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ORIGINAL ARTICLE

Two nested syndromes: fibromyalgia and neuropathic pain in prediabetes—a pilot study

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Abstract

Background This study aimed to determine the prevalence of neuropathic pain (NeP) and fibromyalgia syndrome (FMS) in prediabetics and to compare them with normoglycemic controls, to disclose the impact of NeP and FMS in disease burden.

Methods People, 18–65 years old, who were admitted to a tertiary hospital's internal medicine outpatient clinic for routine health check-ups and then those who were newly diagnosed with prediabetes were recruited as a prediabetic group and those who were normoglycemic were recruited as a control group. Participants' demographics and clinical data were recorded. The ShortForm-36 and Hospital Anxiety-Depression Scale were answered by the participants. The 2016 ACR Fibromyalgia Diagnostic Criteria and the painDETECT questionnaire were used for evaluation of FMS and NeP, respectively. One hundred nine prediabetics and 53 controls were enrolled.

Results Eighty-four (77.1%) of 109 prediabetics and 37 of 53 controls (69.8%) were female. The mean age of the prediabetics was 48.85 (SD = 9.8) and the controls was 47.37 (SD = 11.11). Age, gender, BMI, smoking status, occupational, marital, and educational status were similar between the groups. FMS was more common in prediabetics 32 (29.6%) of 109 than in normoglycemics 7 (13.2 %) of 53 ($p = 0.022$). Eight of the prediabetics (7.4%) and 2 of the normoglycemics (3.8%) had possible or likely NeP ($p = 0.273$). The frequency of possible or likely NeP was higher in prediabetics with FMS than without FMS ($p = 0.001$). The prevalence of FMS was higher in prediabetics with NeP (87.5%) than without NeP (25.5%) ($p = 0.001$). Prediabetics with FMS or NeP had lower QoL than without FMS or NeP ($p < 0.001$, $p = 0.014$, respectively).

Conclusion While evaluating prediabetics, it is important to assess both FMS and NeP.

Keywords Fibromyalgia syndrome · Quality of life · Neuropathic pain · Prediabetes

Introduction

Fibromyalgia syndrome (FMS) has controversies in terms of definition, pathogenesis, and diagnosis in its evolving historical process. However, it is obvious that patients with FMS complain of chronic pain and non-pain symptoms such as fatigue and sleep disturbance [1]. In recent years, it was shown that neuropathic changes in skin small fibers have taken a part in the pathogenesis of pain in FMS [2]. While it was once necessary to exclude FMS in diagnosing neuropathic pain (NeP), new evidence raises the question of whether fibromyalgia is a neuropathic pain [3]. Both FMS and NeP are considered chronic pain syndromes with similar pathogenetic mechanisms. Another common aspect is that both FMS and NeP negatively affect quality of life (QoL) of patients and increase the burden of the disease, which they accompany [4, 5].

Diabetes mellitus (DM) leads to chronic vascular and non-vascular complications. One of the non-vascular complications is chronic pain syndromes, in which FMS and NeP are more frequent in the diabetic population, 17–23.3% [6–10] and 8–26% [11–14], respectively. Due to NeP and FMS being nested syndromes, it was shown in a study that peripheral neuropathy was detected in 61.9% of diabetics with FMS compared to only 2.5% in diabetics without FMS [8]. Prediabetes (PD) is an intermediate stage between DM

This paper was not presented anywhere

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and normoglycemia [15] and may be a window of opportunity to struggle DM and its complications. Although many studies evaluated NeP and FMS in DM, there was only one study evaluating NeP in PD [16] and there was no study evaluating FMS in PD. Simultaneous assessment of the two interrelated diseases, FMS and NeP, is essential to obtain reliable results. Therefore, this study aimed to determine the prevalence of NeP and FMS in prediabetics and to compare them with normoglycemic controls, to disclose the impact of NeP and FMS in disease burden.

