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Neuropathic pain in primary knee osteoarthritis patients: correlation with physical function, quality of life, disease severity, and serum beta nerve growth factor levels

Shereen R. Kamel^{1,2*} , Radwa S. Ibrahim¹, Hend M. Moens³ and Rania M. Mohammed¹

Abstract

Background: Neuropathic mechanisms are thought to play a role in knee osteoarthritis (KOA) pain. Neuropathic pain questionnaires can promote diagnosis of a neuropathic component. Thus, we aimed to assess the frequency of neuropathic pain in primary KOA patients (using clinical questionnaires) and to investigate its correlation with socio-demographic factors, physical function, quality of life, disease severity, and serum beta nerve growth factor (β -NGF) levels.

Results: Seventy primary KOA patients were included. Neuropathic pain was detected in 52.9% of patients based on Douleur Neuropathique en 4 Questions (DN4) questionnaire and in 38.6% of patients based on Leeds assessment neuropathic pain symptoms and signs questionnaire (LANSS). Serum β -NGF levels were significantly higher in KOA patients than controls ($P < 0.0001$), and in KOA patients with neuropathic pain compared with patients with non-neuropathic pain. DN4 score was positively correlated with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and physical function, and it was also negatively correlated with Osteoarthritis knee hip quality of life questionnaire (OAKHQOL) pain scores ($r_s = 0.459$, $P < 0.001$; $r_s = 0.258$, $P = 0.031$; $r_s = 0.307$, $P = 0.010$; $r_s = -0.337$, $P = 0.004$, respectively), while LANSS scale was positively correlated with symptom duration, WOMAC stiffness, Lequesne pain, and Lequesne index ($r_s = 0.260$, $P = 0.020$; $r_s = 0.343$, $P = 0.004$; $r_s = 0.344$, $P = 0.004$; $r_s = 0.322$, $P = 0.007$) and negatively correlated with OAKHQOL physical, OAKHQOL mental health, OAKHQOL social support, and total OAKHQOL scores ($r_s = -0.258$, $P = 0.031$; $r_s = -0.254$, $P = 0.034$; $r_s = -0.283$, $P = 0.018$; $r_s = -0.261$, $P = 0.029$ respectively).

Conclusions: Neuropathic pain symptoms are frequent in primary KOA patients. KOA patients with neuropathic pain have worse quality of life, extreme disability, and higher serum β -NGF levels. Nerve growth factor inhibitors could have a potential role for not only relieving pain in KOA patients but also improving functional disability and quality of life in these patients.

Keywords: Neuropathic pain, Knee osteoarthritis, (DN4) questionnaire, (LANSS) questionnaire, Serum β -NGF

* Correspondence: shereen.refaat@mu.edu.eg

¹Rheumatology and Rehabilitation Department, Faculty of Medicine, Minia University, Minia, Egypt

²Minia University Hospital, Minia, Egypt

Full list of author information is available at the end of the article



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Background

Osteoarthritis (OA) is a multifactorial disease, involving multiple causative factors as aging, trauma, bio-mechanical loading, inflammation, and metabolic disturbances [1, 2]. It is classified into two groups according to its etiology: primary (idiopathic or non-traumatic) and secondary (usually due to trauma or mechanical misalignment or other articular disease). The disease is more common in middle-aged and older people over the age of 50. The prevalence of knee osteoarthritis (KOA) among female patients is higher than that of male patients, and the prevalence rate of individuals aged over 65 years is 68% [3].

Pain and local tenderness or pressure hyperalgesia around the affected joint are frequently manifested in OA [4]. OA pain mechanisms are complex; both peripheral and central processes are involved in creating the OA pain [5].

People with KOA may present with different pain phenotypes, nociceptive, inflammatory, and neuropathic pains [5, 6]. Neuropathic component of OA pain, possibly emerging from peripheral and central pain sensitization mechanisms [7]. Recognizing specific aspects of joint pathology that contribute to different OA pain phenotypes might help identify pain phenotype specific peripheral treatment targets [8].

