# Investigation of knee pain in osteoarthritic and neuropathic pain awareness

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The mechanism of neuropathic pain (NP) and osteo-arthritic (OA) pain, although different, are both defined as chronic pain, and combinations are possible. In this study, the awareness of both types of chronic pain was investigated among patients and doctors. This prospective study was planned and coordinated by the orthopedic and internal medicine clinics and included 100 patients with a diagnosis of knee OA evaluated with the DN4 questionnaire. Patients with an OA diagnosis included those with NP linked to diabetes and those without NP, and these groups were compared using a visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritic Index (WOMAC). Data analysis of both groups focused on descriptive statistics of demographic and clinical characteristics. Twenty-four of the patients with type 2 diabetes mellitus (DM) were diagnosed with NP according to DN4 criteria, and began treatment. Of these patients, 21 (84%) had DM for 10 years or more, while 19 (86.4%) had HbA1c of 7 and above. The average WOMAC pain score for patients with NP was $4.33 \pm 1.2$ while the score for VAS was $8.25 \pm 0.8$. Patients without NP had a WOMAC pain score of $2.49 \pm 0.6$ and a VAS of $6.28 \pm 1.8$. It was observed that in these two knee OA patient groups, NP had a statistically significant enhancing effect on the WOMAC pain score and the VAS ($p < 0.001$). As underlying pathophysiological mechanism of pain caused by OA is complex, and OA is considered to have a component of NP, it has been proven to be useful to use drugs apart from conventional treatments for NP. We believe that, as a source of pain that is not relieved after arthroplasty, awareness level of NP among orthopedists should be increased and multi-disciplinary studies are required on this topic.

**Keywords** : knee osteoarthritis ; neuropathic pain ; diabetes.

## INTRODUCTION

Osteoarthritis (OA) is a chronic multifactorial disease characterized by progressive joint degeneration accompanied by subchondral bone sclerosis, which can lead to the formation of bone cysts and marginal osteophytes (7). Radiographic changes are important in knee OA. However, the impact of pain in OA is known to cause other biological and psychological factors. OA-related pain has been

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attributed to local tissue injury causing 'nociceptive pain' (*12*). However, cumulative data suggest that both neuropathic and nociceptive mechanisms may contribute to the OA pain experience (*3,8,10*). Pain sensitization involves amplification of neuronal activity that can occur at both a local and a generalized level, causing increased sensitivity to nociceptive input and reduced pain thresholds.

Chronic pain can be categorized as inflammatory or neuropathic. Inflammatory pain, found in conditions such as rheumatoid arthritis, is the result of sustained stimulation of nociceptors. In contrast, neuropathic pain (NP) is the result of damage to or dysfunction of, nerves. Principal causes of NP are diabetes, cervical or lumbar radiculopathies, and spinal cord injury (*9,24*).

In people with diabetes, the prevalence of chronic painful peripheral neuropathy in pain clinics ranges from 11% to 20% (*20*). It is more frequent in patients with diabetic neuropathy, which causes substantial morbidity and has a significant impact on the quality of life of patients (*25*).

Different pain mechanisms in OA may explain the variable responses to recommended pain therapies (*26*). A chronic inflammation and NP questionnaire was developed to recognize and identify the type of pain more easily (*16*). According to focus groups on pain experience in knee OA, one third of participants described their OA pain using characteristic NP identifiers (*15*). Using the characteristic NP symptom profile, NP questionnaires have been developed to help distinguish neuropathic from nociceptive pain (*4*). Bouhassira *et al* (*6*) developed a new questionnaire for the assessment of NP. The 10-item questionnaire developed in this study constitutes a new diagnostic instrument, which might be helpful both in clinical research and in daily practice (*6*).

The definition of chronic pain by the patient can be difficult and confusing. Thus, in patients with OA or NP, it can be overlooked by doctors. Among the major causes of NP, diabetes is the most common. Diabetes, in particular, may be ignored by the surgeon in patients with advanced-stage OA. In patients with OA of the knee in this study, we aimed to investigate the awareness of NP due to diabetes.

