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Assessment of Frequency of Neuropathic Pain in Knee Osteoarthritis and its Relation to Functional State, Quality of Life and Depression

Diz Osteoartritinde Nöropatik Ağrı Sıklığı ve Fonksiyonel Durum, Yaşam Kalitesi ve Depresyon ile İlişkisinin Değerlendirilmesi

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ABSTRACT Objective: Neuropathic mechanisms are considered to play a role in development of pain in knee osteoarthritis (OA) as well as nocicieptive mechanisms. The present study aimed to determine neuropathic pain in patients with knee OA and investigate its relation to functional state,,quality of life and depression. **Material and Methods:** The present cross-sectional study enrolled 150 patients with primary knee OA. Demographic data of the patients were recorded. Anteroposterior knee radiographs were assessed using the Kellgren Lawrence staging system. Pain severity was evaluated with Visual Analogue Scale (VAS), the Douleur Neuropathique en 4 Questions (DN4) questionnaire was used to detect the neuropathic pain component, the Lequesne index was used to assess the functional status, the Beck Depression Inventory (BDI) was used to assess depressive symptoms and the Short Form-36 (SF-36) questionnaire was applied to assess the quality of life. **Results:** Of 150 patients,133 (88.7%) were female and 17 (11.3%) were male patients. The mean age was 61.5±9.7 years. The DN4 scale revealed that 40% of the patients had neuropathic pain. In the group with neuropathic pain, VAS resting, VAS movement and Lequesne scores were significantly higher than those of without neuropathic pain (p=0.004, p=0.005, p=0.0001, respectively). There were no significant differences in SF-36 and BDI scores between the two groups (p>0.05). There was no correlations between DN4, SF-36 and BDI scores; however, these scores showed a significant positive correlation with the Lequesne index (r=0.562, p=0.0001). **Conclusion:** Chronic pain in patients with OA has degenerative and neuropathic components. As neuropathic pain is a factor that increases pain and disability and disrupts functional status in osteoarthritis, it should be questioned and neuropathic pain treatment should take place as part of the treatment of osteoarthritis.

Keywords: Knee; neuropathic pain; osteoarthritis

ÖZET Amaç: Diz osteoartritinde (OA) ağrı oluşumu üzerine, nosiseptif mekanizmaların yanı sıra nöropatik mekanizmaların da rol oynayabileceği düşünülmektedir. Bu çalışmada diz osteoartriti olan hastalarda nöropatik ağrı komponenti olup olmadığının belirlenmesi ve nöropatik ağrı komponenti varsa fonksiyonel durum, yaşam kalitesi ve depresyon ile ilişkisinin araştırılması amaçlandı. **Gereç ve Yöntemler:** Bu kesitsel çalışmaya primer diz OA tanısı olan 150 hasta dahil edildi. Hastaların demografik verileri kaydedildi. Hastaların ön-arka diz grafileri Kellgren-Lawrence evreleme sistemi ile değerlendirildi. Ağrı şiddeti için Görsel Analog Skala (VAS), nöropatik ağrı komponentinin tespiti için DN4 anketi, fonksiyonel durumu değerlendirmek için Lequesne indeksi, depresif semptomlar açısından Beck Depresyon Ölçeği (BDÖ) ve yaşam kalitesi için Kısa form-36 (SF-36) anketi uygulandı. **Bulgular:** Hastaların 133'ü (%88,7) kadın, 17'si (%11,3) erkek idi. Yaş ortalaması 61,5±9,7 yıl idi. DN4 skalasına göre hastaların %40'ında nöropatik ağrı mevcuttu. Nöropatik ağrı olan grupta, nöropatik ağrı olmayan gruba göre VAS istirahat, VAS hareket ve Lequesne skorları istatistiksel olarak anlamlı derecede yüksek bulunmuştur (p=0,004, p=0,005 ve p=0,0001). İki grupta, SF-36 ile BDÖ skorları arasında anlamlı bir fark gözlenmedi (p>0,05). DN4 skoru ile SF36 ve Beck depresyon skoru arasında korelasyon olmadığı; Lequesne indeksi ile anlamlı pozitif korelasyon (r=0,562, p=0,0001) olduğu saptandı. **Sonuç:** Bu araştırmanın bulguları, kronik diz osteoartritli hastalarda ağrının nosiseptif komponenti yanı sıra nöropatik komponenti de olduğunu göstermektedir. Nöropatik ağrı, ağrı ve dizabiliteyi arttıran bir faktör olduğundan, osteoartritte fonksiyonel durumu bozan nöropatik ağrı sorgulanmalı ve nöropatik ağrı tedavisi osteoartrit tedavisinin bir parçası olarak uygulanmalıdır.

