J. Phys. Ther. Sci. 28: 2190–2195, 2016

The Journal of Physical Therapy Science

Original Article

Association of neuropathic pain with ultrasonographic measurements of femoral cartilage thickness and clinical parameters in patients with knee osteoarthritis

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Abstract. [Purpose] The aim of this study was to investigate whether neuropathic pain is associated with femoral condylar cartilage thickness, electrical pain threshold, and clinical parameters in patients with knee osteoarthritis. [Subjects and Methods] Sixty patients over the age of 40 diagnosed with knee osteoarthritis were enrolled. The PainDETECT questionnaire, Western Ontario and McMaster Universities Osteoarthritis Index, Hospital Anxiety and Depression Scale, and Short Form-36 questionnaire were completed for all patients. Electrical sensory threshold and electrical pain threshold measurements were obtained. Femoral condylar cartilage thickness was determined by means of ultrasound. [Results] PainDETECT scores of 13 or greater were observed in 28 (46.7%) patients, indicating the presence of neuropathic pain. These patients were found to have greater average pain severity, Western Ontario and McMaster Universities Osteoarthritis Index, and depression and anxiety scores and lower Short Form-36 scores than patients without neuropathic pain. Patients with neuropathic pain showed lower knee electrical sensory threshold and pain threshold values on average than patients without neuropathic pain. Femoral condylar cartilage thickness was not different between the two groups. [Conclusion] Neuropathic pain is associated with increased pain severity and decreased functional capacity and adversely affects quality of life and mood in patients with knee osteoarthritis.

Key words: Neuropathic pain, Osteoarthritis, Pain threshold

(This article was submitted Feb. 20, 2016, and was accepted Apr. 25, 2016)

INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint disorder associated with chronic pain and disability at older age. In recent years, peripheral and central sensitizations have been suggested as two of the underlying mechanisms of pain in osteoarthritis[1, 2)]. It is known that patients with osteoarthritis experience nociceptive and neuropathic pain to varying degrees[1, 3)]. Furthermore, addition of molecules targeting neuropathic pain to conventional therapy has been shown to improve treatment response in the management of osteoarthritis[4)].

Several questionnaires are available for assessment of neuropathic pain. The PainDETECT questionnaire does not require a clinical examination and has been shown to be more sensitive and specific compared with other questionnaires[5)]. It has been used in most of the studies investigating neuropathic pain (NP) in patients with osteoarthritis. The PainDETECT scale was demonstrated to be an important tool for evaluation of a pain phenotype associated with augmented central pain perception[3)].

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Studies examining NP in patients with osteoarthritis have often utilized neuropathic pain questionnaires and quantitative sensory testing for pressure-pain thresholds (PPTs)[2, 3, 6]. No study was identified in the literature that used an electrical pain threshold for quantitative sensory testing in patients with knee osteoarthritis. Furthermore, femoral condylar cartilage thickness has been shown to be an important parameter for monitoring patients with knee osteoarthritis[7]. To the best of our knowledge, there is no study in the literature that has explored the association between neuropathic pain and femoral cartilage thickness (FCT) assessed by ultrasound (US).

In the present study, we aimed to evaluate the neuropathic component of pain in patients with knee OA using the painDETECT questionnaire, electrical sensory threshold, and electrical pain threshold. Additionally, we sought to determine the association of neuropathic pain with several parameters including femoral cartilage thickness, radiological grade, pain severity, functional state, depression, anxiety, and quality of life.

SUBJECTS AND METHODS

The study enrolled 60 patients over the age of 40 who were admitted to our physical therapy outpatient clinics with knee pain and diagnosed with knee OA according to the American College of Rheumatology (ACR) criteria. Approval for conduct of the study was obtained from the institutional ethics committee. All patients gave informed consent prior to initiation of the study.

Patients with a history of trauma or surgical operation in the knee region, inflammatory rheumatic disease, central or peripheral neurological disorder, diabetes mellitus, or severe cardiac, pulmonary, or malignant disease were excluded from the study.

Demographic characteristics including age, gender, height, body weight, body mass index (BMI), and duration of symptoms were recorded for all patients. Patients were asked to score the severity of their current knee pain on a 10-cm visual analogue scale (VAS). Radiographic grading of OA was performed using the Kellgren-Lawrence (K-L) grading system and anterior-posterior X-ray views of the knee[8].

