Relationship between Pancreas Exocrine Insufficiency and Cardiac Autonomic Neuropathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: *The exocrine function of the pancreas is controlled by the autonomic nervous system (ANS), and autonomic neuropathy is a common and serious complication of diabetes. There are many factors contributing to the development of autonomic neuropathy in diabetic patients. Cardiovascular tests have been developed to evaluate the function of the ANS. This study investigated the relationship between cardiovascular autonomic neuropathy (CAN) and pancreas exocrine insufficiency (PEI) in diabetic patients.*

Methods: *This study evaluated 110 individuals with type 2 diabetes mellitus (T2DM) and 40 healthy volunteers. Autonomous neuropathy tests were utilized to diagnose patients, and Ewing and Clarke's criteria were employed to assess the severity of autonomous dysfunction. Stool samples were also collected from patients to measure fecal elastase-1 (FE-1).*

Results: *A 65.5% incidence of PEI was observed in DM patients. There was no significant correlation among the duration of disease, C-peptide, HbA1c, and PEI, respectively (P = .782, P = .521, P = .580). However, a significant difference between DM patients and controls in terms of cardiac dysautonomia (P = .001) was seen. Moreover, a statistically significant correlation between the degree of cardiac dysautonomia and FE-1 level was observed within the patient group (P =.001).*

Conclusion: *It is possible that the disruption of exocrine hormone secretion in the pancreas due to the impairment of enteropancreatic reflexes is secondary to diabetic autonomic neuropathy and resulting in PEI. This study also showed that autonomic neuropathy might develop and cause PEI in diabetic patients without known added confounding factors.*

Keywords: *Pancreas exocrine insufficiency, type 2 diabetes mellitus, cardiovascular autonomic neuropathy*

BACKGROUND

Diabetes mellitus (DM) often induces peripheral, autonomic, and central neuropathy in affected individuals, and diabetic autonomic neuropathy is a common and serious complication of DM. Following diagnosis with diabetes, a patient usually observes 4% of autonomic neuropathy within the first year, 20-30% by the fifth year, and 30-50% over the next 20 years[1]. Diabetic autonomic neuropathy may also be symptomatic or asymptomatic, and subclinical autonomic neuropathy may develop within the first 2 years of diagnosis with type 1 DM and within the first year following diagnosis with type 2 DM. Many organs can be innervated by the parasympathetic and sympathetic fibers of the autonomic nervous system (ANS). DM can affect the nervous system at all levels, so patients may experience many different symptoms. DM generally affects the gastrointestinal, cardiovascular, and genitourinary systems, and it may induce complications, such as resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, erectile dysfunction, constipation, diarrhea, and brittle diabetes. DM commonly results in gastrointestinal complications, as well, and may affect any part of the gastrointestinal tracts.[2]

Cardiovascular tests have been developed to evaluate the parasympathetic and sympathetic nervous systems separately within the ANS. These tests have been prepared based on balancing abnormalities that may occur in the cardiovascular system because of various exercises and maneuvers and activating the ANS. For this purpose, diagnosis is prefaced on Ewing and Clarke's criteria, and the severity of dysfunction is determined.[3] Gastrointestinal complaints, especially fecal incontinence and gastroparesis, are common among

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DM patients and are caused by diabetic neuropathy.[4] On the other hand, diabetic diarrhea and steatorrhea complaints are likely due to pancreas exocrine insufficiency (PEI), which is more common than diabetic neuropathy.[5] Moreover, the incidence of PEI is not infrequent in DM patients. PEI has been observed in an average of 51% (26-74%) of patients with type 1 DM and 32% (28-36%) of those with type 2 DM.[4] The secretion of the pancreas exocrine is controlled by the ANS and is mediated by many hormone secretagogues and neurotransmitters. Impairment of the ANS induces PEI due to the disruption of enteropancreatic reflexes and a deficiency in enzyme secretion.[6,7] This study examined the relationship between cardiovascular autonomic neuropathy (CAN) and PEI.