Materials and methods

A cross-sectional study was conducted from December 2018 to April 2019. Fasting plasma glucose (FPG) and HbA1c levels were measured for all 18–65-year-old participants, who were applied to a tertiary hospital's internal medicine outpatient clinic for routine health check-ups and who agreed to participate in the study. The glucose values of 0 and 2nd hour of the oral glucose tolerance test (OGTT), which is a 2-h test that checks participants' blood sugar levels before and 2 h after participants drink a 75 g anhydrous glucose solution, were conducted for all participants without diagnosed diabetes. Participants, whose plasma glucose levels were in the prediabetic range according to the American Diabetes Association Criteria [15], were recruited to the study as the prediabetic group. Participants, whose plasma glucose levels were in the normal range, were recruited to the study as the normoglycemic control group. PD was defined as OGTT-0 value of 100–125 mg/dl (impaired fasting glucose; IFG) and/or OGTT-2nd hour value of 140 to 199 mg/dl (impaired glucose tolerance; IGT) [15]. HbA1c value of 5.7 to 6.4% was also considered PD [15]. Participants' demographics and clinical data were recorded. General outcome measures, such as the Short Form-36 (SF-36) and the Hospital Anxiety and Depression Scale (HADS), were answered by participants.

Exclusion criteria were as follows: having a previous diagnosis of psychiatric disease, chronic neurologic disease, inflammatory rheumatic disease, hypothyroidism, hyperthyroidism, vitamin B12 deficiency, and pregnancy.

A total of 162 participants (109 prediabetic and 53 normoglycemic control group participants) were enrolled in the study.

Health indicators

Height and weight were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was categorized as normal (BMI < 30 kg/m^2) and obese (BMI: 30 kg/m^2 and above) [17].

Measurement of laboratory parameters

A fasting venous blood sample was collected after an overnight fast of at least 12 h for biochemical investigations, and samples were processed in the hospital laboratory on the same day. Fasting plasma insulin (FPI) and glucose were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). Plasma glucose values at 0 and the 2nd hour were conducted by an oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c) levels were measured for all participants. The level of HbA1c was estimated using an Adams A1c HA-8180 V automatic analyzer (Arkray Diagnostics, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers.

Insulin resistance (IR)

Twelve-hour fasting blood samples were obtained for FPI and FPG determinations in order to calculate the homeostasis model assessment of insulin resistance (HOMA-IR). It was determined by the formula [18]:

HOMA-IR = FPI (mU/L) × FPG (mmol/l)/22.5. If the result is ≥ 2.5, it indicates the presence of insulin resistance. The higher the score, the greater the insulin resistance is measured.

Hospital Anxiety and Depression Scale

The HADS is a self-reported questionnaire to evaluate and measure the risk of depression and/or anxiety [19]. HADS is a reliable and validated psychometric scale, which includes 14 questions; half of them assess anxiety and the other half assess depression with four possible answers (score 0–3). According to the Turkish validation study of the HADS, scores ≥ 11 were accepted as having anxiety, and ≥ 8 were accepted as having depression in the current study [19].

Short Form-36

The SF-36 is a valid and reliable questionnaire to assess both physical and mental components of QoL [20, 21]. The SF-36 contains 36 items associated with 8 dimensions: physical functioning for limitations in performing all physical activities, role-physical for problems with work or other daily activities, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [20]. The SF-36 is also a valid and reliable questionnaire in Turkish people [22].

Assessment of neuropathic pain

The painDETECT questionnaire (PDq) was used to evaluate the presence of NeP by the same experienced physician (KE), who was blinded to the clinical findings of the

participants. The PDq, a Turkish validated and reliable NeP screening tool [23, 24], consists of 3 parts and 12 items. The first section contains 3 items and evaluates the intensity of pain at the moment and the average and maximum pain intensity during the past 4 weeks on a 0- to 10-point numerical rating scale. This first section is not included in the scoring. In the second section, one of the 4 pain course patterns related with nociceptive or neuropathic components are determined. The other item is related to radiating pain. Sensations (burning, tingling or prickling, allodynia, pain attacks, temperature evoked pain, numbness, and pressure-evoked pain) are scored with a 0- to 5-point numerical rating scale in the third section. The total score of the PDq (from 1 to 38) is calculated by summing the scores of the items. A total score of 0–12 indicates "unlikely," 13–18 indicates "possible," and ≥ 19 indicates "likely" for NeP.

