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Original Article

Relationship of neuropathic pain component and osteoarthritis stage in patients with knee osteoarthritis

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Abstract

Aim: The aim of this study was to determine the frequency of neuropathic pain (NP) in patients with knee osteoarthritis (OA) and the relationship between knee OA stage and NP degree.

Materials and Methods: This study included 63 patients (11 male, 52 female; mean age 62.4 ± 11.9 years; range 40-89 years) who were diagnosed with knee OA according to the American College of Rheumatology between January and May 2019. For all the participants, the knee pain was evaluated with the Visual Analog Scale (VAS), the functional evaluation was performed through Western Ontario and McMaster University (WOMAC) Osteoarthritis Index, and the neuropathic pain (NP) component was evaluated through Pain-DETECT Questionnaire (PDQ). The Kellgren-Lawrence grading system was used to determine radiological severity.

Results: Of the total, 18 patients (28.5%) were classified as possible NP and 15 patients (23.5 %) were classified as likely NP. The symptom durations of the patients with final NP diagnosis were longer ($p<0.05$). The PDQ score was determined to be moderate and positively correlated with the WOMAC subscale scores and total score (pain score: $r=0.450$, $p<0.001$; stiffness score: $r=0.4011$, $p=0.001$; physical function score: $r=0.397$, $p=0.001$; total score: $r=0.424$, $p=0.001$). A positive and weak correlation was detected between the knee OA stage and neuropathic pain scores ($p<0.05$; r: 0.265).

Conclusion: This study showed that the underlying cause of knee pain in the significant part of knee-OA patients has the NP component. Knee-OA patients with neuropathic pain component had higher rates of OA-related disability. There was a poor correlation between NP scores and radiographically advanced osteoarthritis symptoms. However, we suggest that further studies should be conducted with larger sample groups, the NP component should be kept in mind and should be included in the treatment plan for the knee-OA patients.

Keywords: Knee osteoarthritis; neuropathic pain

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by joint pain and progressive cartilage destruction. The knee is the joint most commonly exposed to the symptoms of OA (1,2). Pain is the most common symptom of OA and the most common cause to apply to a physician. The most important pathological feature of osteoarthritis is abnormal articular cartilage with avascular and aneural structure that does not cause direct pain (3). All of the joints and periarticular structures are rich in innervation and represent the source of nociceptive pain (4). The pathophysiology of pain in osteoarthritis involves both nociceptive and neuropathic mechanisms. Local joint inflammation and structural changes in the joint affect the nociceptive process. Pain may occur due to deep somatic tissue influence during inflammation (peripheral sensitivity) or when pathological neural signals in the joint cause changes in the central nervous system (central sensitivity) (5). Peripheral and central mechanisms show themselves at different stages. Peripheral mechanisms are seen in the early stage, while central mechanisms are seen in the late stage (3).

The results of the studies on the frequency of neuropathic pain in OA and its progression in different stages of OA differ. In a recently published review of prevalence studies, the rate was found to be 23% (6). Finan et al. suggested that central sensitization in knee OA is especially apparent among patients with reports of high levels of clinical pain in the absence of moderate-to-severe radiographic evidence of pathologic changes of knee OA (7).

Accurate identification of any neuropathic pain contribution to the pain of knee and/or hip OA is important as people with neuropathic pain typically report more severe pain, disability, coexistent anxiety and depression and poorer health-related quality of life compared to those with non-

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neuropathic pain (8-10). Considering all these results, new studies are needed for the frequency of neuropathic pain in knee osteoarthritis, its relationship with the duration and stage of osteoarthritis, and to include NP treatments in treatment protocols.

In this study, our aim is to determine the frequency of neuropathic pain (NP) in patients with knee osteoarthritis (OA) and the relationship between knee OA stage and degree of neuropathic pain.

MATERIALS and METHODS

Patients and Study Design

The study was planned within the scope of Evidence-Based Medicine applications course determined for our Semester-1 medicine students. A total of 63 patients participated in this retrospective study that were over 40 years old and admitted to our outpatient clinic and received knee OA diagnosis according to the criteria of the American College of Rheumatology between January and May 2019 (11). The exclusion criteria for the participants are being younger than 40 years old, having a previous knee surgery, having a history of neurological diseases such as stroke and traumatic brain injury, having an inflammatory joint involvement, active infection in and around the knee joint, having a history of radiculopathy and diabetes mellitus. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by Malatya Clinical Research Ethics committee (Approval No. 2020/1157).

Data Collection

Demographic data (age, sex, body mass index, affected knee and symptom duration) of all the participants were recorded.

The knee pain was evaluated with the Visual Analog Scale (VAS). The VAS pain score (0 cm to 10 cm) was used to determine the severity of pain. On this scale; 0 shows no pain, 10 indicates the highest pain level.

The functional evaluation was performed through Western Ontario and McMaster University (WOMAC) Osteoarthritis Index. WOMAC scale was used to assess the functional status. The WOMAC consists of a total of 24 questions and three subscales. Each question is scored from 0 to 4, which makes the highest score 96. Increasing total scores indicate the worsening of functional status. Turkish validity and reliability studies were conducted by Tüzün et al. (12).