PATIENTS AND METHODS

A total of 150 patients were included in this study. In which, 110 patients aged 30 years and over who had been diagnosed with type 2 DM and expressed gastrointestinal dyspeptic complaints (abdominal pain and discomfort,constipation, diarrhea, fecal incontinence, swelling,soft defecation, steatorrhea). Forty healthy volunteers were enrolled in the study as the control group. Patients excluded from this study were those with known diseases related to the gastrointestinal tracts (irritable bowel syndrome, inflammatory bowel disease, previous abdominal surgery, on diet, regular or recent alcohol consumption, and smoking habits); those using acarbose, orlistat, beta-blockers, and calcium channel blockers; those with a history of malignancy and pancreatitis; alcohol abusers and smokers; those with chronic diarrhea; and those with pancreatic pathology as indicated by abdominal ultrasonography (USG) and computed tomography (CT), if needed. Patients with thyroid dysfunction, biliary stone disease, malabsorption syndromes, such as celiac disease or other autoimmune diseases, ischemic heart disease, myocardial infarction, obstructive sleep apnea syndrome, non-alcoholic fatty liver, or cardiac surgery were also excluded. Patient's neurological examination, eye examination, and urine analysis were performed before the inclusion in the study. Patients with diabetic microvascular complications, such as nephropathy, retinopathy, sensory neuronal neuropathy, and c-peptide level under 1 ng/mL, were excluded from the study. All participants were informed in detail about the study and completed consent forms for scientific research. Moreover, this study was approved by the ethics committee of Gaziantep University Medical Faculty (decision no: 25/01/2017 – 26).

The first phase of the study involved recording the following patient information: age, duration of disease, BMI, dyspeptic complaints, presence of hypoglycemia attack, the status of using an insulin pump, C-peptide levels, insulin levels, low-density lipoprotein (LDL) cholesterol levels, hemoglobin A1C (HbA1c) levels, vitamin D levels, vitamin B12 levels presence of hepatosteatosis, and diabetic micro–macro complications and drugs use. Afterward, neuropathy tests were conducted on the same day in an adequately warm and quiet room. The following instruments were used: a standard electrocardiogram device (Hewlett Packard Page Writer 2004 electrocardiogram Sanborn series, Waltham, MA, USA), a blood pressure-measuring device (ERKA perfect aneroid, ERKA, Bad Tölz, Germany), and a monitor pulse oxymeter (Elance Spacelabs Healthcare Medical, Issaquah, WA, USA). Following these tests, the diagnosis and severity determination of autonomous dysfunction were assessed via Ewing and Clarke's criteria. The autonomous neuropathy tests were comprised of 3 parasympathetic and 2 sympathetic components.

The tests were performed as follows:

- Stand-up response (parasympathetic): ECG and rhythm of D2 derivation were obtained when the patient was in the supine position. Then, the patient was raised and waited for 35 beats, and the ratio of the longest R-R distance to the shortest R-R distance was calculated.
- Response to deep breathing (parasympathetic): The patient in the sitting position was asked to perform deep inspiration and expiration approximately 6 times in 10 minutes. After 3 consecutive cycles, the minimum and maximum heart rates were recorded. The mean differences were calculated.
- Valsalva (Parasympathetic): D2 rhythm was recorded while the patient was in a sitting position and forced expiration to a manometer with a pressure of approximately 40 mmHg. The ratio of the R-R distance to the shortest R-R distance after the Valsalva was calculated.
- Isometric exercise (sympathetic): The patient was asked to squeeze a sphygmomanometer pump for about 5 min with approximately 30% of the hand-squeezing force. Blood pressures were measured before and after exercise. Diastolic blood pressure difference was calculated.
- Cold application (sympathetic): The patient's hand was kept in a container full of ice for 1 min. Blood pressure was measured before and after. Diastolic blood pressure difference was calculated.

CAN tests, including 3 parasympathetic and 2 sympathetic tests, were conducted among patients in order to identify the presence of autonomic neuropathy. The results were subsequently analyzed using Ewing and Clarke's criteria. CAN tests are important for diagnosing and following autonomic neuropathy because they are simple and non-invasive and have been used for a long time.[8,9,10] On the other hand, one disadvantage of these tests is their dependence on the physical and sociocultural characteristics of individuals. Alongside the CAN tests, 100 mg stool samples were collected from patients for FE-1 measurement.

The tests were applied as follows:

The normality of the numerical variable was tested via the Shapiro–Wilk test. A Student's *t*-test was utilized to compare the normally distributed data of 2 groups, while analysis of variance test was used to compare this data among 3 groups. In addition, the Kruskal–Wallis test was used to compare the skewed data among 5 groups. The correlations between categorical variables were determined via a chi-square test, and the correlations between numerical variables were tested via a Pearson correlation test. Statistical Package for the Social Sciences 22.0 software was utilized to analyze the results, and $P < .05$ values were considered as statistically significant.