Assessment of fibromyalgia syndrome

The participants were evaluated and examined for the classification of FMS, by the same experienced physician (KE), who was blinded to the clinical findings of the participants. Participants were classified as having FMS according to the 2016 American College of Rheumatology Fibromyalgia Classification Criteria [25]. To assess the current health status of participants with the FMS, a Turkish validated and reliable version of Fibromyalgia Impact Questionnaire (FIQ) was used [26].

Statistical analysis

A power analysis program, G*Power version 3.0.10 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany), was used to calculate the post hoc power analysis. It was done considering the presence of FMS. The effect size was 0.512. The power was calculated as 0.84 for $\alpha = 0.05$ with a sample size of 53 in the control group and of 109 in the study group.

Statistical analyses were performed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Number of cases and percentages were used for categorical variables. Categorical data was analyzed by chi-square or Fisher's exact test, where appropriate. Shapiro–Wilk test and histograms were used to determine whether continuous variables were normally distributed. Normally distributed variables were presented as means and standard deviations (SD), non-normally distributed variables were presented as medians and interquartile ranges (IQR: per 25–75). Two independent groups of parametric variables were compared using the Student *t*-test. For non-parametric variables, the Mann–Whitney *U* test was administered. The relationship between non-parametric variables was analyzed by Spearman correlation tests and the relationship between parametric variables was analyzed by a Pearson correlation test. A p value of < 0.05 was considered to indicate statistically significant differences.

Results

Eighty-four (77.1%) of 109 prediabetics and 37 (69.8%) of 53 normoglycemic control group subjects were female. The mean age of the prediabetic group was 48.85 (SD = 9.8) years and the control group participants was 47.37 (SD = 11.11) years. The median BMI value of the prediabetics was 32.46 kg/m^2 and the control group participants was 30.67 kg/m^2. Age, gender, BMI, smoking status, professions, marital status, and educational status were similar between the prediabetic and control groups. Two people in both prediabetic (1.8%) and control (3.8%) groups were one unit weekly alcohol drinker. Sociodemographic data is summarized in Table 1. HOMA-IR values were also similar between groups. In prediabetic group, 53 patients (48.6%) had IFG, 15 patients (13.8%) had IGT, 32 patients (29.4%) had both IFG and IGT, and 9 patients (8.3%) had isolated elevated HbA1c.

Presence of comorbidity in participants was as follows: 5 patients (4.7%) in PD group and 1 participant (1.9%) in control group had hyperlipidemia, 2 patients (1.9%) in PD group and no one in control group had coronary artery disease, 2 patients (1.9%) in PD group and no one in control group had chronic obstructive lung disease, and 3 patients (2.8%) in PD group and no one in control group had gastroesophageal reflux. These data were not appropriate for statistical analyses. A total of seven patients (6.5%) in PD group and 6 participants (11.5%) in control group had asthma ($p = 0.281$); 22 patients (20.6%) in PD group and 7 participants (13.5%) in control group had hypertension ($p = 0.277$).

FMS was more common in prediabetics (32 (29.6%) of 109 prediabetics) than in normoglycemics (7 of 53 normoglycemics (13.2)) ($p = 0.022$). FIQ total scores were similar between prediabetics with FMS and normoglycemics with FMS ($p = 0.266$). Eight of prediabetics (7.4%) and 2 of normoglycemics (3.8%) had NeP according to the PDq, but this difference was not statistically significant ($p = 0.273$). PDq total scores were also similar between prediabetics and normoglycemics ($p = 0.095$). Comparison of clinical variables of prediabetic and normoglycemic groups is summarized in Table 2.

