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Original Article

Frequency of carpal tunnel syndrome and hand dysfunction in prediabetes: A cross-sectional, controlled study

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ABSTRACT

Objectives: This study aims to evaluate the frequency of carpal tunnel syndrome (CTS), to investigate the impairment of hand functions in patients with prediabetes (PD), and to compare laboratory findings of PD patients with and without CTS.

Patients and methods: Between June 2018 and January 2019, a total of 115 patients (29 males, 86 females; mean age: 51.4±11.8 years; range, 24 to 78 years) who were recently diagnosed with PD and a total of 54 healthy participants (17 males, 37 females; mean age: 48.4±13.2 years; range, 21 to 78 years) as the control group were included. Demographic and clinical data of the patients including oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) were recorded, and both groups were examined for the presence of CTS. Clinically suspected CTS was confirmed by electrodiagnostic studies. The hand grip strength (HGS) was measured and hand functions were evaluated using the Duruöz Hand Index (DHI).

Results: There were no significant differences in the age, sex, occupation, body mass index (BMI), or insulin resistance between the groups. A total of 24 (20.9%) patients with PD and eight (14.8%) healthy controls had CTS (p=0.349). Hand functions were worse in the PD patients than the control group (p=0.044). Age, occupation, BMI, insulin resistance, OGTT at 0 and 2 h, and HbA1c values were similar between the PD patients with or without CTS.

Conclusion: Our study, for the first time, reveals that CTS is slightly more common and hand functions are impaired in PD compared to the healthy individuals. Based on these findings, we suggest that hand functions should be evaluated in PD patients.

Keywords: Carpal tunnel syndrome, hand function, prediabetes.

Carpal tunnel syndrome (CTS) is a symptomatic compression neuropathy of the median nerve in the wrist region.[1] It is the most common compressive neuropathy in the upper extremity, characterized by increased pressure in the carpal tunnel, leading to decreased function of the median nerve.[1] The main symptoms of CTS are pain and numbness in the hand and arm, tingling in the distribution of the distal median nerve, and weakness of the thenar muscles. The reasons why CTS is an important problem are that it causes poor quality of life and loss of hand functions.[2] In the general population, the estimated prevalence of CTS is 2.7 to 16% and that variety depends on several factors including the method of diagnosis, age, and geographic region.[3-5] The risk factors of CTS, such as female sex, occupation, pregnancy, obesity, and some comorbid diseases, have also an influence on the prevalence of CTS in the general population.[6]

Diabetes mellitus (DM), which increases the prevalence of CTS by several fold, is a well-known risk

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factor for CTS.[7] In the state of chronic hyperglycemia, excess glucose shifts to an alternative glucose pathway by aldose reductase and increases sorbitol synthesis. Sorbitol's permeability through the plasma membrane is low and, when it accumulates in the cells, it takes on a hyperosmotic role that causes neuronal swelling.[8] Due to the activation of an alternative polyol pathway, sodium-potassium (Na/K) ATPase activity may reduce, leading to intra-axonal Na accumulation. This pathological state also contributes to axonal swelling.[9] Chronic hyperglycemia results in the non-enzymatic glycosylation of proteins, forming advanced glycation end-products that may cause neurodegeneration.[8] According to a revised and extended "double crush" hypothesis, metabolic alterations and proximal nerve impingement causes nerve swelling and that may be a "first crush" in the nerve. This crush predisposes chronic compression in nerves in the areas that are anatomically constrained, such as the carpal tunnel. This "second crush" also contributes to entrapment of peripheral nerves in DM.[10] Furthermore, impaired glucose tolerance (IGT) and progressive insulinopenia, even without hyperglycemia, may lead to the impaired synthesis of neuronal growth factor and neuropeptides, which may be associated with neuropathy in an animal model.[11] The increased risk of CTS in IGT and/or insulin resistance (IR) may be related to one of the mechanisms of CTS in prediabetes (PD).[12] The prevalence of CTS in patients with diabetes may vary from 28 to 68.5% due to clinical features, such as the diagnostic method of CTS (clinical, electrophysiological, or imaging) and duration of disease in recruited patients.[13,14]

In the literature, many studies have been conducted on the prevalence of diabetic neuropathy; however, to the best of our knowledge, there is no study evaluating the frequency of CTS involving all the components of PD, such as IGT and impaired fasting glucose (IFG). In the present study, therefore, we aimed to evaluate the frequency of CTS, to investigate the impairment of hand functions in patients with prediabetes (PD), and to compare laboratory findings of PD patients with and without CTS.