Anahtar Kelimeler: Diz; nöropatik ağrı; osteoartrit

Osteoarthritis (OA) pain is considered to have both nociceptive and neuropathic components although the mechanism has not been fully explained yet.[1] Pain conduction is realised via unmyelinated-thin C fibres and thin myelinated A-delta fibres. Stimulants generated as a result of cartilage destruction, bone damage and inflammation stimulate nociceptive receptors. Continuous and extreme sensitivity might lead to central sensitisation, which can clinically result in neuropathic pain. Neuropathic pain occurs due to irritation of the nerve roots caused by mechanical irritation or cytokines released in OA.[2,3] In neuropathic pain, if C fibres, large fibres or large myelinated (A) fibres havebeen sensitized, they can cause epigastric pain, paraesthesia or dysesthesia. Allodynia might occur due to stimulation of either sensitized nociceptors or centrally sensitized A-beta fibres. In knee OA, neuropathic pain might come up with symptoms such as electrification, burning, freezing, formication and paraesthesia.[4] Pain in knee OA might lead to loss of strength by reducing the functional capability of the patient. As a result, the patient faces deterioration in quality of life. Chronic pain treatment is aimed at reducing pain and ensures that the patient returns to their normal activities. Thus, the components of pain should be identified in order to apply the appropriate treatment.[5] Prior studies assessing neuropathic pain in patients with osteoarthritis have used several scales [e.g. pain detect and Douleur Neuropathique en 4 Questions (DN4) scale] to assess neuropathic pain in a small number of patients (60-100 patients) and have investigated the quality of life and functional status of these patients.[6-8] In the present study, we aimed to determine the presence of neuropathic pain using the DN-4 scale in patients with knee OA. Besides, we investigated its relation to functional state, quality of life and depression symptoms.

MATERIAL AND METHODS

PARTICIPANTS

The diagnosis and classification of the patients were determined according to the clinical criteria developed by American College of Rheumatology (ACR): accordingly, the presence of at least 3 of the following six criteria is required for the diagnosis of knee OA. a) age >50 b) morning stiffness <30 minutes c) crepitus on active joint motion d) bone tenderness e) bone enlargement f) knee pain for most days of the prior month.[9]

The inclusion criteria were as follows: a minimum of three pain episodes, age between 30 and 70 years and literacy. The exclusion criteria were previous knee operation, infective or inflammatory disease, cancer or metabolic disease and diabetes or peripheral-central neuropathic disease and drugs (pregabalin,gabapentin and other neuropathic pain drugs). Demographic datawere recorded. Anteroposterior knee radiographs of the patients were assessed using the Kellgren-Lawrence staging system in which stage 0 indicates normal knee joint, stage 4 indicates advanced joint damage.[10]

CLINICAL EVALUATION

Visual Analogue Scale (VAS)

The scale used for evaluation of pain has a 10-cm line; one end reads 'no pain felt'and the other reads'terribly severe pain'. Patients were asked to grade their pain on a 10-cm scale while at rest and functioning based on the following statements: 0 as no pain and 10 as very severe pain.[11]

Lequesne Index

Queries involve the following: night pain, morning stiffness, pain while walking, pain while getting up from the chair without any use of chair arms, maximum walking distance and daily living activities (stair climbing, descending, crouching and walking on an uneven surface). Evaluation is scored by 1-4 points: mild (level 1), 5-7 points: medium (level 2), 8-10 points: severe (level 3), 11-13 points: very severe (level 4) and 14 or more points: extremely severe (level 5).[12]

Short Form-36 (SF-36)

The questionnaire was filled out to evaluate quality of life among the participants. Medical outcome consists of eight scales with 36 items generated via long forms of the study. It might be grouped based on two special dimensions, with physical health in

four dimensions and mental health in four dimensions. For each dimension, scores were coded and collected and converted into a scale with points from 0 (worst state of health) to 100 (best state of health). A Turkish validity and reliability study was carried out by Kocyigit et al.[13]

Beck Depression Inventory (BDI)

BDI is one of the frequently used scales to assess depression levels of adults, and a Turkish validity and reliability study was carried out. The inventory contains 21 questions with four options for each. Each question is scored between 0 and 3. The highest score is 63, in which 0-9 indicates minimal, 10-16 as mild, 17-29 as medium and 30-63 as severe depression.Validity and reliability tests of the Turkish version were performed by Hisli.[14]

ASSESSMENT OF NEUROPATHIC PAIN

Douleur Neuropathique en 4 Questions (DN4)