The presence of neuropathic pain in study patients was assessed using the painDETECT questionnaire. The PainDETECT total score is obtained by summing the scores for 7 pain symptom items with the scores for the pain course pattern item and the pain radiation item. A score between 0–12 indicates that a neuropathic pain component is unlikely, a score between 13–18 indicates that the result in ambiguous, and a score between 19–38 indicates that a neuropathic pain component is likely. Validity and reliability of a Turkish version of the painDETECT questionnaire were demonstrated by Alkan et al[9].

Functional state of the participants was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC consists of 24 questions that assess pain, stiffness, and problems with physical activities. The patient answers all questions on a 5-point Likert-type scale, and the total score ranges from 0 and 96. Validity and reliability of a Turkish version of the index were demonstrated by Tuzun et al[10].

Psychological state of the patients was evaluated using the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item scale; seven of the items relate to symptoms of anxiety, and seven relate to depressive symptoms. Each item in the questionnaire is scored from 0 to 3, and a person can score between 0 and 21 for either anxiety or depression. Validity and reliability of a Turkish version of HADS were demonstrated[11].

Quality of life assessment was performed using the Short Form-36 (SF-36) questionnaire. The SF-36 has eight subscales and consists of a total of 36 questions. The subscales are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. A score of 0 is equivalent to maximum disability (poor quality of life), and a score of 100 is equivalent to no disability (good quality of life). Validity and reliability of a Turkish version of the SF-36 were demonstrated by Kocyigit et al[12].

Electrical sensory threshold and electrical pain threshold measurements were obtained using a Compex-3 electrical stimulator for all patients. During measurement, a rectangular current pulse with a pulse duration of 1 millisecond was used for electrical stimulation[13]. Measurements were obtained from the medial compartment of both knees using the first dorsal interosseous muscle of both hands as the control point. A passive 5 × 5 cm electrode and an active pen electrode were used for measurement. The strength of stimulation was gradually augmented until the patient reported sensation, and the lowest strength at which the patient reported sensation was recorded as the electrical sensory threshold (EST) in milliamperes (mA). Then, the current strength was increased, and the strength at which the patient reported pain was taken as the electrical pain threshold (EPT). Measurements were repeated three times at an interval of 20 minutes at each site, and averaged values were analyzed.

The Thicknesses of the medial femoral condyle, intercondylar, and lateral femoral condyle cartilages were measured in both knees using a Mindray DC-T6 US device (Mindray, Shenzhen, PR China) and a linear 5–10 MHz probe. Measurements were obtained in the supine position with the knee in maximal flexion. Video images of the cartilage thicknesses were recorded by the US device. Subsequently, recorded video images of all patients were interpreted by the same person, and cartilage thickness values were obtained. Measurements were repeated three times for both knees, and averaged cartilage thickness values (in millimeters) were analyzed.

Statistical analyses of study findings were performed using IBM SPSS Statistics for Windows version 19.0. For analysis of study data, descriptive statistical methods (mean, median, standard deviation, minimum-maximum) were used, as well as

Student's t-test for between-group comparisons of normally distributed quantitative data and the Mann-Whitney U test for between-group comparisons of non-normally distributed quantitative data. Correlations between painDETECT scores and other parameters were explored using Spearman's correlation analysis. Results were interpreted at a 95% confidence interval with the significance level set at $p<0.05$.

RESULTS

The mean (± SD) age of the 60 patients was 62.9 ± 10.5 years. Demographic data such as gender distribution and mean body mass index are shown in Table 1. Duration of symptoms ranged between 1 and 20 years. PainDETECT scores were 13 or greater in 28 patients and ranged between 0 and 28. The mean WOMAC, depression, and anxiety scores are presented in Table 1.

Correlation analyses conducted for all 60 patients with gonarthrosis showed that painDETECT scores were strongly positively correlated with VAS and WOMAC scores (p=0.000). However, painDETECT scores negatively correlated with sensory threshold and pain threshold measurements of the knees. Pain duration, radiological grade, and femoral cartilage thickness values did not show significant correlations (Table 2).

Patients were divided into two groups based on their painDETECT scores; patients with a score of 13 or greater were considered to have neuropathic pain, and those with a score of less than 13 were considered to have no neuropathic pain. Based on this classification, there were 28 (46.7%) patients in the neuropathic pain group and 32 (53.3%) patients in the non-neuropathic pain group. The two groups did not differ with respect to mean age, gender distribution, body mass index, and radiological grade (Table 3). The neuropathic pain group was found to have greater mean VAS, WOMAC, and depression, and anxiety scores compared with the non-neuropathic pain group. However, the neuropathic pain group had lower sensory and pain threshold values on average in both knees in comparison with the other group ($p<0.05$). Medial femoral, intercondylar, and lateral femoral cartilage thickness values did not differ between the two groups (Table 3).

