

## Research Article

# A Cross Sectional Study to Assess the Prevalence of Pancreatic Exocrine Insufficiency among Diabetes Mellitus Patients in Turkey

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## Abstract

**Background/Objectives:** Pancreatic exocrine insufficiency (PEI) is a common clinical entity in patients with diabetes mellitus (DM). The aim of the present study was to define the prevalence and demographic and clinical characteristics of PEI in patients with DM in Turkey.

**Methods:** Totally 216 patients diagnosed with DM at least five years ago or more were recruited and evaluated for clinical characteristics and fecal elastase-1 (FE-1) concentrations from stool samples by enzyme-linked immunosorbent assay for the presence of PEI. No additional therapeutic approach or follow-up visits were conducted.

**Results:** The mean age of the patients was 53.8±16.6 years (18.5-85.7 years) and 58.8% (n = 127) of the patients were female. Of the patients, 32.4% had Type 1 DM and 67.6% had Type 2 DM. Totally, 31 (14.3%) patients had PEI. Mild-to-moderate PEI was observed in 12.0% of the patients and severe PEI was observed in 2.3% of the patients. The rates of PEI were 15.7% and 13.7% among Type 1 and Type 2 DM patients, respectively. FE-1 level was not correlated with DM duration and levels of ALP, amylase, HbA1c, and lipase in Type 1 and Type 2 DM patients and entire study population. There was a positive correlation between FE-1 and C-peptide levels in Type 2 DM patients (p = 0.047, rho = 0.168).

**Conclusions:** PEI was not a rare condition both in patients with Type 1 and Type 2 DM. As the clinical presentation of diabetic patient is inconclusive regarding exocrine pancreas functions, PEI should be notably taken into consideration in daily practice.

**Key words:** diabetes mellitus; fecal elastase-1; pancreatic exocrine insufficiency

## Introduction

Exocrine and endocrine functions of pancreas are associated closely in terms of anatomical and physiological patterns [1-3]. Pathological conditions of the exocrine tissue can cause impairment of the endocrine functions and vice versa [1, 2]. Some conditions or diseases such as acute and chronic pancreatitis, pancreatic surgery, hemochromatosis, cystic fibrosis, and pancreatic cancer may cause diabetes mellitus (DM) [4]. Although the older studies revealed that, these diseases were believed to cause DM only in 0.5%-1.2%, a recent review of the currently available studies finds that this ratio is approximately 5%-10% [5]. The impairment of exocrine function and pancreas morphology is frequently seen in diabetic patients and the reduced exocrine function has been reported in 43%-80% of the Type 1 DM in the earlier studies [6-9]. Similar exocrine insufficiency has been shown in Type 2 DM, whereas some studies have suggested normal exocrine function in those patients [6, 7, 10]. In 2000, Hardt *et al.* [1] reported that reduced fecal elastase-1 (FE-1) concentrations were found in 56.7% of Type 1 patients, 35% of Type 2 patients, and

18.1% of the controls and that elastase-1 concentrations were not correlated with alcohol consumption, diabetes duration or diabetes therapy. They also concluded that diabetes secondary to exocrine disease could be much more frequent than that was believed so far. In the following years, exocrine insufficiency in Type 2 DM patients has been studied in many studies and the exocrine insufficiency prevalence has been reported between 23% and 36% [11-14].

In their review, Hardt *et al.* [15] reported the possible mechanisms explaining pancreatic damage in patients with DM, which were insulin as a trophic factor for exocrine tissue, changes in secretion/action of other islet hormones, autoimmunity, and diabetes mellitus as a consequence of underlying pancreatic diseases. Based on these results, the American Diabetes Association defined diseases of the exocrine pancreas as other specific types of diabetes (some authors prefer to identify this entity as Type 3c diabetes) [4, 5, 16].

In a recently published study, Ewald *et al.* [17] described practical criteria based on the American Diabetes Association definition for

Type 3c DM, which were pancreatic exocrine insufficiency (PEI; a FE-1 level of <200 µg/g), presence of pathologic imaging results, and absence of diabetes-associated antibodies. In that particular study, among 1868 patients, 172 (9.2%) patients could be classified as Type 3c DM and only 51.2% (88/172) were initially classified correctly. They concluded that Type 3c DM appeared to be more common than that was generally believed and it was misdiagnosed commonly [17].

Exocrine insufficiency is common in DM patients and it might be explained as a complication of diabetes mellitus. Apparently, some patients with decreased exocrine function have Type 3c DM and are misdiagnosed as Type 2 or Type 1 DM and it is more likely that Type 3c DM is much more frequent than previously believed [18]. There are only few data about PEI in DM patients in Turkey. The primary objective of the present study was to assess the prevalence of PEI among DM patients in Turkey. The secondary objectives were to assess the prevalence of PEI among Type 1 and Type 2 DM sub-groups, to evaluate demographics and medical characteristics of the patients with PEI, and to evaluate the presence of gastrointestinal symptoms among patients with PEI.