Neuropathic pain is evaluated using four questions in this scoring. The first two questions are based on patient interview, whereas the other two questions are based on clinical examination. The first question defines the pain characteristics (burning, coldness or electrical shock). The second question asks about paraesthesia/dysesthesia in the pain area (horripilation, pricking or itchiness). The third question focuses on the emotional deficit identified during examination of the localised pain (numbness to touch, numbness with pain). The fourth question investigates whether friction causes pain or increase in pain. The participants replied with either a *yes* or a *no*. The total score was calculated by allocating one point per yes and 0 points per no. The threshold value for neuropathic pain has been defined as 4/10. The validity and reliability tests of the Turkish version were performed by Celik et al.[15]

Patients were allocated into two groups based on the DN4 score, the group with a score <4 has been considered the group without neuropathic pain, whereas the group with a score ≥4 as the group with neuropathic pain.

The study protocol was approved by the Ethics Committee. Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

STATISTICAL METHODOLOGY

Lilliefors-corrected Kolmogorov-Smirnov test was performed as the normality test. Data not complying with normal distribution are presented as median [interquartile range (IQR)]. Categorical data are provided as number and frequency. The Mann-Whitney U test was used to compare medians of the two groups. Distribution of cases into groups by categorical variables was analysed via likelihood ratio or Pearson chi square test. The correlation between neuropathic pain (DN4 score) and SF36, Beck depression score and Lequesne index was analyzed by Spearman test. For comparing patients with and without neuropathic pain, the variables of demographic, anthropometric and clinical features that exhibited statistically significant differences were subjected to regression analysis.

We used binary logistic regression analysis (forward stepwise-conditional) to determine risk factors for neuropathic pain. In addition, we assessed the relevance of the regression model using the Hosmer-Lemeshow test. The risk ratios were used as Exp (B) (odds ratio). A p value was considered significant if <0.05. PASW Statistics version 18 was used for analyses.

RESULTS

There were 133 (88.7%) females and 17 (11.3%) males, with an average age of 61.5±9.7 (36-84) years. The DN4 scale revealed that 40% of the patients experienced neuropathic pain. Mean patient age in the group with neuropathic pain group was significantly higher than that in the group without neuropathic pain (p=0.020). There was no significant difference among other demographic data between the two groups (p<0.05). Comparison of demographic characteristics of the patients with and without neuropathic pain are provided in Table 1.

The mean duration of pain was 6.45±3.46 years in neuropathic pain group and 5.96±3.21 years in the group without neuropathic pain. There were no

TABLE 1: Comparison of demographic characteristics of the patients with and without neuropathic pain.

	Without Neuropathic Pain	With Neuropathic Pain	p
Age (yrs)	60.0 (12.0)	66.0 (13.8)	0.020
Body Mass Index (kg/m^2)	30.9 (7.2)	28.7 (4.0)	0.073
Gender			
Male	13 (14.4)	4 (6.7)	0.129
Female	77 (85.6)	56 (93.3)	
Occupation			
Retired	11 (12.2)	4 (6.7)	0.145
Active Employee (Office)	3 (3.3)	2 (3.3)	
Active Employee (Physical)	8 (8.9)	2 (3.3)	
Unemployed	25 (27.8)	11 (18.3)	
Housewife	43 (47.8)	41 (68.3)	
Education			
Illiterate	19 (21.1)	19 (31.7)	0.085
Literate	1 (1.1)	5 (8.3)	
Primary-Secondary	58 (64.4)	31 (51.7)	
High School	6 (6.7	2 (3.3)	
University	6 (6.7)	3 (5.0)	
Marital Status			
Married	76 (84.4)	49 (81.7	0.133
Single	4 (4.4)	0 (0.0)	
Widowed	10 (11.1)	11 (18.3)	

Data were given as median (interquartile range) or n [%].

significant differences in pain duration between the two groups (p>0.05). In the group with neuropathic pain, VAS resting, VAS movement and Lequesne scores were significantly higher than those in the group without neuropathic pain (p=0.004, p=0.005, p=0.0001, respectively). In addition, there were no significant differences in SF-36 and BDI scores (p>0.05) between the two groups. Comparison of clinical characteristics of patients with and without neuropathic pain are shown in Table 2.

There was no correlation among DN4, SF-36 and Beck depression scores; however, these scores showed a significant positive correlation with the Lequesne index (r=0.562, p=0.0001). Binary logistic regression analysis indicated that patients with high Lequesne index were at a 1.484-times higher risk of developing neuropathic pain (Nagelkerke R^2, p=0.447; Hosmer-Lemeshow test, p=0.070). Educational status, marital status, disease duration, age, sex, BDI

TABLE 2: Comparison of clinical characteristics of the patients with and without neuropathic pain.