Several screening tools were used to differentiate neuropathic pain from non-neuropathic pain [9]. All screening tools have self-assessment questions. However, sensory examination is present in Leeds assessment of neuropathic pain symptoms and signs (LANSS) and Douleur Neuropathique 4 questions (DN4) questionnaires, which give them an objective significance and crucial findings for the diagnosis of neuropathic pain, among all the others [10].

Nerve growth factor (NGF) is a key mediator of acute and chronic pain. Different biological actions of NGF contribute to its pro-analgesic effects, including NGF-induced sensitization of peripheral nociceptive terminals and NGF-induced sprouting of sensory nerves [11]. Nerve growth factor binds tropomyosin receptor kinase A (TrkA) that is expressed in many sensory and sympathetic fibers and regulates survival of these neurons [12]. Elevated NGF levels are seen in individuals with chronic pain conditions [13], and intradermal or intramuscular injection of NGF causes allodynia and hyperalgesia in healthy subjects [14, 15].

The purpose of this study was to determine the frequency of neuropathic pain in patients with primary KOA (using the DN4 and LANSS questionnaires) and to investigate its correlation with socio-demographic factors, physical function, quality of life, and disease severity. Despite the fact that serum-NGF levels are increased in KOA patients, their probable links to neuropathic

pain have never been investigated. Therefore, we aimed to assess serum β -NGF levels in KOA patients with neuropathic pain versus patients with non-neuropathic pain.

Methods

Study design and population

This study used an analytical cross-sectional design. Seventy patients (43 females and 27 males) with primary KOA who met ACR clinical and radiographic diagnostic criteria for primary KOA [16] were consecutively included. All patients were attending the Rheumatology and Rehabilitation outpatient clinic, Minia University Hospital, Minia governorate, Egypt—in the period from December 2018 to March 2019. All patients had knee pain for more than 3 months. The control population consisted of 21 (13 females/8 males) age-, sex-, and body mass index (BMI)-matched healthy volunteers (who are healthcare workers at the Main Hospital/for assessment of serum β -NGF levels) without any sign or disease suggestive of OA, gout, rheumatoid arthritis, trauma, diabetes, and other orthopedic disorders like tendinitis, bursitis, and knee ligament injuries. Written informed consent was taken from all participants in the study. The study was approved by the ethics committee of the Faculty of Medicine. We had to enlist the help of research assistants who met with each illiterate patient and read out the questions in a way that they could understand, without necessarily affecting their responses.

Excluded from the study are patients with any previous history of knee surgery, history of steroid injections over the past 3 months, trauma, infection, known inflammatory arthritis such as rheumatoid arthritis, gout and other pain/neurological conditions such as radiculopathies, diabetes mellitus, stroke, and traumatic brain injury and patients who were already receiving medical treatment for neuropathic pain.

Clinical assessment

Anthropometrics

Height was measured to the nearest 0.1cm, weight was measured in the upright position to the nearest 0.1 kg, and BMI is calculated as weight in kilograms divided by the square of height in meters.

Visual analogue scale

Visual analogue scale (VAS) is a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they represented their perception of their current state. A higher score indicates greater pain intensity [17].

Western Ontario and McMaster University (WOMAC) Osteoarthritis Index

The WOMAC is a valid and reliable instrument used for the assessment of OA of the lower extremities [18]. It consists of 24 items divided into 3 subscales. The pain scale includes five items asking about pain at activity or rest. The stiffness scale includes two questions. The function dimension explores the degree of difficulty in daily activities. The scores are summed for items in each subscale, with possible ranges as follows: pain=0–20, stiffness=0–8, physical function=0–68, and total WOMAC score is created by summing the items for all three subscales (0–96).

Lequesne index

Lequesne index was used to evaluate severity for knee disease. It is eleven-question survey, five questions pertaining to pain or discomfort, two questions dealing with maximum distance walked, and four questions about activities of daily living. The total questionnaire is scored on a 0 to 24 scale. Lower scores indicate there is less functional impairment [19].

