabilitation outcomes have presented controversial results. Consistent with our results, George et al (38) demonstrated that although depressive symptoms were negatively associated with pain intensity and functional status, they were not associated with the outcome of PT. In line with these results, O'Leary et al (39) found that baseline functional level and anxiety were significant predictors of poor response in patients with knee OA and that depression was not a predictor of the outcomes of rehabilitation. However, these 2 studies did not evaluate PC. Rakel et al (40) showed that following TENS treatment, although PC scores significantly and negatively affected the outcomes, depression did not significantly affect the results. Conversely, in a study involving 42 physiotherapists, 297 patients with various musculoskeletal problems received various PT interventions at the sixth month, and the researchers found that patients with higher PC and depression scores at baseline had worse outcomes (18). Similarly, another study indicated that depression and PC had negative effects on response to rehabilitation treatment in patients with musculoskeletal injuries (24). Numerous explanations have been provided to account for the negative effect of catastrophizing on pain outcomes, including increasing attention to pain sensations, the impairment of endogenous pain modulation mechanisms, and the loss of pain-inhibitory control (19,41). However, the effect of depression on pain treatment outcomes has not been clearly defined (42). Although several studies have concluded that PC has been traditionally determined as the precursor to depression and that they usually coexist (41), others have suggested that PC is an entity distinct from depression (43). One main reason for poor outcomes in patients with depression may be due to poor adherence to treatment (44). Perhaps in our study, the failure of baseline depression alone to predict the poor outcome of PT may be due to the patients' lack of active participation in the treatment process. However, in other studies, it is unclear whether the patients had an active role in the self-training rehabilitation program or whether the applied treatment was performed only by the physiotherapist, as in our study. Although baseline depression was not identified as an independent factor for predicting outcomes following PT in our study, it may be appropriate to view depression as a factor that contributes to poor outcomes.

This study provides an important message for clinicians to screen for PC prior to PT since timely management can improve outcomes. Recent literature shows that CBT in addition to PT may help to improve outcomes in patients with high PC (23,45,46). The major difference between our study and theirs is that our PT interventions included a combination of thermotherapy

and electrotherapy procedures instead of exercise. Based on the theory that CS may be increased by peripheral stimuli such as heat, electrical stimulus, and sound, perhaps screening for and addressing PC may be more important prior to the implementation of thermotherapy and electrotherapy procedures (47). This was supported by Rakel et al (40), which assessed the influence of psychological factors on treatment outcomes in TENS, sham TENS, and standard care groups after total knee surgery; results demonstrated that high PC and anxiety scores significantly and negatively affected the outcomes in the TENS group. Importantly, these factors did not significantly impact the outcomes in the standard treatment group (using analgesic medication alone) or in the sham TENS group. Therefore, we can speculate that PC should be screened for prior to treatment, especially in thermotherapy and electrotherapy interventions. The real challenge is not to screen, but to provide access to considerable psychological assistance for patients with high PC prior to PT. As a viable solution to this challenge, a recent review indicated that combined physiotherapy and psychological interventions delivered by nonpsychologist practitioners (e.g., physiotherapists) who have undergone training in the delivery of psychological interventions might provide positive results (48). In this context, future studies are needed to define which psychological interventions are most appropriate and to clarify how co-management with other health care practitioners can improve PT outcomes for patients who are identified as at risk due to elevated PC.

There are a few limitations of the current study. The first was the combined use of several modalities. It will be useful to conduct studies evaluating each modality separately to understand which one is more appropriate for patients with CS. Second, we chose to analyze 2- and 6-week time points; this time allotment may not be sufficient to determine the effectiveness of PT. Third, patients received only 10 sessions, which may be too brief for adequate effect on knee pain and function, because of the long wait list for PT in our public hospital. More PT sessions may be needed in the long term to help modulate the thought process of patients with significant PC. Addition to these limitations, the generalizability of this study is also limited due to the use of patient self-reported measures and the large proportion of our sample comprised of nonworking middle-aged women from a single center.

CONCLUSION

Our results provided new information on the pre-

dictive role of PC in the improvement of self-reported pain and function following a combination of thermotherapy and electrotherapy procedures. The finding that baseline depression did not predict outcomes of PT was interesting. Additional studies focusing on both depression and PC are warranted to clarify our preliminary results. Our outcomes strongly support the notion that assessing patients' level of PC before PT, and taking the necessary precautions such as CBT, may positively affect treatment outcomes and delay or prevent the use of invasive procedures such as KA.

Conflict of Interest:

All authors declare that they have no conflict of interest.

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Author Contributions: Dr. Aslı Çalıskan Uçkun, Dr. Burcu Köse Dönmez, Dr. Fatma Gül Yurdakul, Dr. Yesim Garip, and Dr. Hatice Bodur had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Aslı Çalıskan Uçkun, Dr. Fatma Gül Yurdakul, and Dr. Hatice Bodur designed the study protocol. Dr. Aslı Çalıskan Uçkun, Dr. Fatma Gül Yurdakul, and Dr. Hatice Bodur designed the study protocol. Dr. Aslı Çalıskan Uçkun, Dr. Burcu Köse Dönmez, and Dr. Yesim Garip managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Dr. Hatice Bodur provided revision of intellectual content and final approval of the manuscript. All authors declare that they have no conflict of interest. Further, the authors have not received any reimbursement or honorarium in any other manner.

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