The radiological evaluation of the patients was conducted through the Kellgren-Lawrence grading system by the physiatrist (13).

The neuropathic pain (NP) component was evaluated through Pain-DETECT Questionnaire (PDQ). PDQ was used to evaluate the presence of neuropathic pain in patients. In the pain Detect neuropathic pain survey, 7 questions are related to pain quality and 2 questions are related to spread and temporal characteristics. Patients with a total survey score of 12 and below were considered to have no neuropathic pain component, those within the range of 13-18 points were considered to be indeterminate (but may have a neuropathic pain component), while those with scores of 19 and above were considered positive. Turkish validity and reliability tests of the scale were conducted by Alkan et al., in 2013 (14). Patients were divided into three groups: likely NP (score ≥19), possible NP (score ≥13 to ≤18), and unlikely NP (score ≤12).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows version 18.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses. We conducted descriptive analyses to summarize the patients' baseline characteristics. Mean value and standard deviation was used for continuous variables and median (minimum-maximum) for discrete variables. Shapiro-Wilk test was performed to assess the distribution of continuous variables. Comparisons of groups were evaluated with Kruskal-Wallis test and One-Way ANOVA test. Correlation analysis between the pain-DETECT scores disease duration, VAS scores were performed with Spearman correlation test; age, WOMAC scores and KL Grade were performed with Pearson correlation test. The statistical significance value was accepted as 0.05.

RESULTS

The average age of 63 patients (11 male, 52 female) who participated in the study was 62.42 ± 11.93 years. Their socio-demographic characteristics are given in Table 1.

Table 1. Socio-demographic characteristics of patients

	n	Mean±SD	Range
Age (year)	63	62.4±11.9	40-89
BMI (kg/m²)	63	30.0±4.6	21-43
Symptom duration (year)	63	5.6±5.2	1-20
Sex: Female/Male	52/11		
Symptomatic knee			
Right/Left/Bilateral	16/13/34		
Kellgren Lawrance			
Grade 1	5		
Grade 2	12		
Grade 3	20		
Grade 4	26		

SD: standard deviation; BMI: body mass index

In this study, 15 patients (23.5%) were classified as likely NP, 18 patients (28.5%) were classified as possible NP, and 30 patients (47.6%) were classified as unlikely NP.

As per the comparison of the clinical parameters among the three groups, it was determined that there was statistically no significant difference among age, BMI and VAS values ($p>0.05$). However, the symptom duration was significantly longer in the likely-NP group and there was a significant difference between each WOMAC subscores and total score ($p <0.05$) (Table 2).

Table 2. Clinical characteristics of the groups

	Unlikely NP (n:30) Mean±SD	Possible NP (n:18) Mean±SD	Likely NP (n:15) Mean±SD	P value
Age (year)	59.63±2.08	63.38±2.53	66.86±3.48	0.14
BMI (kg/m²)	29.51±0,79	30.63±1.80	30.58±1.34	0.65
Symptom duration (year)	3.7±0.59	6.46±1.54	8.94±1.80	0.01*
At rest VAS	4.93±0.43	5.55±0.52	6.20±0.49	0.24
Initial VAS	6.40±0.27	6.94±0.43	7.40±0.32	0.09
VAS while walking	5.93±0.44	6.88±0.55	7.33±0.41	0.09
VAS while ascending and descending stairs	7.20±0.38	7.72±0.48	8.33±0.28	0.15
WOMAC				
Pain	11.26±0.71	13.11±0.89	16.08±10	0.01*
Stiffness	4.23±0.38	5.61±0.38	6.23±0.60	0.05*
Physical function	39.10±2.59	44.65±3.43	53.98±3.17	0.04*
Total	55.62±3.28	63.38±4.36	76.60±4.55	0.02*

VAS: Visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; SD: standard deviation; BMI: body mass index, *:p<0.05

Table 3. Correlation analysis between WOMAC scores, KL Grade and PDQ scores

	r	p
Symptom duration	0.332*	0.008
KL Grade	0.265*	<0.005
WOMAC scores		
Pain	0.490**	<0.001
Stiffness	0.401**	0.001
Physical Function	0.397**	0.001
Total	0.424**	0.001

WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; KL-Grade: Kellgren-Lawrence grading system; PDQ: Pain-Detect Questionnaire; * Pearson correlation coefficent; ** Spearman rho; p<0.05 (significant)

Table 4. Correlation analysis between WOMAC scores, KL Grade and PDQ scores

			95.0% Confidence interval for B	
	B	Sig	Lower Bound	Upper Bound
Symptom duration (month)	0.299	0.016*	0.010	0.095
KL Grade	0.141	0.254	-0.088	0.326
WOMAC total score	-0.047	0.095	-0.102	0.008

WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; KL-Grade: Kellgren-Lawrence grading system; B: Beta value * P<0.05

PDQ score was moderate and positively correlated with the WOMAC pain, stiffness, physical function, total scores (r=0.490, p<0.001; r=0.401, p=0.001; r=0.397, p=0.001; r=0.424, p=0.001, respectively) and duration of symptom (r=0.332, p=0.008). Considering the PDQ scores according to radiological staging, a positive weak correlation was determined (p<0.05, r=0.265) (Table 3) (Figure 1). We found only symptom duration independently and significantly affect pain-DETECT scores according to the linear regression analysis (p < 0.05) (Table 4).