When comparing prediabetic patients with or without FMS, age, BMI, OGTT for the 0 and 2nd hour values, HbA1c, and HOMA-IR values were similar between the groups. Female gender was more common in prediabetics with FMS (96.9%) than without FMS (68.4%), ($p = 0.001$). Patients with FMS had lower SF-36 scores than without FMS ($p < 0.001$). Frequency of risk of anxiety and/or

Table 1 Sociodemographic data of prediabetic patients and control group participants

	Prediabetics (n = 109)	Controls (n = 53)	*p* value
Gender (F/M), n (%)	84 (77.1)/25 (22.9)	37 (69.8)/16 (30.2)	0.319
Age (year), mean (SD)	48.85 (9.80)	47.37 (11.11)	0.337
Occupation, n (%)			0.212
Housewife	77 (72.0)	26 (55.3)	
Officer	10 (9.3)	6 (12.8)	
Worker	9 (8.4)	8 (17.0)	
Retired	11 (10.3)	7 (14.9)	
Marital status			0.821
Married	99 (92.5)	44 (93.6)	
Divorced	1 (0.7)	0 (0)	
Single	7 (6.5)	3 (5.4)	
Education			0.392
Illiteracy	4 (3.7)	0 (0)	
Primary school	82 (76.7)	32 (68.1)	
High school	11 (10.3)	6 (12.8)	
University	10 (9.3)	9 (19.1)	
Menopausal status, n (%)			0.865
Premenopause	44 (52.4)	20 (54.1)	
Postmenopause	40 (47.6)	17 (45.9)	
Smoking, n (%)			0.053
Never	82 (75.2)	38 (71.7)	
Quit	17 (15.6)	3 (5.7)	
Smoker	10 (9.2)	12 (22.6)	
BMI (kg/m^2), median (per 25–75)	32.46 (28.45–38.56)	30.67 (27.34–36.79)	0.150
Obesity (+), n (%)	74 (67.9)/35 (32.1)	31 (60.8)/20 (39.2)	0.378

BMI, body mass index; *F/M*, female/male

depression was higher in prediabetics with FMS than without FMS ($p < 0.001$). VAS-fatigue levels were also higher in prediabetics with FMS than without FMS ($p < 0.001$). Frequency of possibly or likely NeP was higher in prediabetics with FMS than without FMS ($p = 0.001$) (Table 3).

To compare prediabetics with or without NeP, patients having possible or likely NeP were grouped as NeP (+) and patients having unlikely NeP were grouped as NeP (−). Age, gender, BMI, OGTT for the 0 and 2nd hour values, HbA1c, and HOMA-IR values were similar between groups. Patients with NeP had lower SF-36 scores than those without NeP. Frequency of risk of anxiety and/or depression was similar between prediabetics with or without NeP. VAS-fatigue levels were also quite similar between prediabetics with or without NeP. Prevalence of FMS was higher in prediabetics with NeP (87.5%) than in those without NeP (25.5) ($p = 0.001$) (Table 3).

Discussion

In this study, we had three main findings. First, while FMS occurred more in prediabetics than in normoglycemic subjects, NeP occurred similarly between both groups. Second, NeP prevalence was higher in prediabetics with FMS than in those without FMS, and vice versa, where FMS frequency was higher in prediabetics with NeP than in those without NeP. Third, while glycemic levels were similar in prediabetics with or without FMS and in prediabetics with or without NeP, impaired QoL was observed in prediabetics with FMS or NeP.

Whether FMS is a rheumatic disease, a psychosomatic disorder, a central sensitization syndrome, a neuropathic pain syndrome, or a psycho-cultural movement is still being debated [27]. However, the truth is that FMS leads to a serious decrease in QoL, reduces work productivity, and increases the burden of the disease accompanied by it [4]. Based on this, FMS prevalence was investigated in DM, as with many chronic diseases. Wolak et al. found the prevalence of FMS was 23.3% in women with type 2 DM and Tishler et al. found it was 15.5% [6, 7]. Both found that the prevalence of FMS was higher in diabetics than in healthy subjects. Yanmaz et al. found the prevalence of FMS was 18% in patients with type 2 DM [10]. In this study, the first study evaluating FMS in PD shows that the prevalence of FMS was 29.6% in prediabetics and was 13.2% in normoglycemic subjects and the difference was statistically significant. The prevalence of FMS was higher in our study than in abovementioned three studies that evaluated FMS in type 2 DM [6, 7, 10]. In all three studies, FMS was

Table 2 Comparison of clinical variables of prediabetic patients to control group participants