RESULTS

A total of 150 individuals were included in this study as the control group and the patient group. Of these, 54.7% ($n = 82$) were male and 45.3% ($n = 68$) were female. There was no statistically significant difference between the groups in terms of gender ($P = .288$).

The mean age of the patient group was 39.03 ± 12.31 years, and the mean age of the control group was 46.76 ± 16.65 years. There was a statistically significant difference between the groups in terms of age ($P = .003$). In the control group, the relationship between age and FE-1 levels was investigated, and a moderate correlation was identified as statistically negative ($P = .005$, $r = -0.437$). The mean FE-1 value of the patient group was 179.67 ± 74.95 μg/g, and that of the control group was 262.40 ± 94.98 μg/g. There was a statistically significant difference between the groups ($P = .001$).

A comparison of the data between the groups is presented in Table 1.

Table 1. Comparison of Group Characteristics

	Patients	Control	*P*
Age**	39.03 ± 12.31	46.76 ± 16.65	.003*
Sex***			
Male	63 (57.3)	19 (47.5)	.288
Female	47 (42.7)	21 (52.5)	
BMI**	27.91 ± 6.04	26.74 ± 4.35	.265
FE-1 level**	179.67 ± 74.95	262.40 ± 94.98	.001*
Cardiac dysautonomia			
Normal	38 (345%)	40 (100%)	.001*
Abnormal	72 (65.5%)	0 (0%)	

*$P < .005$; **mean ± standard deviation.

In the current study, the incidence of PEI was determined to be 65.5% in DM patients. Of these, mild-to-moderate PEI was observed in 60.9%, and severe PEI was observed in 8.2%. No significant correlation was found between the duration of disease and PEI ($P = .782$). The mean c-peptide level of the patients was 3.09 ± 2.00 ng/mL, and the mean HbA1c level was 10.23 ± 2.37%. There was no significant correlation between the c-peptide level and PEI ($P = .521$). There was no correlation between HbA1c and vitamin D level and PEI ($P = .580, .557$). Patients were classified according to their FE-1 levels as exhibiting mild, moderate, or severe PEI. Those with a median of 100 μg/g were classified as having severe PEI. In the patient group, 34 patients (30.9%) exhibited normal, 67 patients (60.9%) exhibited mild-moderate, and 9 patients (8.2%) exhibited severe PEI. In the control group, 37 (92.5%) were classified as having normal PEI, and 3 (7.5%) were classified as having mild-to-moderate PEI. No member of the control group exhibited severe PEI. In 34.5% of the patient group, the cardiac dysautonomia was not detected by CAN tests and was evaluated as normal. The atypical combination was found in 12 patients (10.9%), early cardiac dysautonomia in 35 patients (31.8%), definite cardiac dysautonomia in 13 patients (11.8%), and severe cardiac dysautonomia in 12 patients (10.9%). No cardiac dysautonomia was detected by CAN tests in the 40-person control group. In the comparison of c-peptide, insulin, LDL cholesterol, and vitamin D levels in the patient group, no statistical relationship was found in the comparison of the degree of cardiac dysautonomia. There was a statistically significant correlation between the degree of cardiac dysautonomia and FE-1 levels in the patient group ($P = .001$). Moreover, there was a modest, statistically significant negatively correlation between the