PATIENTS AND METHODS

This prospective, cross-sectional, controlled study was conducted at Kayseri City Hospital, internal medicine outpatient clinic between June 2018 and January 2019. Individuals aged over 18 years who were admitted to our clinic for routine health control and were, then, diagnosed with PD according to the American Diabetes Association (ADA) Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes criteria[15] were recruited to the study. Among them, those who were not diagnosed with diabetes or PD were recruited as the control group. Participants with hypothyroidism, acromegaly, pregnancy or rheumatic and traumatic hand disorders were excluded, as these conditions may affect the prevalence of CTS and hand functions.[16] Finally, the study group included a total of 115 patients (29 males, 86 females; mean age: 51.4±11.8 years; range, 24 to 78 years) who were recently diagnosed with PD, while the control group included a total of 54 healthy participants (17 males, 37 females; mean age: 48.4±13.2 years; range, 21 to 78 years). A written informed consent was obtained from each participant. The study protocol was approved by the Erciyes University Faculty of Medicine Ethics Committee (date/no: 2019/141). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Interventions and definitions

Data including age, sex, and occupation were recorded. The height and weight were measured, and body mass index (BMI) was calculated as weight in kg divided by height in meters squared (kg/m^2). The BMI was classified as normal (<30 kg/m^2) and obese (≥30 kg/m^2).[17]

Plasma glucose values at 0 and 2 h were measured by an oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) levels were measured for all participants. Prediabetes was defined as a 0-h plasma glucose value (OGTT-0th) of 100 to 125 mg/dL (IFG) and/or 2-h plasma glucose value (OGTT-2nd) of 140 mg/dL to 199 mg/dL (IGT). An HbA1c value of 5.7 to 6.4% was also considered PD.[15] A fasting venous blood sample was collected after overnight fasting of at least 12 h for biochemical investigations, and the samples were processed in the hospital laboratory on the same day. Glucose levels were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, IN, USA). The level of HbA1c was estimated using the Adams A1c HA-8180V automatic analyzer (Arkray Diagnostics, MN, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers.

A total of 12-h fasting blood samples were obtained for fasting plasma insulin (FPI) and fasting plasma glucose (FPG) determinations for calculating the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) using the following formula: HOMA-IR= FPI (mU/L) × FPG (mmol/L)/22.5.

TABLE 1
Comparison of PD patients and control group

	PD (n=115)						Control (n=54)						
	n	%	Mean±SD	Median	Min-Max	IQR, 25th-75th	n	%	Mean±SD	Median	Min-Max	IQR, 25th-75th	*p*
Age (year)			51.4±11.84						48.4±13.16				0.222
Sex													0.394
Female	86	74.8					37	68.5					
Male	29	25.2					17	31.5					
Occupation													0.165
Housewife	80	70.2					26	54.2					
Officer	10	8.8					5	10.4					
Worker	8	7.0					8	16.7					
Retired	16	14					9	18.8					
BMI (kg/m²)				33.78		28.64-39.19				30.46		27.44-34.75	0.096
Obesity (+)	81	70.4					30*	57.7					0.106
OGTT-0				106		101-110				92		87.5-95.5	<0.001
OGTT-2				129		105.25-168.50				104		92.5-118.50	<0.001
HbA1c				6		5.73-6.20				5.6		5.35-5.60	<0.001
HOMA-IR				2.62		1.64-4.24				2.12		1.32-3.16	0.077
IR (+)	55**	50.5					19***	43.2					0.415
CTS (+)	24	20.9					8	14.8					0.349
CTS grade													-
Mild	13	54.2					5	71.4					
Moderate	9	37.5					1	14.3					
Severe	2	8.3					1	14.3					
CTS													-
Unilateral	10	41.7					2	25					
Bilateral	14	58.3					6	75					
HGS (kg)													
Right				23.82		19.15-27.99				25.73		21.05-34.47	0.073
Left				20.8		18.01-26.31				24.4		22.07-32.57	0.005
DHI													
Kitchen				0	0-29	0-5.75				0	0-12	0-0	0.069
Dressing				0	0-9	0-0				0	0-0	0-0	0.005
Hygiene				0	0-9	0-0				0	0-3	0-0	0.219
Office				0	0-9	0-0				0	0-3	0-0	0.037
Other				0	0-12	0-0				0	0-2	0-0	0.038
Total score (0-90)				0	0-58	0-7				0	0-16	0-0	0.044

PD: Prediabetes; SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostasis model assessment of insulin resistance; CTS: Carpal tunnel syndrome; HGS: Hand grip strength; DHI: Duruöz Hand Index; * Number of patients with complete data: n=52; ** Number of patients with complete data: n=109; *** Number of patients with complete data: n=44.

