Evaluation of interoceptive accuracy in diabetic individuals with or without polyneuropathy

Polinöropatisi olan ve olmayan diyabetik bireylerde interoseptif keskinliğin değerlendirilmesi

Abstract

Aim: Diabetic peripheral neuropathy (DPN) is a heterogeneous disease with a complex pathophysiology that can affect both autonomic and somatic components of the nervous system. Interoception is a perceptual and cognitive concept expressing the internal sensory perception that evaluates signals from the body and internal organs. Interoceptive abilities have been indicated to be reduced in various chronic pain syndromes and chronic neuropathies. That said, interoceptive skills in individuals with Type 2 Diabetes Mellitus with and without a previous DPN comorbidity have not been comparatively examined. We aimed to examine whether there is a difference in terms of interoceptive accuracy in individuals diagnosed with Type 2 Diabetes Mellitus with and without DPN for the first time.

Methods: 20 individuals with a diagnosis of Type 2 Diabetes Mellitus with a co-diagnosis of DPN and 20 individuals with a diagnosis of Type 2 Diabetes Mellitus without a co-diagnosis of DPN were recruited in the Electroneurophysiology Laboratory of Muğla Sıtkı Koçman University. The presence of DPN was evaluated with both Toronto Clinical Scoring System and electromyographic examination. General cognitive status was evaluated with the Mini-Mental State Examination, general psychiatric status with the Patient Health Questionnaire-9, and cardiac interoceptive accuracy with the Heartbeat Counting Test.

Results: No difference was found in terms of cardiac interoceptive accuracy in individuals with Type 2 Diabetes Mellitus with and without DPN.

Conclusions: The potential decrease in cardiac interoception might be related to chronic pain or autonomic neuropathy rather than the presence of DPN. Studies examining interoception in these subgroups are required.

Keywords: Cognition; diabetic polyneuropathy; neurophysiology; Type 2 Diabetes Mellitus

Öz

Amaç: Diyabetik periferik nöropati (DPN), kompleks bir patofizyolojisi olan ve sinir sisteminin otonom ve somatik olmak üzere her iki komponentini de etkileyebilen heterojen bir hastalıktır. Interosepsiyon ise bedenden ve iç organlardan gelen sinyallerin değerlendirildiği iç duyu algısını ifade eden algısal ve bilişsel bir kavramdır. Interoseptif becerilerin çeşitli kronik ağrı sendromlarında ve kronik nöropatilerde azalmış olabileceği gösterilmiştir. Bu bilgiyle beraber daha önce DPN eştanısı olan ve olmayan Tip 2 Diyabetes Mellitus tanılı bireylerde interoseptif beceriler karşılaştırmalı olarak incelenmemiştir. Bu çalışmada ilk kez DPN olan ve olmayan Tip 2 Diyabetes Mellitus tanılı bireylerde interoseptif keskinlik açısından fark olup olmadığının incelenmesi amaçlanmıştır.

Yöntemler: Muğla Sıtkı Koçman Üniversitesi Elektronörofizyoloji Laboratuvarında DPN eştanısı olan 20 Tip 2 Diyabetes Mellitus tanılı birey ile DPN eştanısı olmayan 20 Tip 2 Diyabetes Mellitus tanılı birey çalışmaya dahil edildi. DPN varlığı Toronto Klinik Skorlama Sistemi ve elektromyografik inceleme ile değerlendirildi. Standardize Mini Mental Test ile genel bilişsel durum, Hasta Sağlık Anketi-9 ile genel psikiyatrik durum, Kalp Hızı Sayma Testi ile kardiyak interoseptif keskinlik incelendi.

Bulgular: Bu çalışmada DPN tanısı olan ve olmayan Tip 2 Diyabetes Mellitus tanılı bireylerde kardiyak interoseptif keskinlik açısından fark saptanmamıştır.

Sonuçlar: Kardiyak interoseptif becerilerdeki potansiyel azalmanın DPN varlığından ziyade kronik ağrı ya da otonom nöropati ile ilişkili olabileceği düşünülmüştür. Bu alt gruplarda interosepsiyonu inceleyen çalışmalara gereksinim duyulmaktadır.