## SUBJECTS AND METHODS

The orthopedic and internal medicine clinics collaborated to determine whether DM patients at the internal medicine clinic had knee pain and whether they had received any treatment for this pain. All patients with OA at the orthopedic clinic were assessed by an orthopedist. Of 112 patients seen at the orthopedic clinic with an OA diagnosis, 100 patients above the age of 50 were included in the study. Patients with previous knee surgery, those with a neuropathy diagnosis for other reasons than diabetes, patients with infection or patients with OA due to rheumatoid arthritis were excluded from the study.

The study was prospectively planned, and was approved by the local Research Ethics Committee. Decision of 10.12.2014 date, 050.99-231 number received ethics committee approval.

### Questionnaire form

Patients were asked questions from the prepared questionnaire and then examined with a form completed by the orthopedist. The form included demographic characteristics along with previous knee surgery, additional diseases, whether the patient had diabetes and its duration, and medications used. Body mass index (BMI) was calculated. Patients with diabetes were divided into groups based on those with illness duration of more than 10 years or less than 10 years, and HbA1c values above or below 7 mg/dl. In terms of medications used, patients were divided into three groups : those using non-steroidal anti-inflammatory drugs (NSAIDs), insulin, or oral anti-diabetics (OAD). The aim was to compare patients with a diagnosis of OA in two groups, those with NP linked to diabetes and those without NP. For the assessment, the criteria listed below were used.

### Diagnosis and classification

The patients' diagnoses and classifications were determined according to the clinical criteria developed by the American College of Rheumatology (ACR) (*1*), which are as follows :

1. Age > 50 years.
2. Knee pain for most days of the prior month.
3. Morning stiffness of the knee for < 30 minutes.
4. Crepitus on active joint motion.
5. Bony enlargement.
6. Bony tenderness.

OA of the knee was considered to be present when the combinations of 1, 2, 3, and 4 ; 1, 2, and 6 ; or 2, 4, and 6 were found.

### Radiographic evaluation

The severity of knee OA was determined by a specialized orthopedist according to radiologic evaluation of the knees using the criteria of Kellgren and Lawrence (K & L) (*17*). Radiographic classification of knee OA severity was based on the K & L scale with patients having a score of 2 classified as mild knee OA, a score of 3 classified as moderate knee OA, and a score of 4 classified as severe knee OA.

### Osteoarthritis pain scores

The severity of pain was measured using the visual analogue scale (VAS) for knee pain. The intensity of current levels of pain was assessed with the VAS using a 10-cm horizontal line. In addition, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire was used. The WOMAC questionnaire consists of subsections for pain, stiffness, and physical function. We used only the WOMAC pain score, and removed stiffness and physical function to save time while administering the questionnaire.

### Evaluation of neuropathic pain

A neuropathy diagnosis for diabetic patients was made according to the NP diagnostic questionnaire (DN4) and sensory examination. The DN4 test determines the existence of a burning feeling in the feet, a painful feeling of cold, a feeling of electricity or tingling with pain, pins and needles, lack of feeling accompanied by itching, localized touch hypoesthesia, needle hypoesthesia, and brushing causing or increasing pain in the painful area. DN4 scores of 4 or above indicate a diagnosis of NP. If the patient's score was $\geq 4$, the test was positive (sensitivity 82.9% ; specificity 89.9%).

## RESULTS

A total of 112 patients with knee OA were found to be eligible to participate in the study. Twelve patients were excluded due to the exclusion criteria of the study. One hundred patients were evaluated and included in the study.

Of the 100 knee OA patients in the study (66 male, 34 female) 54 (54.0%) had type 2 diabetes mellitus (DM). Of the patients with DM, 24 had NP according to the DN4 criteria, and began treatment. Of the patients with NP, 21 (87.5%) had DM for 10 years or more and 19 (79.2%) had HbA1c of 7 and above. Of those with NP, 20 used insulin (83.3%), 18 used OAD (40.8%), and only 6 used NSAIDs (25.0%). It is worth noting that of the patients without NP, 26 (86.7%) had DM for less than 10 years and 27 (90.0%) had HbA1c of below 7. Additionally in this patient group, there were 48 (63.2%) patients using NSAIDs regularly, as summarized in Table I.