The result of ≥2.5 indicates IR. Higher scores indicate greater IR.[18]

Hand grip strength (HGS) and hand function

All the participants' HGS was measured three times in both hands with a handheld digital dynamometer by a single experienced physician who was blinded to the participants' clinical data. The patients were sitting with their elbow at 90° of flexion. The average value of the three measurements was recorded as the HGS.

All the patients' hand functions were evaluated using the Duruöz's Hand Index (DHI), which is a self-reported questionnaire and valid for patients with diabetes.[19] The DHI evaluates five groups of hand abilities that cover hand use in the kitchen, during dressing, while performing personal hygiene, while performing office tasks, and other general items. Patients rate their hand abilities from 0 (no difficulty) to 5 (impossible to do) for 18 items, and the total score ranges from 0 to 90. Higher scores indicate worse hand functions. The DHI takes about 2 or 3 min to complete.

Carpal tunnel syndrome diagnosis

The participants were questioned and examined by a rheumatologist who was blinded to the participants' clinical data. There are two criteria to be fulfilled for the clinical diagnosis of CTS: *(i)* There must be at least one of these findings: presence of pain, paresthesia, and/or sensorial loss at the distribution of the median nerve; and *(ii)* There must be one of the following findings: nocturnal enhancement of CTS-related symptoms, positivity of the Tinnel and/or Phalen test, or weakness of abductor pollicis brevis muscle.[20] A sensorial examination was performed with 10-g monofilament in the thenar area of the hand.

Participants who were diagnosed with clinical CTS were referred to a neurologist for electrophysiological testing. Neurophysiological studies were performed using standard procedures through a Neuropack X1 MEB-9200K, (Nihon Kohden Corp., Tokyo, Japan) by the same neurologist who was blinded to the participants' clinical data. All measurements were taken at a temperature of 33 to 34°C. Motor and sensorial nerve conduction examinations of the median and ulnar nerves of both upper extremities were conducted. Sensory nerve potentials were recorded antidromically with ring electrodes.

Electrodiagnostic tests were performed according to the recommended electrodiagnostic study protocol in CTS.[21] In the median nerve sensory conduction studies, stimulation was applied at the wrist and sensory nerve action potential (SNAP) was recorded from the index finger. In median nerve motor conduction studies, stimulation was applied to the wrist and elbow. The compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis muscle. The SNAP peak amplitude, sensory nerve conduction velocity, CMAP peak amplitude, distal motor latency, and motor nerve conduction velocity were measured. The participants who were clinically diagnosed with CTS and confirmed with an electrodiagnostic test were considered to have CTS.

Carpal tunnel syndrome was classified as mild, moderate, or severe as follows: *(i)* Mild-median sensory nerve conduction slowing and/or median sensory amplitude decreased more than 50% of the reference value (no motor involvement); *(ii)* Moderate-median sensory and motor slowing and/or SNAP amplitude less than 50% of the reference value; and *(iii)* Severe-Absence of median SNAP with motor slowing, median motor slowing with decreased

TABLE 2
The presence, severity, and laterality of CTS in subgroups of PD patients and control group

	IFG (n=57)		IGT (n=17)		IFG+IGT (n=36)		Elevated HbA1C (n=5)		Control (n=54)	
	n	%	n	%	n	%	n	%	n	%
CTS (+)	11	19.3	4	23.5	8	22.2	1	20	8	14.8
CTS severity										
Mild	5	45.5	3	75	4	50	1	100	5	71.4
Moderate	5	45.5	0	0	4	50	0	0	1	14.3
Severe	1	9.1	1	25	0	0	0	0	1	14.3
CTS										
Unilaterally	4	36.4	2	50	4	50	0	0	2	25
Bilaterally	7	63.6	2	50	4	50	1	100	6	75

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; CTS: Carpal tunnel syndrome.