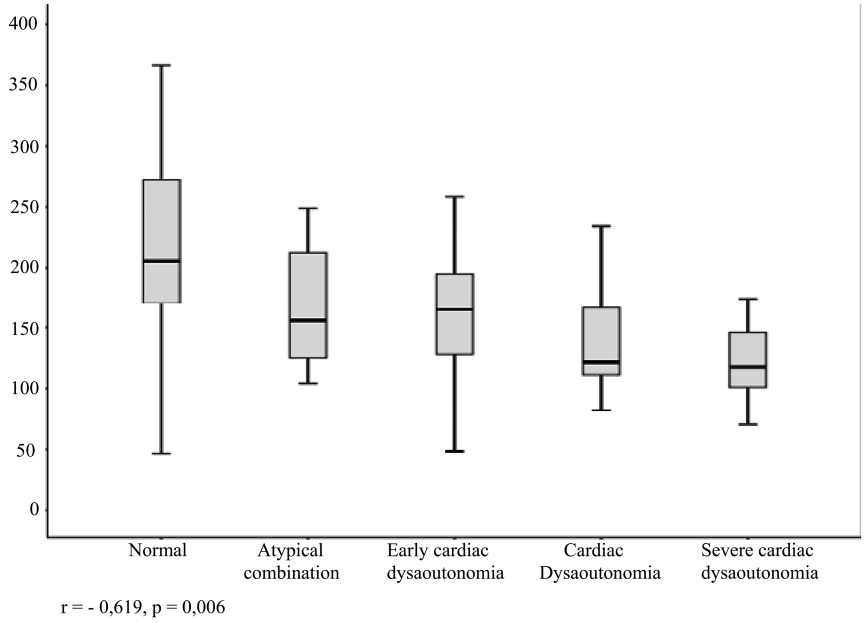

Figure 1. The relationship between fecal elastase-1 level and cardiac dysautonomia.

degree of cardiac dysautonomia and the degree of PEI (r = −0.619, P = .006) (Figure 1).

DISCUSSION

Disruption of enteropancreatic reflexes by autonomic neuropathy may significantly impair exocrine pancreatic function.[11] The prevalence of PEI increases proportionally with hyperglycemia, advanced age, duration of diabetes, and insulin deficiency in DM patients.[12,13] Moreover, severe PEI is observed in 22% of DM patients. This rate may be higher in patients with a longer history of diabetes, poor glycemic control, microvascular damage, and low BMI.[14] However, studies have also reported that PEI is not associated with the duration of diabetes, glycemic control, and complications.[15,16,17] There are several studies that showed the relationship between prediabetes and autonomic dysfunction.[18,19,20,21] The present study demonstrated that there was no correlation between disease duration, c-peptide level, HbA1c, vitamin D level, and PEI presence.

Hardt et al.[14] found the prevalence of PEI to be 40.7% in 1201 diabetic patients. In terms of PEI degree, mild-to-moderate insufficiency was observed in 17.8% of patients and severe insufficiency in 22.9%. In the current study, the incidence of PEI was determined to be 65.5% in DM patients. The relatively low rate was observed in Hardt et al.'s study, which may be due to the fact that DM patients were included in their study regardless of the presence of complaints. In their study of 150 DM patients in Slovenia, Vusajinovic et al.[22] found the prevalence of PEI to be mild-to-moderate in 5.4% of patients and severe in 2.7%. The very low rate of PEI in their study may owe itself to the fact that the inclusion criteria were strict, involved a detailed search for pathologies that might have caused PEI through imaging methods, and included patients without considering the presence of symptoms. In another study conducted by Yılmaztepe et al.,[23] among 32 patients in Turkey who had only type 2 DM, the prevalence of PEI was found to be 28.1%, with 25% being mild-to-moderate and 3.1% being severe. On the other hand, the present study found the prevalence of PEI to be 67.6% in DM patients. This data is similar to our study. In terms of degree, mild-to-moderate PEI was observed in 58.1% of patients, and severe PEI was observed in 9.5%. Considering all studies, it is not easy to create an entirely ideal working pattern in autonomous dysfunction studies in diabetes.

In terms of CAN rates, the present study determined this rate to be 65.5% among DM patients, which is similar to the results of Pappachan et al.'s study, which found the rate of CAN among 100 DM patients to be 60%.[24] No cardiac dysautonomia was observed in the control group of the present study, and there was a significant difference between the 2 groups. This indicates that the control group was well-selected in terms of cardiac dysautonomia and that the healthy asymptomatic volunteers would not develop cardiac dysautonomia. In addition, the absence

of cardiac dysautonomia in healthy volunteers increased the accuracy of the CAN test.

Similar to numerous other studies which found no significant correlation between gender and the development of PEI in DM patients,[25,26,27,28] the present study also did not observe a significant correlation between FE-1 levels and gender. Moreover, no correlation between age and gender and cardiac dysautonomia was observed. The mean age of the control group was older than the diabetic group. Despite this, the fact that PEI is more common in the young diabetic patient group reveals how important diabetes is as a risk factor for PEI. This finding is similar to that of a study conducted by Rathman et al. regarding mortality which found that autonomic neuropathy is a risk factor independent of age and gender.[29]

In the literature, it is evident that hyperglycemia plays a role in the development of microvascular complications of diabetes. However, in some studies, especially in The European Diabetes (EURODIAB) Prospective Complications study, it has been shown that diabetic neuropathy may develop despite intensive glucose control.[30] Diabetes patients in our study were moderate and poorly controlled patients. There was no relationship between the duration of the disease and diabetes control and autonomic dysfunction and PEI. This made us think that autonomous dysfunction in diabetes patients could actually be an independent condition. As a matter of fact, there is a lot of data in this direction in the studies in the literature. In this respect, we think that it makes an additional contribution to the literature.