The mean (SD) age of patients with NP was 64 (6.5) years while the mean (SD) age without NP was 63 (9) years. Other demographic data are shown in Table II. In both patient groups, the WOMAC pain score and VAS scores were investigated. The mean (SD) WOMAC pain score for patients with NP was 4.33 (1.2) while the VAS was 8.25 (0.8). Patients without NP had a WOMAC pain score of 2.49 (0.6) and a VAS of 6.28 (1.8). It was observed that in these two knee OA patient groups, NP had a statistically significant enhancing effect on the WOMAC pain score and VAS ($p < 0.001$) (Table II).

The patients with and without NP were investigated using the K & L radiological OA staging. Patients without NP were mainly Stage 1 and 2, while those with NP were mainly Stage 2 and 3 OA patients (Fig. 1). There was a statistical difference found for this comparison ($p < 0.001$). However, as there were insufficient patient numbers in the groups, only the VAS and WOMAC scores of patients in Stage 2 with and without NP were compared, and the statistical difference was found to be significant ($p < 0.001$). The VAS and WOMAC pain scores of those with NP were higher. In terms of obesity, there was no statistically significant difference observed ($p = 0.101$) (Table III).

A strong positive correlation was found between WOMAC pain score and VAS score ($p < 0.001$, $r = 0.528$). A weak positive correlation was found between WOMAC score and age ($p = 0.022$, $r = 0.229$). A weak positive correlation was found between VAS score and age ($p = 0.018$, $r = 0.236$) (Fig. 2).

Table I. — Characteristics of patients.

| | Neuropathic pain + n = 24 (%) | Neuropathic pain – n = 76 (%) | p |
|---|---|---|---|
| | n (%) | n (%) | |
| Gender Male | 17 (70.8) | 49 (64.5) | 0.566 |
| Gender Female | 7 (29.2) | 27 (35.5) | |
| DM 10 – year | 3 (12.5) | 26 (86.7) | |
| DM 10 + year | 21 (87.5) | 4 (13.3) | < 0.001 |
| HbA1c 7 < | 5 (20.8) | 27 (90.0) | |
| HbA1c 7 ≥ | 19 (79.2) | 3 (10.0) | < 0.001 |
| NSAID | 6 (25.0) | 48 (63.2) | < 0.001 |
| OAD | 18 (40.8) | 31 (75.0) | 0.003 |
| Insulin | 20 (83.3) | 5 (6.6) | < 0.001 |
| KL grade 1 | 6 (7.9) | 7 (29.2) | < 0.001 |
| 2 | 23 (30.3) | 16 (66.7) | |
| 3 | 36 (47.4) | 1 (4.2) | |
| 4 | 11 (14.5) | 0 (0.0) | |

KL, Kellgren-Lawrence. % : percentage column.

## STATISTICAL ANALYSIS

Analysis of obtained data was completed using SPSS version 17.0 software. A value of p < 0.05 was accepted as statistically significant. Descriptive data are presented as mean, standard deviation, frequency, and percentage values. After investigation with the Kolmogorov-Smirnov test to determine normal distribution of data, the Mann-Whitney U test was used for non-parametric analysis. Parametric tests were completed using the independent samples t-test. For univariate analyses of dependent and independent variables, the chi-square test was used. Correlations between continuous variables in the patient groups were investigated with Spearman's correlation test.

## DISCUSSION

Pain caused by OA has also a NP component, therefore apart from traditional therapies, drugs for treating NP have been used and have been shown to have greater benefits than classic treatments (*19,21*). In this study, we investigated the effect of diabetic polyneuropathy seen in around 50% of DM patients and NP seen in 7.5%-24% of these 50% (*27*) on pain