Osteoarthritis knee hip quality of life questionnaire (OAKHQOL)

The patient's health-related quality of life was assessed using the OAKHQOL questionnaire, including 43 items in five main domains: physical activities (16 items), mental health (13 items), pain (4 items), social support (4 items), social functioning (3 items), and three independent items; each item is scored on a scale from 0 to 10, and the normalized scores were obtained by computing the sum of item scores for each domain and calculated to a scale from 0 (worst) to 100 (best) [20]. We had to enlist the help of research assistants who met with each illiterate patient and read out the questions in a way that they could understand, without necessarily affecting their responses.

Evaluation of neuropathic pain

Detailed history taking, neurological examination, and two standardized screening tools were performed on all KOA patients. Screening tools were used for the purpose of distinguishing neuropathic pain from non-neuropathic pain.

Douleur Neuropathique 4 questions (DN4 questionnaire)

It was developed and validated in French and translated into 15 languages. It consists of 10 items that are either answered as YES or NO. Seven of these items assess pain quality, while the other 3 items detect the presence or absence of sensory allodynia and touch needle hypoesthesia based on clinical examination. Each item answered as "yes" yields 1 point, and a total score at or

above 4/10 is evaluated as positive [21]. Arabic version of DN4 questionnaire was used [22].

Leeds assessment of neuropathic pain symptoms and signs (LANSS scale)

The LANSS scale is a valid tool used for discriminating between neuropathic and nociceptive pain. It contains 5 symptom items and 2 clinical examination items, score ≥ 12 suggest likely neuropathic pain [23]. Arabic version of LANSS scale was used in the present study [24].

Radiological evaluation

Grading of knee OA severity was performed using the Kellgren–Lawrence (KL) grading scale. The radiological severity was categorized into four grades as follows: very mild (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4) [25].

ELISA for serum β -NGF

Five millimeters of venous blood was withdrawn, collected in serum separator tubes, and allowed to clot for 10–20 min at room temperature. Centrifuge at 2000–3000 RPM for 20 min and stored at -80°C for later use. Serum β -NGF levels were measured for patients and healthy controls using an enzyme-linked immunosorbent assay (ELISA) kit (SHANGHAI CRYSTAL DAY BIOTECH CO., LTD, China). Construct a standard curve by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and draw a best fit curve through the points on the graph. These calculations can be best performed with computer-based curve-fitting software and the best fit line can be determined by regression analysis.

Statistical analysis

The statistical analysis was performed using SPSS 22.0. Descriptive statistics were done by number and percent as well as mean and SD. Statistical differences between groups were tested using chi-square (χ^2) test for qualitative variables and independent sample *t*-test for quantitative normally distributed variables. Correlations were calculated using Spearman's correlation coefficient. Linear regression analysis was used to predict the risk factors for neuropathic pain in primary KOA patients. The level of statistical significance was set at a $P \leq 0.05$.

Results

Sociodemographic data of the studied population are shown in Table 1. Nineteen patients (27.1%) had knee effusion, 12 (17.1%) had limited range of motion, and 9 (12.9%) had joint deformity. Treatment included non-steroidal anti-inflammatory drugs (NSAIDs) in 58 (82.9%) patients and chondroprotective agents (polysulfated glycosaminoglycans) in 30 (42.9%) patients. Thirty-

Table 1 Sociodemographic data of the studied population

	KOA patients (n=70)	Healthy control (n = 21)
Sex, female/male	47/23	13/8
Age (years)	53.39±8.004 (32–68)	51.19 ± 9.4 (31–70)
BMI (kg/m²)	25.71±4.286 (18.75–35.9)	24.15± 3.12 (19.2–30)
Symptom duration (month)	14.91±2.78 (4–180)	NA
Educational level		
Primary school	35 (50%)	NA
Illiterate	30 (42.9%)	
Secondary school	4 (5.7%)	
University	1 (1.4%)	
Residence		
Rural	65 (92.9%)	NA
Urban	5 (7.1%)	

Values are labeled as mean ± SD (range) or n. KOA knee osteoarthritis, BMI body mass index, NA not applicable. No statistically significant differences between groups ($P > 0.05$)

six patients (51.4%) were having mild OA, i.e., KL Grade II, whereas the rest were moderate to severe OA [28 (40%) were having Grade III and 6 (8.6%) were having Grade IV].