Regarding the relation between CAN and PEI, the current study has proven that the disruption of exocrine hormone secretion in the pancreas due to the impairment of enteropancreatic reflexes may be secondary to diabetic autonomic neuropathy, resulting in PEI. CAN is a distinct form of diabetic autonomic neuropathy with prominently affected cardiac functions. However, only a few studies have investigated the relationship between CAN and PEI. In a study conducted by Hardt et al., it was found that PEI may result from diabetic autonomic neuropathy.[14] The present study directly compared CAN and FE-1 levels, and a statistically significant correlation was found to exist between the 2. This indicates that CAN may be associated with PEI. In other words, CAN developed in DM patients may further induce the development of PEI. It is not possible to explain PEIs pathophysiology in diabetes with a single mechanism, but we believe that data that can contribute to the literature can be accessed if the development of exocrine insufficiency is not followed by a single pathway and is acted on the hypothesis that it may be independent of the degree and severity of diabetes.

LIMITATIONS

This study possessed several limitations. A potential difference in terms of FE-1 and CAN levels between patients with and without complaints was not examined. In addition, future studies might include an equal number of DM subtypes so as to make a more accurate comparison. Another limitation regards the fact that some patients with type 3c DM are also diagnosed with type 2 DM, and PEI is much more common in type 3c DM. Thus, a clear investigation of whether or not patients possess type 3c DM before inclusion may provide a more reliable determination of PEI prevalence in type 2 DM patients. Besides, some researchers claimed that the use of FE-1 to diagnose EPI; FE-1 has high sensitivity and specificity only in diagnosing severe PEI or high negative predictive value.[31] Our results were between 100 and 200 μg/g. Also, the chicken and egg question may arise in our study: whether autonomic neuropathy induces pancreatic dysfunction or whether this latter induces autonomic neuropathy is not clear. In fact, people with a pancreatic deficiency can reduce essential diet elements, which in turn can induce neuropathy. Finally, future studies might include patients with pancreatic pathologies such as chronic pancreatitis, as these pathologies were eliminated only via USG and CT screening. Imaging methods such as magnetic resonance imaging, and Endoscopic ultrasound (EUS) which can better reveal pancreatic pathologies, were not utilized in this study.

Table 2. Cardiac Dysautonomia Level and PEI Severity Degree of the Diabetic Patients

	n	%
Cardiac dysautonomia level		
Normal	38/110	34.5%
Atypical combination	12/110	10.9%
Early cardiac dysautonomia	35/110	31.8%
Cardiac dysautonomia	13/110	11.8%
Severe cardiac dysautonomia	12/110	10.9%
PEI Severity		
Normal	34/110	30.9%
Mild-Moderate-PEI	67/110	60.9%
Severe PEI	9/110	8.2%

CONCLUSION

This study demonstrated that diabetic patients with autonomic neuropathy might develop CAN and PEI. Although clinicians well recognize CAN as being associated with autonomic neuropathy in DM patients, it should be considered that in the presence of CAN, PEI may also develop. Nevertheless, studies regarding this issue are scarce. The association between CAN and PEI is possible and autonomous dysfunction in diabetes patients could actually be an independent condition, but further studies investigating this relationship are needed to verify this relationship.

Ethics Committee Approval: Ethics committee approval was received for this study from the Gaziantep University School of Medicine. (Decision Date: 25/01/2017; Decision No:26)

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – A.E.Y.; Design – A.E.Y.; Supervision – A.E.Y. Z.A.S.; Resource – A.E.Y. Z.A.S.; Materials – A.E.Y. Z.A.S.; Data Collection and/or Processing – A.E.Y. Z.A.S., N.U.; Analysis and/or Interpretation – A.E.Y., Z.A.S., N.U.; Literature Search – A.E.Y., Z.A.S., N.U.; Writing – A.E.Y., Z.A.S., N.U.; Critical Reviews – A.E.Y. Z.A.S.

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