Table II. — Distribution of demographic characteristics according to the incidence of neuropathy

| | NP – (n = 76) | NP + (n = 24) | P value | NP+/– Total |
|---|---|---|---|---|
| | mean ± SD | mean ± SD | | mean ± SD |
| Age in years (SD) | 63 ± 8.9 | 64 ± 6.3 | 0.386* | 63.4 ± 8.4 |
| Height in cm (SD) | 162.3 ± 7.2 | 161.6 ± 7.4 | 0.682 | 162.2 ± 7.2 |
| Body Mass Index (kg/$m2$) (SD) | 28.9 ± 5.5 | 29.9 ± 4.4 | 0.181 | 29.1 ± 5.3 |
| Weight in kg (SD) | 77 ± 14.5 | 78 ± 11,7 | 0.716 | 77.7 ± 13.8 |
| WOMAC pain score | 2.49 ± 0.6 | 4.33 ± 1.2 | < 0.001 | 2.93 ± 1.1 |
| VAS | 6.28 ± 1.8 | 8.25 ± 0.8 | < 0.001 | 6.75 ± 1.8 |

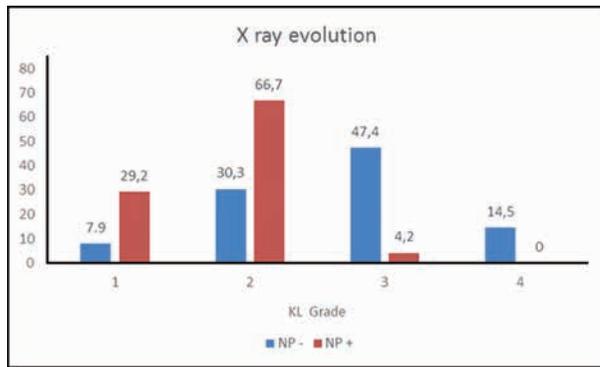SD : standard deviation ; *: t test ; P : Mann-Whitney U test.

**Fig. 1.** — Percentage distribution of radiographic severity of KOA, according to neuropathic pain.

scores of the patients with symptomatic knee OA. In this way, we attempted to understand whether or not the NP component, left unaffected by treatment of OA patients, really affects pain scores. At the same time, we wished to assess the awareness levels of physicians about possible NP in patients with symptomatic knee OA.

As there is no relation between the degree of radiographic damage and severity of pain in symptomatic knee OA, it is thought that other factors affect the severity of pain. OA pain is probably caused by two components : a nociceptive and a neuropathic component (22). It is thought that 34% of patients with knee OA have NP ; however, the mechanism of NP in OA is not fully understood (15). A positive relationship has been found in patients with symptomatic knee OA, between the presence of NP and the severity of OA symptoms (22). In our study, we found that the WOMAC and VAS pain scores of patients with symptomatic knee OA and diabetic NP were higher. The patients with NP included in our study were considered to only have NP linked to diabetic neuropathy. The increase in pain scores of

NP linked to diabetes supports the idea that the NP component of pain in OA increases the severity of pain.

Though there are many conventional and interventional treatment approaches for OA, the major clinical problem of the disease is that pain control may be suboptimal. The reason for this is that the underlying pathophysiological mechanism of pain in OA is complex (11). In addition to the limited effect of treatment results with analgesic medications, worries about the safety of some medications may lead to insufficient treatment. In spite of these worrying side effects, insufficient pain control leads to patients consuming more NSAIDs ; however, the increased dose increases the incidence of side effects (22). As a result, apart from traditional treatment methods, drugs used for NP treatment have begun to be used for OA pain control. The effectiveness of duloxetine on pain due to symptomatic knee OA has been proven alone (14) and combined with NSAIDs (13). The combination of pregabalin and meloxicam has been shown to be more effective on WOMAC and VAS pain scores than treatment with either meloxicam or pregabalin alone. As a result of the benefits of medications used for NP treatment for pain linked to OA, it is thought that OA pain is a combination of inflammation and neuropathic pain (19).