Patients who had scores ≥ 4 from the DN4 questionnaire and scores ≥ 12 from the LANSS scale were accepted to have neuropathic pain. According to this, neuropathic pain was detected in 37 patients (52.9%) based on the DN4 questionnaire and in 27 patients (38.6%) based on the LANSS scale. DN4

scale ranged between 2 and 8 with a mean of 4.39 ± 1.51 while LANSS score ranged between 9 and 19 with a mean of 12.2 ± 3.03 .

The frequency of responses for individual items of DN4 questionnaire and LANSS questionnaire among OA patients is shown in Tables 2 and 3.

Comparison of WOMAC scores, Lequesne scores, Kellgren-Lawrence scale, and normalized OAHKOQL scores between patients with neuropathic pain and those with non-neuropathic pain is shown in Tables 4 and 5.

The mean serum β NGF levels were significantly higher in KOA patients than control: 590.7 ± 244.83 pg/ml versus 27.52 ± 6.87 pg/ml respectively, $P < 0.0001$. Moreover, the mean serum β NGF levels were significantly higher in patients with neuropathic pain than patients with non-neuropathic pain as shown in Table 5.

The correlations of neuropathic pain scores with all of the studied parameters are shown in Table 6.

Linear regression analysis was employed to analyze the risk factors for neuropathic pain in primary knee OA. According to DN4 score, higher WOMAC pain, higher WOMAC physical function, higher total WOMAC, and higher β NGF were significant risk factors ($P < 0.001$, $P < 0.001$, $P = 0.002$, $P = 0.039$ respectively). While according to LANSS score, longer symptom duration, higher WOMAC stiffness, higher Lequesne pain, lower social support OAKHQOL, lower total OAKHQOL, and higher serum β NGF level were significant risk factors for neuropathic pain ($P = 0.026$, $P < 0.001$, $P = 0.048$, $P = 0.019$, $P = 0.036$, $P < 0.001$ respectively).

Table 2 Frequency of responses for individual items of DN4 questionnaire among OA patients

	OA patients (n=70)		t	P
	Patients with neuropathic pain (n=37)	Patients with non-neuropathic pain (n=33)		
Does the pain have one or more of the following characteristics?				
Burning	23 (32.86%)	9 (12.9%)	8.556	0.003*
Painful cold	25 (35.7%)	9 (12.9%)	11.338	<0.001*
Electric shocks	34 (48.7%)	14 (20%)	19.806	<0.001*
Is pain associated with one or more of the following in the same area?				
Tingling	16 (22.9%)	8 (11.4%)	2.795	0.095
Pins and needles	31 (44.3%)	11 (15.7%)	18.498	<0.001*
Numbness	21 (30%)	4 (5.7%)	15.136	<0.001*
Itching	16 (22.9%)	11 (15.7%)	0.723	0.395
Is the pain located in an area where physical examination may reveal?				
Touch hypoesthesia	21 (30%)	15 (21.4%)	0.892	0.345
Pricking hypoesthesia	16 (22.9%)	11 (15.7%)	0.723	0.395
In the painful area, can the pain be caused or increased by:				
Brushing	5 (7%)	1 (1.4%)	2.446	0.118

Values are labeled as n (%). DN4 Douleur Neuropathique 4, OA Osteoarthritis

*Significant P value ≤ 0.05

Table 3 The frequency of responses for individual items of LANSS questionnaire among OA patients