Anahtar Sözcükler: Biliş; diyabetik polinöropati; nörofizyoloji; Tip 2 Diyabetes Mellitus

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Received/*Geliş* : 02.08.2023
Accepted/*Kabul*: 01.10.2023

DOI: 10.21673/anadoluklin.1336415

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common neurological disorder and the most common form of chronic neuropathy worldwide, with a wide range of distinct symptoms stemming from abnormalities in motor, sensory, and autonomic nerves (1). DPN is also among the most common complications of diabetes mellitus, thus constituting a public health concern (1). Complex pathophysiology and course of DPN have not yet been resolved clearly while multitudinous pathophysiological factors possibly stemming from the disruptive effects of chronic hyperglycemic state have been proposed (2).

Interoception is an umbrella term that refers to the internal sense perception in which signals from the body and internal organs are evaluated as well as the cognitive evaluation of these signals (3).

Ever-increasing attention towards interoception led to a myriad of studies regarding interoceptive abilities which revealed a complex interplay between brain and body, thus confirming the presence of three concepts representing distinct aspects of interoception, namely interoceptive accuracy (IA), interoceptive sensitivity, and interoceptive awareness (3). IA is the cognitive component of interoception which is more related to physiological factors rather than psychological determinants. While IA encompasses the physiological outputs of several organ systems, cardiac IA is considered to reflect general IA. Thus, cardiac IA is the most commonly studied form of it which can be practically evaluated with the Heartbeat Counting Task (4).

The mechanistic roles of IA in several physical and psychological conditions have been extensively studied, which not only helps to disclose the manifold interactions between brain circuitry and the peripheral nervous system but also provides the rationale for novel treatment modalities attempting to promote interoception (5,6). However, causal links between pathophysiology and dysregulated interoceptive processing have not been overtly revealed (3). Moreover, data regarding the contributing role of IA in type 2 diabetes mellitus are scarce. A few studies associated IA with fear of hypoglycemia or blood glucose estimate accuracy while no studies have evaluated IA in DPN thus far (7,8).

Aside from the above, cognitive impairment is a frequently observed and considerably debilitating complication of diabetes mellitus (9,10). Additionally, involvement and overlapping impairment of the central nervous system have been depicted in DPN (11). Thus, it is not surprising that individuals with DPN have recently been indicated to have higher cognitive deficits than diabetic individuals with DPN (9,12). Since IA is the cognitive component of interoception, alteration of IA might also be higher in individuals with DPN than diabetic individuals without DPN. Bearing these in mind, we hypothesized that individuals with DPN might have more diminished IA than diabetic individuals without DPN. The present study aimed to evaluate cardiac IA in diabetic individuals with and without DPN for the first time.

MATERIALS AND METHODS

Setting

The study was conducted at the Electromyography (EMG) clinic of the Department of Neurology in the Faculty of Medicine, Muğla Sıtkı Koçman University. 40 individuals diagnosed with Type 2 Diabetes Mellitus were recruited. Type 2 Diabetes Mellitus was diagnosed according to the American Diabetes Association's criteria (13). The presence of diabetic polyneuropathy (DPN has been established by both clinical examinations and EMG evaluation. The established EMG-supported criteria were used to diagnose the presence of DPN (14). Participants were divided into two groups as DPN group and the Diabetes Mellitus without Diabetic Polyneuropathy (DMwDPN) group. Individuals without neuropathic symptoms and electromyographic findings were considered to be in the DMwDPN group. Both the DPN group and the DMwDPN groups consisted of 20 participants.

The inclusion criteria were as follows: Diagnosed with Type 2 Diabetes Mellitus according to the American Diabetes Association's criteria, aged between 18-80 years old, education level to understand and cooperate with the study procedures, Body Mass Index below 35, Mini-Mental State Examination (MMSE) score above 24. Participants with active major depressive disorder, present diagnosis or previous history of alcohol and substance use disorder, diagnosis of any

serious or uncontrolled medical conditions and other comorbidities that might cause neuropathy, individuals with a previously diagnosed neurological disorder that might affect the cognitive status, significant hearing loss or visual impairment were excluded.

Procedures

All procedures were conducted in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. Written informed consent was collected from all participants before enrolment. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (date: 19.01.2023, decision no: 2/XIII).

Demographic and clinical variables of the participants were collected. The percentages of glycosylated hemoglobin (HbA1c) were denoted as an indicator of glycemic control. Toronto Clinical Scoring System and the Self Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) Metin girmek için buraya tıklayın veya dokunun. were administered to assess the degree of neuropathy (15-17). General mental health status and the level of depression were evaluated with the Patient Health Questionnaire-9 (PHQ-9) (18). EMG was administered to further validate the diagnosis of DPN. The Mini-Mental State Examination (MMSE) was utilized to screen for general cognitive decline (19). The Heartbeat Counting Task was administered to evaluate interoceptive accuracy (IA).