As observed recently, the formation mechanism of OA pain is not linked to inflammation alone, but the consideration that it has a neurogenic component has gained acceptance. At this point, there is no doubt that OA patients should be evaluated for NP, and if necessary, treatment with medications used for NP treatment should be attempted. In our study, we assessed the situation of diabetic OA patients with NP, along with OA patients without NP. None of the diabetic patients with NP were using NP

Table III. — Percentage distribution of BMI according to neuropathic pain

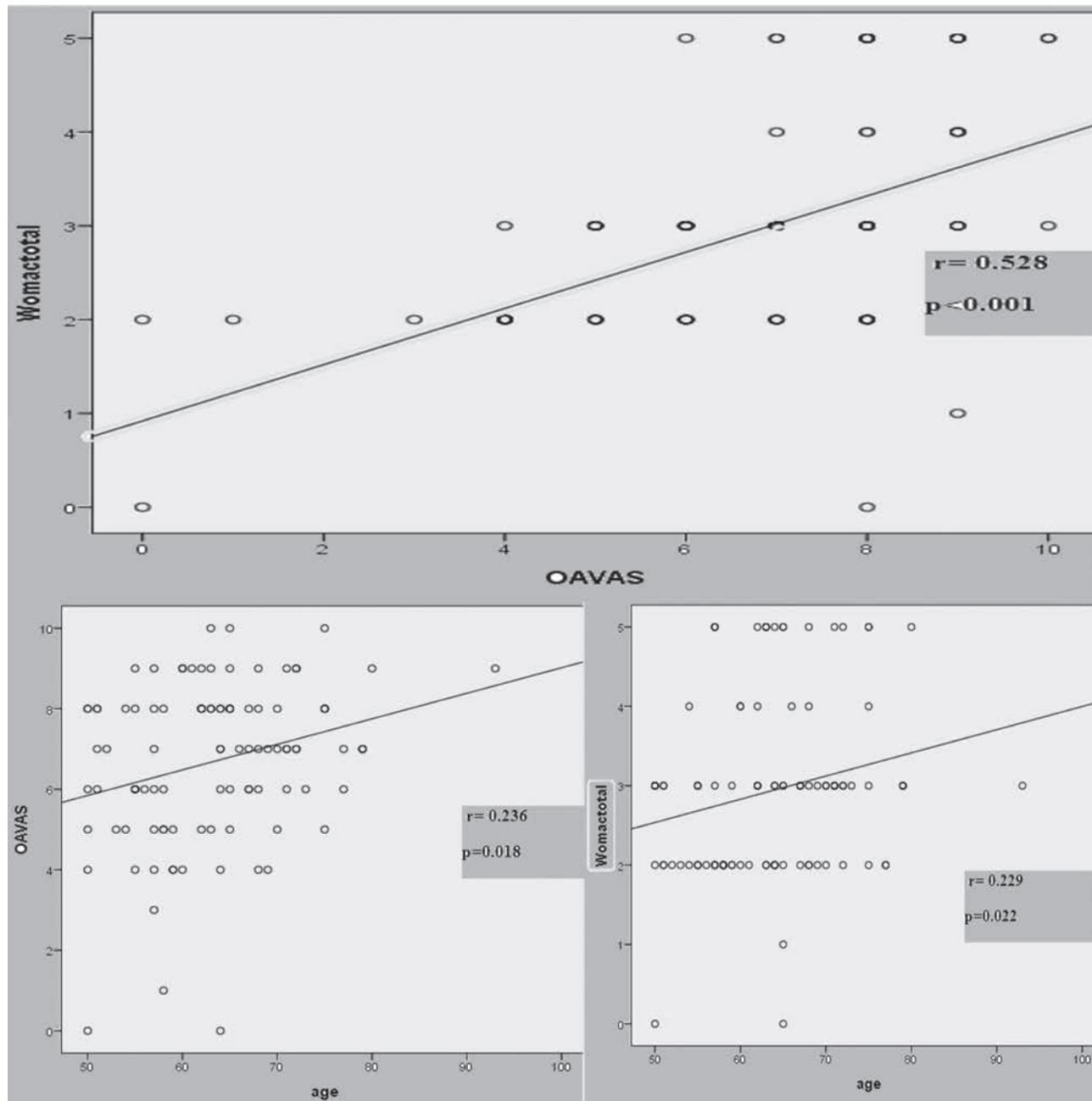| According to BMI | NP – n (%) | NP + n (%) | p |
|---|---|---|---|
| Normal | 52 (68.4) | 12 (50.0) | 0.101 |
| Obese | 24 (31.6) | 12 (50.0) | |

p : Chi-square test    % : percentage column.