	OA patients (n=70)		t	P
	Patients with neuropathic pain (n=27)	Patients with non-neuropathic pain (n=43)		
Knee pain quality				
Pins and needles, tingling or pricking	25 (35.7%)	20 (28.6%)	15.340	< 0.001*
Autonomic skin changes	18 (25.7%)	28 (40%)	0.018	0.894
Sensitive to light touch	18 (25.7%)	24 (34.3%)	0.814	0.367
Sudden pain/electric shocks	12 (17.1%)	10 (14.3%)	3.455	0.063
Burning pain	24 (34.3%)	21 (30%)	11.588	< 0.001*
Sensory testing				
Pins and needles, tingling or burning on rubbing on painful area	10 (14.3%)	6 (8.6%)	5.012	0.025*
Numbness or tenderness felt when pressing on painful area	17 (24.3%)	20 (28.6%)	1.801	0.180

Values are labeled as n (%). LANSS Leeds assessment neuropathic pain symptoms and signs, OA osteoarthritis

*Significant P value ≤ 0.05

Discussion

In the present study, neuropathic pain was detected in 52.9 % of patients based on the DN4 questionnaire and in 38.6 % of patients based on the LANSS scale. According to DN4 questionnaire, the most frequently described

neuropathic pain characteristic in KOA patients with neuropathic pain was a sensation of electric shock (48.7%) with a significant difference compared to KOA patients with non-neuropathic pain, and on physical examination up to 30% had touch hypoesthesia, while

Table 4 Comparison of WOMAC scores, lequesene scores and Kellegren Lawrance scale between patients with neuropathic pain and those with non-neuropathic pain

Parameter mean ± SD (range)		DN4				LANSS			
		DN4 ≥4 (n=37)	DN4 ≤3 (n=33)	t	P value	LANSS ≥12 (n=27)	LANSS <12 (n=43)	t	P value
VAS		6.57±1.59 (3-9)	6±1.46 (3-8)	1.550	0.126	6.56±1.55 (3-9)	6.14±1.54 (3-9)	1.098	0.276
WOMAC	Pain score (0 to 20)	9.86±2.1 (5-12)	6.79±3.59 (3-15)	4.439	<0.0001*	8.26 ± 3.46 (3-15)	8.51±3.17 (3-14)	0.313	0.755
	Stiffness score (0 to 8)	3.57±1.2 (1-6)	4±1.2 (2-6)	1.527	0.131	4.07±1.07 (2-6)	3.58±1.24 (1-6)	1.704	0.093
	Physical functional score (0 to 68)	44.24±5.43 (35-56)	39.39±10.36 (21-60)	2.491	0.015*	42.89±8.4 (28-60)	41.37±8.7 (21-59)	0.730	0.468
	Overall score (0 to 96)	56.81 ± 6.62 (42-70)	52.52±11.36 (31-75)	1.959	0.054	56.67±8.21 (39-74)	53.6±9.9 (31-75)	1.342	0.184
Lequesne	Pain score (0 to 8)	4.5±1.9 (2-10)	4.2±2.13 (2-10)	0.629	0.532	5±1.96 (2-8)	3.98±1.93 (2-10)	2.144	0.036*
	Maximum distance walked score (0 to 8)	3.84±1.36 (1-7)	3.76±1.64 (2-8)	0.223	0.824	4.19±1.52 (2-8)	3.56±1.44 (1-7)	1.739	0.087
	Activities of daily living score (0-8)	3.53±1.14 (1-5.5)	3.44±1.3 (1-5)	0.300	0.765	3.7±1.1 (2-6)	3.35±1.3 (1-6)	1.195	0.236
	Overall score (0 to 24)	11.9±3.5 (6-21)	11.45±3.83 (6-19)	0.485	0.629	12.9±3.46 (6-19)	10.9±3.55 (6-21)	2.351	0.022*
KL scale	Grade II	17(45.9%)	19(57.6%)	1.124	0.570	12(44.4%)	24 (55.8%)	2.422	0.298
	Grade III	16(43.2%)	12(36.4%)			11(40.7%)	17(39.5%)		
	Grade IV	4 (10.8%)	2(6.1%)			4 (14.8%)	2 (4.7%)		