TABLE 3
Comparison of PD patients with or without CTS

	With CTS (n=24)						Without CTS (n=91)						*p*
	n	%	Mean±SD	Median	Min-Max	IQR, 25th-75th	n	%	Mean±SD	Median	Min-Max	IQR, 25th-75th	
Age (year)			52.7±12.3						50.8±11.5				0.510
Sex													**0.001**
Female	24	100					62	68.1					
Male	0	0					29	31.9					
Occupation													
Homemaker	22	91.7					58	64.4					-
Officer	0	0					10	11.1					-
Worker	1	4.2					7	7.8					-
Retired	1	4.2					15	16.7					-
Obesity (+)	19	79.2					62	68.1					0.292
BMI (kg/m^2)			36.0±8.2						33.3±7.1				0.150
OGTT-0			104.0±8.7						105.6±7.7				0.408
OGTT-2			141.8±30.5						130.7±33.9				0.132
HbA1c				6.10		5.95-6.30				5.90		5.70-6.20	0.230
HOMA-IR				2.67		1.38-5.36				2.42		1.64-4.04	0.520
IR (+)	15	62.5					40*	47.1					0.182
HGS (kg)													
Right				20.10		12.70-23.85				24.35		19.88-28.75	**0.002**
Left				19.10		15.91-21.67				21.77		18.11-28.62	**0.003**
DHI													
Kitchen				3	0-29	0-11.5				0	0-18	0-3	**<0.001**
Dressing				1	0-8	0-3.5				0	0-9	0-0	**<0.001**
Hygiene				0	0-6	0-0.5				0	0-9	0-0	**0.017**
Office				2	0-6	0-5				0	0-9	0-0	**<0.001**
Other				0	0-12	0-4				0	0-6	0-0	**<0.001**
Total score (0-90)				9	0-58	0-20.5				0	0-37	0-4.5	**<0.001**

CTS: Carpal tunnel syndrome; SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostasis model assessment of insulin resistance; HGS: Hand grip strength; DHI: Duruöz Hand Index; * Number of patients with complete data: n=86.

median motor amplitude, or CMAP abnormalities with evidence of axonal injury on needle testing of the thenar muscles.[22]

Statistical analysis

Study power analysis and sample size calculation were performed using the G*Power version 3.0.10 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The DHI scores were taken into consideration for the post-hoc power analysis. The effect size of DHI post-treatment values was 0.478. The study power was calculated as 0.82 for α=0.05 with a sample size of 54 in the control group and of 115 in the study group.

Statistical analysis was performed using the IBM SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) for normally distributed continuous variables and in median and interquartile range (IQR, 25^{th}-75^{th} percentiles) for non-normally distributed continuous variables. Categorical variables were expressed in number and frequency. The Shapiro-Wilks test and histograms were used to determine whether continuous variables were normally distributed. Categorical data were analyzed using the chi-square or Fisher's exact test, where appropriate. To ensure more descriptive data, minimum-maximum (min-max) values were given with percentiles for the DHI scores. Two independent groups of parametric variables were compared using the Student's t-test. For non-parametric variables, the Mann-Whitney U test was administered. A p value of <0.05 was considered statistically significant.

RESULTS

There were no significant differences between the groups in terms of age, sex, BMI, and occupation (p=0.222, p=0.394, p=0.096, and p=0.165, respectively). The HOMA-IR and the presence of IR did not significantly differ between the groups (p=0.077 and p=0.415, respectively). A total of 24 (20.9%) patients with PD and eight (14.8%) healthy controls had CTS, indicating no significant difference (p=0.349). Baseline demographic, clinical, and laboratory data of the patient and control groups are summarized in Table 1.

The frequency and severity of CTS in subgroups of PD, such as those with isolated elevation of HbA1c (5.7 to 6.4%), IFG, and IGT are shown in Table 2.

The PD patients with or without CTS were similar in terms of age, presence of obesity, BMI, OGTT at 0 and 2 h, HbA1c, HOMA-IR, and IR. However, the HGS and hand functions were found to be worse in the PD patients with CTS than those without CTS (for right HGS, p=0.002; for left HGS, p=0.003, and p<0.001, respectively). Additionally, all CTS patients were females (Table 3).