*Fig. 2.* — A strong positive correlation was found between WOMAC pain score and VAS score (p < 0.001, r = 0.528). A weak positive correlation was found between WOMAC score and age (p = 0.022, r = 0.229). A weak positive correlation was found between VAS score and age (p = 0.018, r = 0.236).

treatments. In our study, the NP patients were first diagnosed with diabetic NP and were not treated. Assessing the patient groups with and without NP in terms of radiology, there was no clear difference between the groups ; in fact, the NP group had more

patients in Stage 2 according to the K & L scale than in Stage 3. However, the WOMAC and VAS pain scores linked to OA in the patients with NP were higher compared to the group without NP. Our results show, in parallel to previous studies, that

Table IV. — WOMAC pain score and VAS scores in osteoarthritis patients, examining the relationship between age, weight and BMI

| Womac | Vas | age | weight | BMI |
|-------|-----|-----|--------|-----|
| r | 0.528 | 0.229 | -0.100 | 0.059 |
| p | *< 0.001* | *0.022* | 0.322 | 0.0563 |
| Vas | | | | |
| r | | 0.236 | 0.047 | 0.155 |
| p | | *0.018* | 0.639 | 0.123 |

p : Spearman's correlation ; r : correlation coefficient.

NP increases the WOMAC and VAS pain scores in OA.

Late-stage complications of diabetes include diabetic polyneuropathy, lower quality of life, shortened life expectancy, and increased treatment-spending linked to diabetes (*18*). Sleep disorders may develop in patients with NP linked to diabetes. The loss of energy due to lack of sleep may reduce functioning in daily life due to depression and anxiety, and the individual may become more dependent on others (*5*). If NP is not treated, the dependence on others for daily life activities may increase. In addition, OA is one of the main causes of loss of function and disability among adults in Western countries (*2*). As observed among our patients, those with NP were not receiving any treatment. In other words, as a result of lack of appropriate treatment for NP among these patients, they experienced the limitations of both OA and NP on daily life activities. We consider that the pain due to OA was focused on in these patients, with treatments planned and carried out, but NP was ignored. At the same time, as with patients in our study, they complained that severity of pain was greater. This situation leads to patients who are not sufficiently satisfied with OA treatment. Medical and/or surgical treatment choices made and carried out without paying attention to NP will result in dissatisfaction. It may be that the major source of knee pain that does not resolve after arthroplasty by orthopedists is due to lack of attention to NP.

When diabetic patients with NP are compared to those without NP, there is a greater increase in economic load. Among the reasons for this are greater use of prescription and non-prescription medica-tion, as well as frequent doctor visits, leading to an indirect effect on economic load and loss of labor (*23*). Limitations of our study include the fact that we did not assess the economic load caused by NP, other parameters of the WOMAC score, or the pain scores after treatment. As our patients were mainly of advanced age, insufficient treatment would not have caused loss of labor ; however, the limitations of daily life and dependence on others would have increased the economic load.

We did not find any study assessing the level of awareness or level of attention given by physicians to NP in painful situations like OA. Our findings lead us to consider that the awareness of NP in orthopedic clinics is low. In fact, this problem may be widespread in developing countries such as our own. Concepts such as quality in health services are newly emerging and as the patient numbers attending clinics are high, sufficient anamnesis is not obtained.

In conclusion, according to the data obtained in our study, there is a need to increase awareness of NP among orthopedists and for multidisciplinary studies on this medical topic.

## REFERENCES

1. **Altman R, Asch E, Bloch D** *et al.* Development of criteria for the classification and reporting of osteoarthritis : classification of osteoarthritis of the knee. *Arthritis Rheum* 1986 ; 29 : 1039-1049.
2. **Arden N, Nevitt MC.** Osteoarthritis : epidemiology. *Best Pract Res Clin Rheumatol* 2006 ; 20 : 3-25.
3. **Bajaj P, Bajaj P, Graven-Nielsen T, Arendt-Nielsen L.** Osteoarthritis and its association with muscle hyperalgesia : an experimental controlled study. *Pain* 2001 ; 93 : 107-114.

4. **Bennett MI, Attal N, Backonja MM** *et al.* Using screening tools to identify neuropathic pain. *Pain* 2007 ; 127 : 199-203.