BMI body mass index, DN4 Douleur Neuropathique 4, LANSS Leeds assessment neuropathic pain symptoms and signs, VAS Visual analogue Scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, KL Kellegren Lawrance

*Significant P value ≤ 0.05

Table 5 Quality of life and serum β NGF levels in patients with neuropathic pain versus those with non-neuropathic pain

	DN4				LANSS			
	DN4 ≥ 4 (n=37)	DN4 ≤ 3 (n=33)	t	P value	LANSS > 12 (n=27)	LANSS < 12 (n=43)	t	P value
Normalized physical activity OAKHQOL (0 to 100)	51.35 \pm 19.12 (0–100)	48.84 \pm 19.91 (0–100)	0.537	0.593	47.47 \pm 19.05 (0–100)	51.87 \pm 19.63 (0–100)	–0.923	0.359
Normalized mental health OAKHQOL (0 to 100)	55.04 \pm 23.47 (0–100)	53.63 \pm 22.54 (0–100)	0.256	0.799	47.64 \pm 24.35 (0–100)	58.6 \pm 21.1 (0–100)	–1.992	0.06
Normalized pain OAKHQOL (0 to 100)	38.05 \pm 20.33 (0–100)	51.05 \pm 24.63 (0–100)	–2.418	0.018*	42.88 \pm 21.06 (0–100)	44.99 \pm 24.71 (0–100)	–0.368	0.714
Normalized Social support OAKHQOL (0 to 100)	37.84 \pm 20.82 (0–100)	43.87 \pm 27.3 (4.76–100)	–1.046	0.299	33.69 \pm 23.33 (0–100)	45.07 \pm 23.79 (0–100)	–1.963	0.054
Normalized Social functioning OAKHQOL (0 to 100)	48.65 \pm 21.19 (0–100)	52.94 \pm 23.02 (0–100)	–0.812	0.419	47.06 \pm 22.31 (0–82.35)	52.94 \pm 21.78 (0–100)	–1.09	0.28
Normalized Total OAKHQOL (0 to 100)	45.36 \pm 20.39 (0–100)	46.74 \pm 20.19 (0–100)	–0.284	0.777	41.16 \pm 19.99 (0–100)	49.05 \pm 19.89 (0–100)	–1.612	0.112
Serum β NGF (pg/ml)	661.3 \pm 246.3 (203–1083)	511.57 \pm 220.8 (200–528)	4.852	0.01*	693.9 \pm 260.5 (200–1083)	525.9 \pm 212.8 (200–600)	2.9	0.004*

Values are labeled as mean \pm SD (range). OAKHQOL osteoarthritis knee hip quality of life, DN4 Douleur Neuropathique 4, LANSS Leeds assessment neuropathic symptoms and signs, β NGF serum beta nerve growth factor

*Significant P value ≤ 0.05

Table 6 Correlations of total DN4 score and LANSS score with the studied parameters

	DN4 score		LANSS score	
	r_s	P	r_s	P
Symptom duration	0.056	0.647	0.260	0.020*
Educational level	0.061	0.616	0.065	0.590
VAS	0.213	0.077	0.170	0.160
WOMAC pain	0.459	<0.001*	–0.015	0.902
WOMAC stiffness	0.258	0.031*	0.343	0.004*
WOMAC physical function	0.307	0.010*	0.145	0.231
Total WOMAC	0.233	0.052	0.217	0.072
Lequesne pain	0.128	0.291	0.344	0.004*
Lequesne maximum distance walked	0.017	0.891	0.213	0.076
Lequesne daily activity	0.062	0.608	0.143	0.239
Total Lequesne	0.060	0.619	0.322	0.007*
OAKHQOL physical	0.017	0.891	–0.258	0.031*
OAKHQOL mental health	0.029	0.81	0.254	0.034*
OAKHQOL pain	–0.337	0.004*	–0.074	0.541
OAKHQOL social support	–0.107	0.376	0.283	0.018*
OAKHQOL social function	–0.12	0.323	0.145	0.232
Total OAKHQOL	–0.073	0.551	0.261	0.029*
KL scale	0.107	0.379	0.099	0.414
β NGF	0.341	0.004*	0.313	0.008*