Measures

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a relatively short but practically useful instrument to evaluate depressive symptoms in distinct samples (18). It consists of nine Likert-type items and has a maximum score of 27. Having a score above 10 has been associated with the possible presence of clinically significant depression (18).

Mini-Mental State Examination (MMSE)

The MMSE is a commonly used screening tool to evaluate general cognitive status in both healthy older adults and individuals with neuropsychiatric disorders (19). It provides an overall evaluation of distinct cognitive domains practically and helps clinicians to detect individuals with cognitive impairment and refer them for further cognitive evaluation. Individuals with a total score above 24 have been less likely to have a significant neurocognitive disorder.

Self-Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)

The S-LANSS is a modified version of the Leeds Assessment of Neuropathic Symptoms and Signs for self-report administration (17). The primary purpose of the instrument is to discriminate individuals with nociceptive or neuropathic pain. A score equal to or above 12 indicates probable neuropathic pain.

Electromyographical Evaluation

A four-channel Nihon-Kohden Neuropack MEB 9400 EMG device (Nihon-Kohden, Tokyo, Japan) was used for EMG evaluations. The device was calibrated before each measurement. Measurements were taken with bipolar electrodes. A 20–2,000 Hz bandpass filter for the sensory nerve studies and a 2–10,000 Hz bandpass filter for the motor nerve studies were used. The limb temperature of all subjects was maintained above 31–32 Celsius degree.

Distal latencies (DL) were recorded for the median motor nerve, post-tibial motor nerve, ulnar motor nerve, and peroneal motor nerve. Nerve conduction velocities (NCV) were recorded for the median motor nerve, post tibial motor nerve, ulnar motor nerve, peroneal motor nerve, median sensory nerve, ulnar sensory nerve, and sural sensory nerve. Compound Motor Action Potentials (CMAP) were recorded for the median motor nerve, post tibial motor nerve, ulnar motor nerve, peroneal motor nerve, median sensory nerve, ulnar sensory nerve, and sural sensory nerve. F wave latencies were recorded for the median motor nerve, post-tibial motor nerve, ulnar motor nerve, and peroneal motor nerve.

Heartbeat Counting Task

The Heartbeat Counting Task was developed in 1981 and is still a widely adopted and the most commonly used tool to assess cardiac IA (4). The task is initiated after a 5-minute rest period, and participants are asked to count their heartbeat between the predetermined intervals and report their predictions verbally at the end of each interval. Objective recording of heartbeat

Table 1. Differences in demographic and clinical features between diabetic individuals with or without peripheral neuropathy

Variables	DPN (n=20)	DMwDPN (n=20)	Z/t*	*P-values*
A. Demographic				
Age (years)	63.75 ± 11.05	61.05 ± 9.51	0.828	0.413
Gender (Male/Female)	19/1	8/12		**<0.001****
Education (years)	5.0 (6.3)	9.0 (7.0)	-0.298	0.766
BMI	29.18 ± 5.01	29.72 ± 5.12	-0.337	0.738
B. Clinical				
Disease onset (age)	49.85 ± 13.76	47.75 ± 10.29	0.546	0.588
Duration of diabetes (years)	15.95 ± 9.36	13.10 ± 11.83	0.845	0.404
Glycosylated hemoglobin (HbA1c) (%)	8.15 (1.30)	6.60 (2.11)	-2.998	**0.003**
PHQ-9 (score)	6.5 (8.25)	8.50 (10.75)	-1.628	0.109
S-LANSS (score)	13.45 ± 5.52	10.65 ± 7.39	1.357	0.183
MMSE (Score)	29.0 (2.0)	28.0 (2.0)	-2.589	**0.010**
IA (Score)	0.622 ± 0.253	0.556 ± 0.241	0.838	0.407

*t scores for Independent Samples-T tests, Z scores for Mann-Whitney U tests. **Fisher's Exact Test. Mean ± Standard Deviations are shown for normally distributed variables. Medians (Interquartile Ranges) are shown for non-normally distributed variables. DPN: Diabetic Polyneuropathy, BMI: Body Mass Index; DMwDPN: Diabetes Mellitus without Diabetic Polyneuropathy; PHQ-9: Patient Health Questionnaire-9; S-LANSS: Self-Leeds Assessment of Neuropathic Symptoms&Signs; VAS: Visual Analogue Scale; MMSE: Mini-Mental State Examination; IA: Interoceptive Accuracy. Significant p-values are bold.

count was also concomitantly performed using an electrocardiogram device. Three distinct time intervals (25-35-45 second blocks) were recorded twice in a random order without telling the exact duration of the time intervals to the participants. Thirty-second breaks were left between recording blocks, and participants were instructed to begin or stop counting at the onset or the end of each recording interval. A higher index of IA means better interoceptive skills. IA is an index ranging between 0 and 1, calculated as follows: $1/6 \sum (1 - (|\text{recorded heartbeats} - \text{counted heartbeats}|)/\text{recorded heartbeats})$.