Table 4 shows comparison of the two groups with regard to scores for the SF-36 quality of life scale. The neuropathic pain group had lower scores in physical functioning, bodily pain, general health perceptions, mental health, and physical component scores compared with the non-neuropathic pain group. No significant difference was found between the two groups in the scores for other SF-36 subscales (Table 4).

DISCUSSION

In contrast to nociceptive pain, neuropathic pain is characterized by burning, stabbing, and throbbing pain and cannot be treated adequately with conventional pain management modalities. A significant association was not found between the severity of radiological joint damage and disease symptoms in patients with osteoarthritis[14]. Thus, it was suggested that some mechanisms other than nociceptive mechanisms may be involved in pain formation in OA patients[2]. Studies have shown evidence of central pain sensitization in patients with knee osteoarthritis[2, 3].

PainDETECT scores of 13 or greater were demonstrated in only 8.6% of patients by Soni et al.[15] and 20.6% of patients by Ohtori et al[16]. Hochman et al. reported neuropathic symptoms in 34% of patients with knee osteoarthritis[17]. Moreton et

Table 1. Characteristics of the study participants

Characteristic (n=60)	Value
Age, years	62.9 ± 10.5
Gender	
Male	14 (23.3%)
Female	46 (76.7%)
BMI, kg/m^2	29.6 ± 4.9
Duration of symptom, years	4.5 (1–20)[a]
Pain (VAS)	6.1 ± 1.9
Paindetect score	11.7 ± 6.6
WOMAC total score	51.2 ± 19.4
Depression score	6.4 ± 3.6
Anxiety score	7.7 ± 4.6
Kellgren Lawrence grade	2 (2–4)[a]

[a]Median (minimum–maximum). BMI: body mass index; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 2. Relations between PainDETECT score and other parameters

	PainDETECT correlation coef.
Pain duration	0.014
VAS	0.541**
WOMAC	0.598**
K-L grade	0.030
FCT_{Medial}	−0.000
$FCT_{Intercondylar}$	−0.064
$FCT_{Lateral}$	−0.091
Knee ST	−0.415*
Knee PT	−0.312*

*p<0.05; **p<0.01. Coef.: coefficient; FCT: femoral cartilage thickness; K-L: Kellgren-Lawrence; ST: sensorial threshold; PT: pain threshold; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

al. detected NP in 30% of patients using several questionnaires[3]. Roubille et al. found that 25 out of 50 patients with knee osteoarthritis (50%) had painDETECT scores of 13 or greater[1]. These results are comparable to our findings.

There is still no gold standard method for diagnosis of neuropathic pain. NP questionnaires that are easy to administer are usually employed for this purpose. Means of quantitative sensory testing are available that examines pain threshold values obtained by application of heat, pressure, and electrical stimulation for assessment of central sensitization[13, 18–20]. According to Finan et al., PPT values are lower in patients with greater pain severity[2]. These results are consistent with our findings showing lower EST and EPT values in the knee region. There is no study available in literature that has used EPT for quantitative sensory testing in patients with knee osteoarthritis, so we could not directly compare our findings with any other study. Soni et al. showed that heat, pain, and mechanical pain sensitivity were associated with painDETECT scores[15] and Moreton et al. detected a correlation between lower PPT and higher painDETECT scores in patients with knee OA[3].

Our results showed that increased pain severity was associated with an increase in the neuropathic pain component. This finding is also consistent with literature data showing that increased pain severity correlates with higher neuropathic pain