Spearman's correlation test; *significant P value ≤ 0.05 , VAS visual analogue scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, OAKHQOL osteoarthritis knee hip quality of life, DN4 Douleur Neuropathique 4, LANSS Leeds assessment neuropathic pain symptoms and signs, KL= Kellgren–Lawrence, β NGF= beta nerve growth factor

according to LANSS scale the most frequently knee pain quality symptom was pins and needles tingling or pricking (35.7%) followed by burning pain (34.3%) with a significant difference compared to KOA patients with non-neuropathic pain; however self-exam items revealed that 24.3% of patients had numbness or tenderness which felt when pressing on the painful area with a significant difference compared to patients with non-neuropathic pain and 14.3% had pins and needles, tingling or burning on rubbing on the painful area.

In agreement with our results, several studies reported the frequency of neuropathic pain in patients with KOA which was ranged from 17.6 to 51.9% (based on the DN4 questionnaire and/or LANSS scale) [26–34]. Other studies reported neuropathic pain in OA patients (based on the painDETECT questionnaire) in frequencies ranged from 20.7 to 66.7% [31, 35–37].

Aşkın et al. [31] refereed the wide variation in the reported prevalence of neuropathic pain in OA to differences in methodology between studies and pain assessment tools.

Our results revealed that KOA patients with neuropathic pain as detected by DN4 questionnaire have significantly higher WOMAC pain, WOMAC physical function scores, and significantly lower normalized pain OAKHQOL score than patients with non-neuropathic pain ($P < 0.0001$, $P = 0.015$, $P = 0.018$ respectively). Moreover, significantly higher Lequesne pain score and Lequesne index were found in KOA patients with neuropathic pain as detected by LANSS scale compared with patients without neuropathic pain ($P = 0.036$, $P = 0.022$ respectively).

In consistent with our results, Gölge et al. [27] found a highly significant difference between neuropathic and non-neuropathic groups as regards WOMAC pain score ($p < 0.001$), Aşkın et al. [31] also found a significant difference between both groups as regards WOMAC physical function ($p = 0.04$), Narayan et al. [32] found a significant difference between both groups as regards WOMAC total score ($p = 0.024$) and WOMAC physical function score ($p = 0.008$), Mahmoud et al. [38] study showed that the total score and normalized pain domain score were worst in the neuropathic group than the non-neuropathic group, and Radwan and Borai [33] found a highly significant difference between neuropathic and non-neuropathic pain groups as regards WOMAC physical function score, WOMAC pain score, and WOMAC total score ($p < 0.001$ for all of them).

We assessed serum β -NGF levels in the present study and we have found a significantly higher serum β -NGF levels in KOA patients than controls ($P < 0.001$), and significantly higher serum β -NGF levels in KOA patients with neuropathic pain “as detected by DN4 questionnaire and LANSS scale” compared with patients without

neuropathic pain ($P = 0.01$, $P = 0.004$ respectively). In agreement with our results, a study of Montagnoli et al. [39] reported significantly higher serum and synovial β -NGF levels in KOA patients than controls. To our knowledge, no previous studies in the literature assessed serum β -NGF levels in KOA patients with neuropathic pain versus patients without neuropathic pain.

In the present study, the correlations of neuropathic pain scores with sociodemographic data, physical function, quality of life, and disease severity were investigated and we found that DN4 score was positively correlated with WOMAC pain, WOMAC stiffness, and WOMAC physical function and negatively correlated with OAKHQOL pain scores ($r_s = 0.459$, $P < 0.001$; $r_s = 0.258$, $P = 0.031$; $r_s = 0.307$, $P = 0.010$; $r_s = -0.337$, $P = 0.004$ respectively), while LANSS scale was positively correlated with symptom duration, WOMAC stiffness, Lequesne pain, and Lequesne index ($r_s = 0.260$, $P = 0.020$; $r_s = 0.343$, $P = 0.004$; $r_s = 0.344$, $P = 0.004$; $r_s = 0.322$, $P = 0.007$) and negatively correlated with OAKHQOL physical, OAKHQOL mental health, OAKHQOL social support, and total OAKHQOL scores ($r_s = -0.258$, $P = 0.031$; $r_s = -0.254$, $P = 0.034$; $r_s = -0.283$, $P = 0.018$; $r_s = -0.261$, $P = 0.029$ respectively). In this way, we consider that KOA patients with neuropathic pain may have longer symptom duration, severe pain, extreme disability, and worse quality of life than patients with non-neuropathic pain.