Statistical Analyses

The SPSS Statistics for Windows (Statistical Package for the Social Sciences package program version 25.0, IBM Corp., Armonk, N.Y., USA) was utilized to perform statistical analyses in the present study. The assumption of normality was checked using Shapiro-Wilk tests. Levene's tests were used to assess variance homogeneity. The number of educated years, the percentage of glycosylated hemoglobin A1c, the PHQ-9 total score, the MMSE score, post-tibial motor F wave latency, and peroneal motor distal latencies were non-normally distributed. Frequencies or percentages are shown for categorical variables. Fisher's Exact Test was used to determine gender differences. Means ± standard deviations were presented for normally distributed variables while medians (Interquartile Ranges) were presented for non-normally distributed variables. The Independent Samples T-tests or Mann-Whitney *U* tests were used to determine differences between the DPN and the DMwDPN groups. Spearman correlations were used to examine relationships between demographic, clinical, and electromyographical variables and the IA. A *p*-value of 0.05 was set as a significance level. The primary outcome measures were the EMG variables and the IA.

RESULTS

Table 1 indicates the demographics and clinical features of the present sample. The whole study sample had a mean age of 62.4 (±10.2), a mean number of educated years of 8.1 years, a mean disease onset of 48.8 years, and a mean disease duration of 14.5 years. 13 female and 27 male participants were recruited. The ratio of males was higher in the DPN group ($p<0.001$). The Toronto Clinical Scoring System scores were higher in the DPN group ($p<0.001$). The percentage of HbA1c was higher and the MMSE scores were higher in the DPN group. No differences were observed be-

Table 2. Differences in electromyographic variables between diabetic individuals with or without peripheral neuropathy

Variables	DPN (n=20)	DMwDPN (n=20)	Z/t*	*P-values*
A. Median nerve (motor)				
DL (ms)	4.35 (1.41)	3.51 (0.99)	-2.572	**0.01**
NCV (m/s)	45.90 ± 8.29	54.85 ± 4.63	-4.191	**<0.001**
CMAP (mV)	10.258 ± 4.171	12.123 ± 1.988	-1.767	0.089
F wave latency (ms)	32.736 ± 3.095	27.290 ± 2.133	6.369	**<0.001**
B. Post tibial nerve (motor)				
DL (ms)	4.550 ± 0.925	3.942 ± 0.767	2.154	**0.038**
NCV (m/s)	37.05 ± 3.96	46.01 ± 3.91	-6.789	**<0.001**
CMAP (mV)	6.088 ± 4.304	10.703 ± 3.472	-3.563	**0.001**
F wave latency (ms)	60.20 (10.45)	48.70 (3.75)	-4.744	**<0.001**
C. Ulnar nerve (motor)				
DL (ms)	2.936 ± 0.627	2.434 ± 0.270	3.264	**0.002**
NCV (m/s)	46.56 ± 7.74	55.51 ± 3.66	-4.625	**<0.001**
CMAP (mV)	9.36 ± 3.13	12.76 ± 3.01	-3.411	**0.002**
F wave latency (ms)	33.76 ± 4.59	27.53 ± 2.27	5.084	**<0.001**
D. Peroneal nerve (motor)				
DL (ms)	4.718 ± 0.965	3.802 ± 0.677	-3.217	**0.001**
NCV (m/s)	37.36 ± 5.11	46.80 ± 3.09	-6.837	**<0.001**
CMAP (mV)	3.551 ± 3.094	6.010 ± 3.059	-2.385	**0.023**
F wave latency (ms)	58.50 ± 6.66	48.49 ± 4.03	5.462	**<0.001**
E. Median nerve (sensory)				
NCV (m/s)	41.91 ± 8.51	49.21 ± 9.15	-2.450	**0.020**
CMAP (µV)	9.950 ± 8.815	19.330 ± 11.488	-2.690	**0.011**
F. Ulnar nerve (sensory)				
NCV (m/s)	45.02 ± 5.79	55.15 ± 2.96	-6.751	**<0.001**
CMAP (µV)	9.53 ± 7.27	15.55 ± 4.88	-2.928	**0.006**
G. Sural nerve (sensory)				
NCV (m/s)	34.60 ± 2.67	48.45 ± 4.97	-8.533	**<0.001**
CMAP (µV)	5.20 ± 3.40	10.44 ± 3.42	-4.084	**<0.001**