DISCUSSION

The present study revealed that one of five PD patients had CTS and, although not statistically significant, PD patients were more likely to have CTS, compared to the healthy controls. Also, hand functions of PD patients were worse than the control group.

There are many studies showing that DM is a risk factor for CTS and prevalence of CTS increases in DM, compared to the general population.[23,24] The estimated prevalence of CTS varies from 28 to 68.5% in patients with diabetes[13,14] and from 2.7 to 16% in the general population.[3-5] Diagnostic methods, demographic features, geographic regions, and the presence of risk factors of CTS are the main reasons of discrepancies in the prevalence rates of CTS. Additionally, disease duration in DM is an important factor for development of CTS. Rota et al.[13] reported that the frequency of CTS was 28% in patients who were recently diagnosed with type 2 DM. In our study, we found CTS at a frequency of 20.9% in patients newly diagnosed with PD. As expected, this percentage is lower than the newly diagnosed patients with DM and it is higher than the prevalence of CTS in general population.[3-5,13,14] Therefore, the PD state may be a 'window of opportunity' to prevent diabetic neuropathies and their burdens.[25]

In our study, we excluded patients with hypothyroidism, acromegaly, pregnancy, and rheumatic and traumatic hand disorders, as these conditions may affect the true prevalence of CTS and hand functions.[16] It is well known that frequency of obesity is high in PD patients.[26] Confounding factors for CTS such as age, sex, BMI, and occupations were found to be similar between the groups in our study. Thus, there is a suitable condition to compare the groups in terms of prevalence of CTS. The frequency of CTS in PD patients was slightly higher than the control group, although not statistically significant. Of note, this is the first study to compare CTS frequency in PD patients and normoglycemics. The frequency of CTS in the control group (14.8%) and in general population studies (2.7 to 16%) were comparable.[3-5]

The current study is also the first to determine CTS frequency in PD subgroups, such as those with an isolated elevation of HbA1c (5.7 to 6.4%), IFG, and IGT. There are controversial results obtained from studies on whether the prevalence of neuropathy increases in patients with IGT.[27-29] However, there is an increased frequency of IGT in peripheral neuropathy cohorts.[30] These conflicting results can be attributed to the presence of obesity and/or metabolic syndrome, age, sex, or hyperlipidemia. However, it was previously shown that IGT was three-times more prevalent than normal glucose tolerance in patients with small fiber neuropathy.[31] However, there are not enough large-scale, prospective studies investigating the association between IFG and CTS, yet. In our study, the frequency of CTS was found to be higher in the IGT group (23.5%) than the other subgroups of PD. However, the number of participants were not appropriate for statistical analysis.

It has been well established that CTS is associated with an impaired hand function.[6] In a meta-analysis including patients with diabetes, Gundmi et al.[32] showed that hand grip and pinch strength decreased and hand functions were lost, compared to the control group. In our study, due to the similar frequency of CTS in the PD and control groups, it was expected that there was no significant difference in hand functions between the two groups. However, impaired hand functions were found in patients with PD, compared to the control group, suggesting that other factors such as limited joint mobility syndrome or other diabetic hand disorders may play a role. Therefore, there is a need for further studies to evaluate diabetic hand complications in patients with PD.

In our study, age, BMI, OGTT at 0 and 2 h, HbA1c, and HOMA-IR values were similar in the PD patients with and without CTS. However, the HGS and hand functions were worse in patients with CTS. This might be associated with median nerve dysfunction as shown in previous studies.[6,32] Consistent with the literature, all patients with CTS were females in our study. Also, the review of the literature reveals no clear association of IGT and/or IR with CTS. Our study showed that glycemic levels and IR were not significantly different in PD patients with or without CTS.

Our study has strengths and limitations. The former include that we assessed prediabetic patients both clinically and neurophysiologically and we evaluated participants' hand functions with DHI which is a validated and reliable questionnaire. We also compared them with healthy controls. The main limitations of our study is that it was monocentric and that our patient population was, therefore, comprised from one geographic area and with a similar socio-cultural background.

In conclusion, our study is the first study to reveal that CTS is slightly more common and hand functions are impaired in PD compared to the controls. Nonetheless, further large-scale, prospective studies are needed to evaluate diabetic hand complications in patients with PD and to draw a firm conclusion on this issue.

Declaration of conflicting interests

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