A number of evidences indicate that β -NGF plays a significant role in osteoarthritis, not only in pain and hyperalgesia by nociceptor sensitization, but also as a key element of the inflammatory process [40, 41]. Neuropathic pain is unresponsive to common analgesics, such as NSAIDs. Systemic central acting drugs as duloxetine, an antidepressant, have proven effective in controlling this type of pain in OA [42]. Agents blocking NGF might have therapeutic utility for pain [43].

Female sex, age, and BMI are well-known risk factors for OA, as shown in previous studies [44–46]. Also, a low level of education was found to be a significant factor associated with OA [47]. In the present study, we have found no correlation between neuropathic pain scores and risk factors. Study of Polat et al. [37] was consistent with our findings. In contrary to our results, Hochman et al. [35] found that the patients with neuropathic pain were younger and were more likely to be females, but there was no significant difference in level of education between patients with neuropathic pain and those without neuropathic pain.

Our results revealed no correlation between neuropathic pain scores and the Kellgren–Lawrence grades and this was consistent with the previous results of Narayan et al. [32], Polat et al. [37], and Radwan and Borai [33]. In contrary to our results, Ohtori et al. [36] reported that neuropathic pain tended to be seen in

patients with KL grades of late stages OA; however, the majority of our patients had mild to moderate OA.

In the present study, according to linear regression analysis, longer symptom duration, higher pain scores, lower OAKHQOL score, and higher serum β NGF levels were considered as significant risk factors for the development of neuropathic pain in KOA patients.

Our study has some limitations. Firstly, this study was cross-sectional with a relatively small number of patients. Secondly, we have not assessed for central sensitization by measuring pain pressure thresholds. Lastly, we did not assess β -NGF levels in synovial fluid and/or synovial tissue.

Conclusions

Neuropathic pain is frequent in KOA patients. Our study is the first one that assessed serum β -NGF levels in Egyptian primary KOA patients, and studied its correlation with the presence of neuropathic pain in OA. We recommend further studies which include larger number of KOA patients, in order to classify patients according to β -NGF levels, and further investigations to assess the role of β -NGF antagonists in relieving pain and improving functional status and quality of life in KOA patients.

Abbreviations

KOA: Knee osteoarthritis; β -NGF: Beta nerve growth factor; TrkA: Tropomyosin receptor kinase A; BMI: Body mass index; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster University; OAKHQOL: Osteoarthritis knee hip quality of life questionnaire; DN4: Douleur Neuropathique 4 questionnaire; LANSS: Leeds assessment of neuropathic pain symptoms and signs scale; KL: Kellgren–Lawrence grading scale; NSAIDs: Non-steroidal anti-inflammatory drugs

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Authors' contributions

SK wrote the manuscript with input from all authors and supervised the work. RI examined the patients, collected the data, and performed the analysis. HM performed laboratory investigations. RM discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article. The raw data can be requested from the corresponding author.

Declarations

Ethics approval and consent to participate

Written consent was taken from all participants in the study which was approved by the research ethics committee of the Faculty of Medicine, Minia University, Egypt. The study is a thesis and the committee's reference number is 112-11/2018.

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

Author details

¹Rheumatology and Rehabilitation Department, Faculty of Medicine, Minia University, Minia, Egypt. ²Minia University Hospital, Minia, Egypt. ³Clinical Pathology Department, Faculty of Medicine, Minia University, Minia, Egypt.

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