	PD (n = 109)	Control (n = 53)	*p* value
OGTT-0 (mg/dl), mean (SD)	104.86 (8.24)	91.36 (5.53)	**< 0.001**
OGTT-2 (mg/dl), mean (SD)	131.08 (32.50)	107.17 (16.90)	**< 0.001**
HbA1c, median (per 25–75)*	5.9 (5.7–6.2)	5.5 (5.3–5.6)	**< 0.001**
HOMA-IR, median (per 25–75)**	2.36 (1.59–3.83)	2.12 (1.33–3.26)	0.218
IR (+), n (%)	45 (46.9)	18 (42.9)	0.663
SF-36 dimensions, median (per 25–75)			
SF-36/ PCS	54.06 (31.72–83.91)	87.50 (57.50 94.06)	**< 0.001**
SF-36/ MCS	52.56 (35.38–76.56)	78.65 (67.44 87.00)	**< 0.001**
SF-36/ TS	51.59 (35.08–79.64)	80.66 (60.99 90.27)	**< 0.001**
HADS			
Anxiety (+), n (%)	27 (25.2)	1 (2.2)	**< 0.001**
Depression (+), n (%)	39 (36.4)	6 (13)	**0.004**
VAS-fatigue, median (per 25–75)	6 (4–7)	3 (2–6)	**< 0.001**
FMS (+), n (%)	32 (29.6)	7 (13.2)	**0.022**
FIQ-t, mean (SD)	54.75 (16.86)	45.41 (12.87)	0.266
PDq-t, median (per 25–75)	1 (1–3)	1 (0–3)	0.095
PDq-NeP			0.273
Unlikely, n (%)	101 (92.7)	51 (96.2)	
Possible, n (%)	5 (4.6)	0 (0)	
Likely, n (%)	3 (2.8)	2 (3.8)	

FIQ-t, fibromyalgia impact questionnaire-total score; *FMS*, fibromyalgia syndrome; *HADS*, Hospital Anxiety and Depression Scale; *HbA1c*, glycated hemoglobin; *HOMA-IR*, homeostasis model assessment of insulin resistance; *IR*, insulin resistance; *NeP*, neuropathic pain; *OGTT*, oral glucose tolerance test; *PDq-t*, painDETECT questionnaire total score; *SF-36*, Short Form-36; *SF-36/MCS*, Mental Component Score; *SF-36/PCS*, Physical Component Score; *SF-36/TS*, Total Score

*Coefficient of variations of HbA1c are 5.57 for PD group and 3.31 for control group

**Coefficient of variations of HOMA-IR are 82.51 for PD group and 64.01 for control group

classified according to the ACR 1990 Criteria and this may be the reason for this difference. This study determined FMS according to the ACR 2016 Diagnostic Criteria, which is a more sensitive diagnostic criteria compared to the ACR 1990 Criteria [28]. It should be noted that we also evaluated control group participants with the ACR 2016 Criteria. Consequently, increased FMS prevalence was found in the prediabetics when compared to the normoglycemic subjects, in this study. Other possible reason of the higher prevalence of FMS in the groups may be the mean age of participants which were 48.85 years in PD group vs 47.37 years in control group. Topbaş et al. noted that the prevalence of FMS was found to increase with age which was the highest in the 50–59 age group (10.1%) [29]. In the study, FMS prevalence was found 3.7% in 20–64 years women in Turkey [29]. Another possible reason of the higher prevalence of FMS in the groups may be the mean BMI of the participants which were 32.46 kg/m^2 in PD group vs 30.67 kg/m^2 in control group. Several mechanisms have been proposed to explain "the hidden link between FMS and higher BMI values," but at this time, it is not possible to ascertain whether obesity is cause or consequence of FMS [30]. Branco et al. found the prevalence of FMS was 2.2–6.6% in general population of five European countries [31]. They concluded that the prevalence of FMS was age- and gender-related and varied among countries [31]. In our study, the PD group was similar with the normoglycemic control group in terms of age, gender, occupation, marital status, educational status, BMI, and insulin resistance. This provides a favorable condition for comparing groups. Thus, it could be thought that increased FMS prevalence in PD is associated with own nature of PD.