*t scores for Independent Samples-T tests and Z scores for Mann-Whitney U tests. Mean ± Standard Deviations are shown for normally distributed variables. Medians (Interquartile Ranges) are shown for non-normally distributed variables. DL: Distal latency; NCV: Nerve Conduction Velocity; CMAP: Compound Motor Action Potential; Ms: milliseconds; m/s: meter/second; mV: millivolt; **µV**: Microvolt DPN: Diabetic Polyneuropathy; DMwDPN: Diabetes Mellitus without Diabetic Polyneuropathy. Significant p-values are bold.

tween groups in any other baseline demographic and clinical variables.

No difference in IA was observed between groups. Differences in EMG variables are indicated in Table 2. There were significant differences between groups except for left median nerve motor amplitude. The S-LANSS score correlated negatively with the IA (r=-0.440; p=0.005).

The IA correlated with the median motor nerve DL (r=0.374; p=0.019), median motor NCV (r=-0.371; p=0.020), median motor nerve F wave latency (r=0.481; p=0.002), ulnar motor nerve DL (r=0.348; p=0.032), ulnar motor NCV (r=-0.350; p=0.031), ulnar motor nerve F wave latency (r=0.370; p=0.024), median sensory NCV (r =-0.445; p=0.006) and median CMAP amplitude (r =-0.357; p=0.033).

DISCUSSION AND CONCLUSION

The present study aimed to determine the differences in cardiac IA between diabetic individuals with or without DPN for the first time and did not reveal any differences in IA between diabetic individuals with or without DPN.

Similar to the previously indicated relationship between some cognitive functions and NCV in DPN,

correlations between the EMG indices and the IA were found, conceivably indicating a possible relationship between the stability of peripheral nerve conduction and interoceptive abilities (20). Nonetheless, interoceptive abilities might still be intact in individuals with DPN. The proposed deficits in IA might be associated with the severity and duration of chronic pain instead of the presence of the DPN. Mounting evidence suggests a strong link between chronic pain and interoceptive processing (21,22). This link seems to be transdiagnostic as deficits of IA have been indicated in a variety of chronic pain conditions like musculoskeletal, primary, and neuropathic pain conditions (21). Moreover, IA has been negatively correlated with pain severity in some specific disorders (22). Decrement of interoceptive abilities in chronic pain conditions was considered to be due to the disruptive and misbalancing effects of chronic pain on descending pain pathways and the interoceptive network in the brain (22). Thus, proposed deficits of cardiac IA in DPN might also be an epi-phenomenon due to the alteration of pain-related pathways rather than the presence of peripheral neuropathy itself. As a result, further studies might focus on painful DPN.

Besides, deficits in cardiac IA might also be apparent in individuals with moderate or severe diabetic autonomic neuropathy on account of the relationship between the autonomic nervous system and interoceptive abilities (23,24). While the Toronto Clinical Scoring System has a good correlation with the electromyographical indices, it was not adequate to evaluate the presence of autonomic neuropathy (16). Thus, we did not clearly determine the presence of diabetic autonomic neuropathy in the present sample. On the other hand, diabetic autonomic neuropathy is commonly observed and mostly affects the cardiovascular system (25). Thus, further studies evaluating cardiac IA in individuals with diabetic autonomic neuropathy are warranted.

The present study has some strengths, including the assessment of the presence of neuropathy using both the Toronto Clinical Scoring System and EMG. Individuals with morbid obesity or global cognitive impairment were excluded due to their proposed relationship between interoceptive abilities. Nevertheless, a few limitations of the present work should be noted. The lack of pain severity assessment, interoceptive sensitivity and awareness assessment, and the small number of participants are among the limitations of the present work.

Overall, the present findings do not point out a difference in interoceptive abilities between diabetic individuals with or without DPN. As the research regarding the role of IA in DPN is still in its infancy, additional inquiry is needed to confirm the interplay between interoceptive abilities and DPN. Moreover, studies assessing cardiac IA in individuals with or without diabetic autonomic neuropathy are required.

Conflict-of-Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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