5. **Benbow S, Wallymahmed M, MacFarlane I.** Diabetic peripheral neuropathy and quality of life. *Qjm* 1998 ; 91 : 733-737

6. **Bouhassira D, Attal N, Alchaar H** *et al.* Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005 ; 114 : 29-36.

7. **Buckwalter JA, Lane NE.** Athletics and osteoarthritis. *Am J Sports Med* 1997 ; 25 : 873-881.

8. **Coderre TJ, Katz J, Vaccarino AL, Melzack R.** Contribution of central neuroplasticity to pathological pain : review of clinical and experimental evidence. *Pain* 1993 ; 52 : 259-285.

9. **Daousi C, MacFarlane IA, Woodward A** *et al.* Chronic painful peripheral neuropathy in an urban community : a controlled comparison of people with and without diabetes. *Diabet Med* 2004 ; 21 : 976-982.

10. **Dieppe PA, Ayis S, Clarke S** *et al.* 471 Quantitative sensory testing in osteoarthritis of the knee. *Osteoarthritis Cartilage* 2008 ; 16 : S204.

11. **Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH.** Neuropathic pain in osteoarthritis : A review of pathophysiological mechanisms and implications for treatment. *Semin Arthritis Rheum* 2014 ; 44 : 145-154.

12. **Felson DT.** The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* 2005 ; 17 : 624-628.

13. **Frakes E, Risser R, Ball T, Hochberg M, Wohlreich M.** Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis : results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin* 2011 ; 27 : 2361-2372.

14. **Hochberg MC, Wohlreich M, Gaynor P, Hanna S, Risser R.** Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. *J Rheumatol* 2012 ; 39 : 352-358.

15. **Hochman JR, French MR, Bermingham SL, Hawker GA.** The nerve of osteoarthritis pain. *Arthritis Care Res* 2010 ; 62 : 1019-1023.

16. **Jensen TS, Baron R, Haanpää M** *et al.* A new definition of neuropathic pain. *Pain* 2011 ; 152 : 2204-2205.

17. **Kellgren J, Lawrence J.** *Atlas of Standard Radiographs : The Epidemiology of Chronic Rheumatism*. vol. 2, Blackwell Scientific, Oxford, 1963.

18. **McCarberg B, Billington R.** Consequences of neuropathic pain : quality-of-life issues and associated costs. *Am J Manag Care* 2006 ; 12 : 263-268.

19. **Ohtori S, Inoue G, Orita S** *et al.* Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. *Yonsei Med J* 2013 ; 54 : 1253-1258.

20. **Partanen J, Niskanen L, Lehtinen J** *et al.* Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995 ; 333 : 89-94.

21. **Pergolizzi JV, Raffa RB, Taylor R** *et al.* A Review of Duloxetine 60 mg Once-Daily Dosing for the Management of Diabetic Peripheral Neuropathic Pain, Fibromyalgia, and Chronic Musculoskeletal Pain Due to Chronic Osteoarthritis Pain and Low Back Pain. *Pain Pract* 2013 ; 13 : 239-252.

22. **Roubille C, Raynauld JP, Abram F** *et al.* The presence of meniscal lesions is a strong predictor of neuropathic pain in symptomatic knee osteoarthritis : a cross-sectional pilot study. *Arthritis Res Ther* 2014 ; 16 : 507.

23. **Schaefer C, Sadosky A, Mann R** *et al.* Pain severity and the economic burden of neuropathic pain in the United states : BEaT neuropathic Pain Observational study. *Clinicoecon Outcomes Res* 2014 ; 6 : 483-496.

24. **Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ.** A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* 2003 ; 103 : 249-257.

25. **Vinik A, Ullal J, Parson HK, Casellini CM.** Diabetic neuropathies : clinical manifestations and current treatment options. *Nat Clin Pract Endocrinol Metab* 2006 ; 2 : 269-281.

26. **Zhang W, Moskowitz RW, Nuki G** *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II : OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008 ; 16 : 137-162.

27. **Zilliox L, Russell JW.** Treatment of diabetic sensory polyneuropathy. *Curr Treat Options Neurol* 2011 ; 13 (2) : 143-159.