Patients suffering from FMS have impaired QoL compared with the general population. These patients also suffer from anxiety, depression, and fatigue, possibly related to a central sensitization disorder [27]. In this study, although having similar OGTT and HbA1c values, prediabetic patients with FMS had worse QoL and more common anxiety, depression, and fatigue levels compared to prediabetic patients without FMS. We think that underlying and/or accompanying pathogenetic mechanisms of prediabetes such as dysregulated inflammatory cytokines and sleep disturbance may be the reason of similar metabolic variables between prediabetic patients with FMS and without FMS [27, 32, 33]. Another issue that needs to be clarified is that there are increased anxiety and/or depression risks and impaired QoL cause or consequence of the presence of FMS in prediabetes. These questions are also related to complex

Table 3 Comparison of clinical variables of prediabetic patients in terms of presence of FMS and NeP

	FMS (+);(n = 32)	FMS (−);(n = 76)	*p* value	NeP (+); (n = 8)	NeP (−); (n = 101)	*p* value
Gender (F/M), n (%)	31(96.9) / 1(3.1)	52(68.4)/24(31.6)	**0.001**	8 (100) / 0(0)	76 (75.2)/25(24.8)	0.194
Age (year), mean (SD)	50.28 (9.44)	48.25 (10.01)	0.320	49.63 (10.11)	48.79 (9.82)	0.828
Obesity (+), n (%)	24 (75)	49 (64.5)	0.286	5 (62.5)	69 (68.3)	0.710
BMI (kg/m^2), mean (SD)	34.56 (6.36)	33.40 (8.02)	0.427	36.98 (7.13)	33.47 (7.53)	0.217
OGTT-0 (mg/dl), mean (SD)	104.22 (8.29)	105.35 (8.09)	0.529	101.50 (8.57)	105.11 (8.16)	0.283
OGTT-2 (mg/dl), mean (SD)	130.34 (30.32)	132.04 (33.31)	0.836	122.88 (18.23)	131.50 (33.27)	0.259
HbA1c, median (per 25–75)	5.9 (5.75–6.2)	5.9 (5.7–6.2)	0.659	5.9 (5.75–6.3)	6.0 (5.7–6.2)	0.667
HOMA-IR, median (per 25–75)	2.94 (1.65–4.22)	2.26 (1.59–3.71)	0.384	3.51 (2.15–6.05)	2.28 (1.60–3.81)	0.295
IR (+), n (%)	14 (30)	56 (42.9)	0.258	4 (80)	41 (45.1)	0.183
SF-36, median (per 25–75)	27.5 (16.88–37.81)	67.81 (44.69–88.66)	**< 0.001**	26.25 (16.88–48.75)	58.13 (32.81–85.00)	**0.011**
SF-36/PCS	34.13 (23.63–44.48)	66.06 (40.31–82.78)	**< 0.001**	35.25 (20.75–57.19)	53.63 (35.81–88.78)	**0.031**
SF-36/MCS	31.44 (20.47–39.56)	66.59 (43.28–84.89)	**< 0.001**	33.44 (19.13–51.31)	52.81 (36.65–81.49)	**0.014**
SF-36/TS						
HADS	16 (51.6)	11 (14.7)	**< 0.001**	2 (28.6)	25 (25)	1.000
Anxiety (+), n (%)	20 (64.5)	19 (25.3)	**< 0.001**	4 (57.1)	35 (35)	0.255
Depression (+), n (%)						
VAS-fatigue, median (per 25–75)	7 (6–9)	5 (3 7)	**< 0.001**	8 (4–8.5)	6 (4–7)	0.052
FMS (+), n (%)	-	-	-	7 (87.5)	25 (25)	**0.001**
FIQ-t, mean (SD)	-	-	-	61.81 (16.38)	53.22 (16.92)	0.331
PDq-t, median (per 25–75)	3 (1–5)	1 (0.25–1)	**< 0.001**	-	-	-
PDq-NeP	25 (78.1)	75 (98.7)	**0.001**	-	-	**-**
Unlikely, n (%)	4 (12.5)	1 (1.3)				
Possible, n (%)	3 (9.4)	0 (0)				
Likely, n (%)						