Table 3. Comparison of patients with or without neuropathic pain

Characteristics	With neuropathic pain group (n=28)	Without neuropathic pain group (n=32)
Age, mean (SD), years	62.5 ± 9.6	63.3 ± 11.2
Gender (female), n (%)	21 (75%)	25 (78.1%)
BMI, mean (SD), kg/m^2	29.8 ± 4.6	29.4 ± 5.3
Duration of pain, mean (SD), years	5 (1–15)[a]	4 (1–20)[a]
Radiological grade, n (%)		
Grade 2	17	23
Grade 3	6	7
Grade 4	5	2
Pain (VAS), mean (SD)	7.1 ± 1.3	5.3 ± 1.9**
WOMAC, mean (SD)	63.7 ± 10.1	40.7 ± 18.7***
Depression score, mean (SD)	7.6 ± 3.8	5.3 ± 3.2*
Anxiety score, mean (SD)	9.5 ± 5.1	6.1 ± 3.7*
Knee ST, mean (SD), mA	11.8 ± 2.8	15.1 ± 5.1*
Knee PT, mean (SD), mA	25.6 ± 6.3	31.1 ± 8.8*
FCT_{Medial}, mean (SD), mm	1.7 ± 0.20	1.7 ± 0.16
$FCT_{Intercondylar}$, mean (SD), mm	1.9 ± 0.14	1.9 ± 0.19
$FCT_{Lateral}$, mean (SD), mm	2.0 ± 0.14	1.9 ± 0.18

[a]Median (minimum–maxsimum). *p<0.05; **p<0.01; ***p<0.001. BMI: body mass index; FCT: femoral cartilage thickness; mA: miliampere; mm: milimeter; PT: pain threshold; SD: standard deviation; ST: sensorial threshold; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 4. Comparison of SF-36 scores between groups

SF-36 subscale	With NP Median (min–max)	Without NP Median (min–max)
Physical functioning	20 (0–90)	40 (0–90)*
Role physical	0 (0–100)	25 (0–100)
Bodily pain	32 (10–74)	52 (31–84)**
Vitality	35 (10–80)	45 (10–100)
General health	55 (15–77)	67 (20–92)*
Social functioning	37.5 (12.5–100)	62.5 (12.5–100)
Role emotional	33.3 (0–100)	66.7 (0–100)
Mental health	60.0 (20–88)	72 (20–96)*
Physical component	28.5 (15.1–48.1)	36.9 (18.3–52.2)*
Mental component	41.5 (22.5–62)	50.3 (19.4–66)

*p<0.05; **p<0.01. NP: neuropathic pain; SF-36: Short Form-36

scores as assessed by questionnaires[1, 16, 17, 21]. Higher WOMAC scores observed in patients with neuropathic pain in our study are also consistent with the literature[1, 16, 17].

To the best of our knowledge, there is no study in the literature that has explored the association between neuropathic pain and femoral condylar cartilage thickness assessed by ultrasound. In a study by Roubille et al., no difference was found between patients with our without neuropathic pain with respect to cartilage volumes as detected by magnetic resonance imaging scans[1]. This finding is consistent with our results, which showed no association between femoral cartilage thickness and painDETECT scores. Our finding of no association between neuropathic pain and radiological OA severity was similar to the result of Ohtori et al[16].

In the current study, duration of symptoms and age were not correlated with neuropathic pain. Ohtori et al. also reported no association between painDETECT scores and age or duration of disease[16].

Based on our findings, quality of life decreases with increased neuropathic pain scores in patients with knee osteoarthritis. Hyperalgesia and poor quality of life were shown to be associated in patients with knee osteoarthritis[6]. There are other studies that have reported an association between higher painDETECT scores and decreased quality of life in patients with osteoarthritis[22]. The presence and severity of neuropathic pain are known to have an adverse effect on the quality of life in several conditions aside from rheumatic diseases[23]. While there are no studies that have adequately examined the association of neuropathic pain with mood in patients with knee osteoarthritis, it is well known that greater pain severity is associated with depressive symptoms[2, 24]. Our study found higher depression and anxiety scores among patients with neuropathic pain. The findings of Hochman et al., which showed an association between depression and neuropathic pain, support our result[21].

According to Nielsen et al., pain modulation is impaired in patients with knee osteoarthritis due to dysfunctional endogenous pain inhibiting mechanisms[25]. It has also been reported that peripheral nociceptors may be sensitized by, for example, an inflamed synovium and damaged subchondral bone and that chronic nociceptive stimulations may drive central sensitization and neuropathic pain[26].

In conclusion, in light of our findings and published literature data, there seems little doubt about the existence of a neuropathic component of the pain associated with knee osteoarthritis. Neuropathic pain appears to occur predominantly in patients with severe pain and reduced functional capacity and to be not associated with radiological grade, cartilage thickness, or disease duration. It is obvious that quality of life is impaired and mood is adversely affected in patients with neuropathic pain from knee OA. For this reason, treatment approaches focusing on the neuropathic pain component should not be overlooked while treating knee osteoarthritis.

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