	Without Neuropathic Pain	With Neuropathic Pain	P
Pain Duration	5.96±3.21	6.45±3.46	0.376
VAS rest	4.0 (2.0)	5.0 (2.0)	**0.004**
VAS motion	6.0 (2.3)	7.0 (2.0)	**0.005**
Lequesne	11.0 (4.3)	16.5 (5.0)	**0.0001**
Beck depression	8.0 (6.0)	9.0 (6.8)	0.831
SF-36	46.3 (28.6)	60.0 (36.5)	0.263

Data has been provided as median (IQR) and mean±sd. Comparisons were made via Mann Whitney U testing and Student t testing.

VAS: Visual Analogue Scale; SF-36: Short Form 36.

TABLE 3: Risk factors for neuropathic pain regression model.

	B	S.E.	Wald	df	Sig.	Exp (B) (Odds)	95% C. I. for EXP (B)	
							Lower	Upper
Lequesne	0.395	0.065	36.760	1	0.000	1.484	1.306	1.686
Constant	-5.808	0.929	39.064	1	0.000	0.003		

scores and SF-36 scores were insignificant as risk factors (Table 3).

DISCUSSION

Neuropathic pain exerts a negative impact on the quality of life and functional status of patients with pain.[6,8,16,17] In this study, quality of life and depression there was no difference between groups with regard to.

Diagnosis and identification of neuropathic pain is crucial in the treatment of people with severely symptomatic knee OA. Even if there is no golden standard diagnostic method for neuropathic pain, many scoring methods are used clinically. In the present study, we used DN4 scoring to assess neuropathic pain which survey is beneficial to differentiate between pain due to nerve system damage via simple symptom combinations and somatic pain and represents various mechanisms in the pathophysiology of pain.[18]

Perhaps, a bidirectional correlation exists between neuropathic pain and quality of life or pain and depression, consistently with the positive feedback effect. Low quality of life may affect pain perception or development, and pain may impair the quality of life. Because the impact of psychological factors on pain is known, it was included in the regression model to determine whether low quality of life or single lifestyle is a risk factor for neuropathic pain development.

Golge et al. studied 100 patients and found that 24% of the patients had neuropathic pain, whereas this ratio was found to be 33.3% as identified using DN4 in another study.[8,19] In the present study, 38.52% of the patients had neuropathic pain. Pain detection scoring was used in previous studies to identify neuropathic pain in knee OA, and the neuropathic pain ratio was 17.6% according to Ohtori et al. and 46.7% by Mesciet al., 26.7% by Rienstra et al.[16,17,20] Although such studies identified the neuropathic pain ratio, varying number of patients and use of different scales might be the basis for the difference in results. Askin et al. used both pain detection and DN4 scale for detecting neuropathic pain in 60 patients, which identified 66.7% and 46.7%, respectively. Similarly to our study, the correlation among neuropathic pain and function, quality of life and depression was investigated in another study, wherein the PainDETECT questionnaire scores showed a significantly positive correlations with the VAS resting, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) all scores and anxiety-depression scores but a significantly negative correlation with SF-36 all scores.[6] In the present study, VAS rest, VAS motion and Lequesne scores were significantly higher in the group with neuropathic pain than in the group without neuropathic pain. A significant correlation has been identified for VAS and functional state score.[6,8,16,19] In the light of these studies, neuropathic pain is a serious issue and reduces functional capability.Deterioration in the quality of life is observed as a result of pain and deterioration in the functional state associated with knee OA. Even though the SF-36 scores of the groups with and without neuropathic pain were increased, a significant difference between the two groups could not be identified in our study.

One of the factors that change pain behaviour is depression. Depression and other mental disorders frequently co-exist with chronic pain related to OA.[21] Although depression and anxiety scores of patients with neuropathic pain were found to be higher in studies by Ohtori, Mesci and Hochmann, neuropathic pain was observed not to change the depression ratio of the patients in our study, wherein

we used BDI.[16,17] Based on BDI, depression was diagnosed in 8% of the patients without neuropathic pain, whereas this ratio was 9% for those with neuropathic pain.We could not identify a significant difference in the depression ratio between groups with and without neuropathic pain. Notably, the psychological mechanism of pain has a predominant role in chronic pain; therefore, a psychiatric evaluation is required. Even though the number of patients in the present study is higher than in other studies, this sample size may still be considered a limitation. In addition, the present study has no control group matched in age and sex, and factors that might cause neuropathic pain were not evaluated.

In conclusion, considering the results of the present study and literature data, chronic pain in OA has degenerative and neuropathic components. Because neuropathic pain increases pain and disability, thus disrupting the functional state of patients with OA, it should be a concern in OA treatment and a part of therapy.

Declaration of conflicting interests

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