BMI, body mass index; *FIQ-t*, fibromyalgia impact questionnaire-total score; *FMS*, fibromyalgia syndrome; *F/M*, female/male; *HADS*, Hospital Anxiety and Depression Scale; *HbA1c*, glycated hemoglobin; *HOMA-IR*, homeostasis model assessment of insulin resistance; *IR*, insulin resistance; *NeP*, neuropathic pain; *OGTT*, oral glucose tolerance test; *PDq-t*, painDETECT questionnaire total score; *SF-36*, Short Form-36; *SF-36/MCS*, Mental Component Score; *SF-36/PCS*, Physical Component Score; *SF-36/TS*, Total Score

nature of FMS. These outcomes are the first data regarding the impact of FMS to disease burden in PD and this sheds light for future studies on this topic.

NeP, caused by a lesion or disease of the somatosensory nervous system, contains a cluster of symptoms and signs such as burning, tingling, and numbness [34]. Sometimes the etiology of NeP is not determined in routine clinical procedures. Although affected by factors such as disease duration, disease severity, and diagnostic method, the prevalence of NeP was found to be 8–30% in various studies in type 2 DM [11–14, 35]. Ziegler et al. found that the prevalence of NeP was 8.7% in patients with IGT, 4.2% in patients with IFG, and 1.2% in normoglycemic subjects [16]. In accordance with this study, the prevalence of possible or likely NeP was 7.4% in the prediabetics. However, the prevalence of NeP in prediabetics was similar with the normoglycemic subjects in our study. The reason for this similarity may be that the prevalence of NeP in normoglycemic subjects was a little higher in our study than in Ziegler et al.'s study [16]. In Ziegler et al.'s study, there was only a statistically significant difference between the prevalence of NeP in IGT and in the normoglycemic group [16]. Thus, another possible reason of similar NeP prevalence in this study is that the number of patients is not enough to compare the prevalence of NeP in subgroups of PD such as IGT and IFG with normoglycemic groups. That this study group included newly diagnosed patients with PD may be another reason for the similarity.

It is well known that NeP is related to lower levels of QoL [36–38]. Lower QoL levels were also reported in diabetic patients with NeP than in those without NeP [39, 40]. However, there is no study evaluating the burden of disease including QoL in prediabetic patients with or without NeP. Although the presence of anxiety and/or depression was similar in prediabetics with or without NeP, we found lower QoL levels in prediabetics with NeP than in prediabetics without NeP in our study.

With a new NeP definition by the International Association for the Study of Pain, FMS was not considered a NeP because it was thought that there was no somatosensorial nervous system disease in FMS [41]. However, new evidence shows a role of small fiber neuropathy in pathogenesis of FMS [2]. Additionally, central sensitization takes a role in the pathogenesis of both NeP and FMS [3]. It was shown in a study based on the question "Is fibromyalgia a

NeP?" that FMS may have a NeP component [42]. In this study, prediabetics with FMS had more common NeP than prediabetics without FMS and vice versa that the prediabetics with NeP had more common FMS than prediabetics without NeP. Thus, it has been demonstrated in prediabetics that FMS and NeP are nested syndromes.

The present study has a few limitations. This is a monocentric study performed in a small number of patients, who were admitted to a tertiary center. Small fiber tests and comprehensive neurologic examination were not performed. Sleep disturbance and physical activity level were not evaluated separately. The strengths of this study include that we diagnosed FMS and NeP with a valid and reliable method and we investigated laboratory and clinical markers. In addition, our results should be complemented by future large studies, to obtain stronger results.

In conclusion, many prediabetic patients suffer from FMS that reduces their QoL. While NeP prevalence was similar between prediabetics and normoglycemics, prediabetics who had NeP had a lower QoL. While evaluating prediabetic patients, it is important to assess both FMS and NeP because they are nested syndromes.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analyses were performed by all authors. The first draft of the manuscript was written by KE and all authors commented on previous versions of the manuscript.

Data availability Available.

Code availability N/A.

Declarations

Ethics approval Erciyes University Local Ethical Committee approval was received (Date: 20.02.2019; No: 2019/141).

Consent to participate This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The patient's written informed consent to publish the clinical information and materials was obtained.

Consent for publication All authors have seen and approved the revised manuscript for publication.

Competing interests The authors declare no competing interests.

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