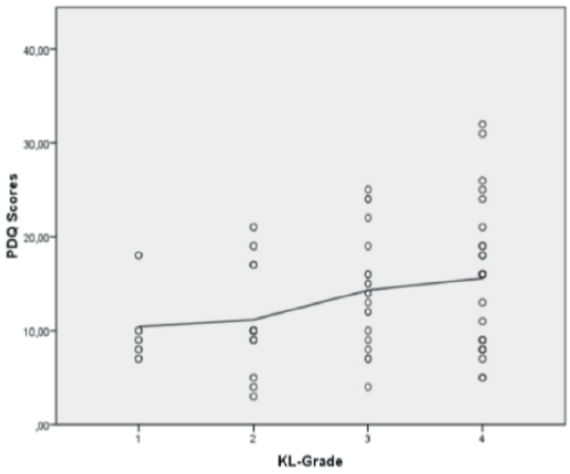

Figure 1. Relationship between KL stages and PDQ scores

DISCUSSION

This study demonstrated the presence of the NP component in the majority of patients with knee OA. Knee-OA patients with a predominant neuropathic

pain component had longer symptom periods, more advanced stages of osteoarthritis, and higher rates of OA-related disability. Therefore, in knee-OA patients, the NP component should be kept in mind and should be evaluated within the treatment plan.

Osteoarthritis-related pain is traditionally linked to peripheral pain mechanisms that involve the activation of primary nociceptors in somatic tissues such as joints or periarticular structures. The mismatch between pain severity and radiographic stage in osteoarthritis patients directed researchers to verify different pain mechanisms. While there is evidence of the contribution of central pain hypersensitivity to present pain in some patients with osteoarthritis, the likely contribution of neuropathic pain has also been suggested. Studies evaluating the frequency of neuropathic pain in patients with knee-OA yielded different results depending on the number of sample and the methodology of the study. The presence of exact neuropathic pain in knee-OA in these studies varies between 5.4% and 32% (15-18). In our study, 23.5% patients were classified as likely NP and 28.5% patients as possible NP.

OA pain is generally recognized to be a pain with peripheral mechanism caused by the activation of nociceptors in somatic tissues such as joints and periarticular tissues. However, in animal studies, peripheral and central mechanisms have been shown to play a role in OA pain. Inflammatory cytokines, neuropeptides and various chemical mediators play a role in these mechanisms (19). It was revealed that, in the early phase of osteoarthritis, there is an increase in the level of inflammatory neuropeptides innervating the sensory nerves in the knee and it was also shown that, subsequently, subchondral bone pathologies together with advanced-stage osteoarthritis caused bone damage and neuropathy. These findings support a transition in OA from early inflammatory pain to neuropathic pain (19,20). The results of the studies vary that were conducted in the light of the knowledge that peripheral mechanisms are seen in the early stage and central mechanisms are seen in the late stage (21). In a study conducted on 50 patients with symptomatic knee-OA, Roubille et al. (18) determined that pain-DETECT score was associated with VAS pain score, but not with the Kellgren-Lawrence stage. In another study conducted by Polat et al., it was found that NP severity and the symptom duration were related, without having a relation with the OA stage (22). In a study conducted by Koçyiğit et al., it was determined that the symptom duration was not associated with NP but was closely related to the OA stage (23). Aşkın et al. reported that there was a relationship between radiological stage and pain-DETECT score (24). It has been observed that in the advanced stages of OA, it contributes to the development of NP due to a decrease in joint fluid and degeneration in the sub-chondral structure (15). In our study, we found that patients with NP had longer symptom durations and that patients with advanced OA stage had more NP components. However, in our patients there were very few patients with radiographic stage 1, which is known as the early stage of OA, so we believe that further studies are needed with larger groups of patients with close patient distribution in relation to the phases.

On the other hand, it was shown in many studies that the presence of NP accompanying OA leads to higher levels of functional restriction and disability in patients. In our study, WOMAC scores were higher in patients with NP, and disease-related disability rates were higher (23,25).

LIMITATIONS

There are several limitations of our study. Sample size is very small (especially patients with early stage OA) and most of the patients are female. We did not assess healthy controls. Depression and anxiety levels of the patients were not evaluated. Further studies are needed, which involve larger sample groups and quantitative measurements, indicating the importance of NP accompanying OA in both diagnosis and treatment.

CONCLUSION

As the conclusion, we found that the ratio of NP-detected patients in knee OA was quite high and that functionality was more impaired in these patients. The neuropathic component of OA should be considered particularly when determining treatment strategies in moderate-to-severe OA.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: This study was approved by Malatya Clinical Research Ethics committee (Approval No. 2020/1157).

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