## Methods

This was a cross sectional non-interventional study which was conducted in Istanbul University Faculty of Medicine from September 2013 through February 2014 and included patients admitting to the Gastroenterology or Endocrinology Outpatient Clinic with or without symptomatic gastrointestinal problems. The study was approved by local and central ethical committees. Patients who were aged  $\geq 18$  years old, previously diagnosed with DM (Type 1 or Type 2) at least 5 years ago or more and treated before enrolment, had absolute insulin deficiency and were diagnosed as Type 1 DM, and those who met at least one criteria of the Society of Endocrinology and Metabolism of Turkey on DM [19] were included. These criteria included having a blood glucose level  $\geq 126$  mg/dL after 8 hours of fasting, having a 2<sup>nd</sup> hour plasma glucose level  $\geq 200$  mg/dL after oral glucose tolerance test with 75 g glucose, having DM symptoms and spontaneous plasma glucose level of  $\geq 200$  mg/dL, and having glycated hemoglobin (HbA1c) level of  $\geq 6.5\%$  with standardized measurement technique. Patients who were pregnant or on breast feeding or had insufficient medical records were excluded. Written informed consents of the patients were obtained before the study.

All enrolled patients were evaluated only once during the study period (24 weeks). Demographic parameters and laboratory tests including the measurements of HbA1c, C-peptide, amylase, lipase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), calcium, phosphorous, and vitamin D levels were recorded. FE-1 concentrations were measured for the presence of PEI from the stool samples by enzyme-linked immunosorbent assay based on monoclonal human specific antibodies, which is widely used as a diagnostic parameter of PEI [20, 21]. PEI is classified by FE-1 level as normal exocrine function (a FE-1 level of  $\geq 200$  µg/g stool), mild-to-moderate PEI (a FE-1 level of  $\geq 100$  but <200 µg/g stool), and severe PEI (a FE-1 level of <100 µg/g stool) [22].

## Statistical analysis

Descriptive statistics were expressed as number, percentage, and 95% confidence interval for categorical variables and as mean, standard deviation, median, inter-quartile range, minimum, maximum, and percentiles for continuous variables. Sub-groups were compared using Chi-square or Fisher's exact or Mantel-Haenszel test for categorical variables, using analysis of variance and/or Student test for normally distributed continuous variables and Kruskal-Wallis and/or Mann-Whitney U test for non-normally distributed variables. Correlation between PEI and other parameters was evaluated by univariate tests (Chi-square or Fisher's exact test for categorical variables and Student T test or Mann-Whitney U test for continuous variables) and by multivariate tests (logistic regression models).

Raw prevalence was calculated by number, percentage, and 95% confidence interval using Wilson methodology [23]. Prevalence was adjusted for age and gender according to the results of annual census of Turkey published by Turkish Statistical Institute [24]. Prevalence was also adjusted according to the results of the TURDEP II study [25].

## Results

Among the patients (n = 216) included in the study, 58.8% (n = 127) were female. The mean age of the patients was  $53.8 \pm 16.6$  years (18.5-85.7 years). The rates of patients who had a history of Type 1 and Type 2 DM were 32.4% (n = 70) and 67.6% (n = 146), respectively. The duration of diabetes in type 1 and type 2 DM patients were  $16.7 \pm 9.1$  years (5.0-43.6 years) and  $14.8 \pm 6.2$  years (5.5-37.5 years), respectively.

The most frequent DM complication was neuropathy (25.0%) in the entire group, retinopathy (21.4%) in the patients with Type 1 DM, and cardiac diseases (22.6%) in the patients with Type 2 DM. Of the patients, 42.1% had at least one DM complication. All patients with Type 1 DM were on insulin therapy, whereas 56.2% of Type 2 DM patients were on insulin therapy. The characteristics of the patients with Type 1 and Type 2 DM and the entire study population are presented in Table 1.

**Table 1.** Baseline characteristics of the patients.

	Type 1 DM (n=70)	Type 2 DM (n=146)	Entire Group (n=216)
Age	34 ± 11.3 (18.5-69.4)	63.2 ± 8.3 (44.7-85.7)	53.8 ± 16.6 (18.5-85.7)
BMI (kg/m <sup>2</sup> )	24.3 ± 3.9 (16.8-35.7)	30.0 ± 4.8 (20.1-44.1)	28.1 ± 5.3 (16.8-44.1)
DM duration	16.7 ± 9.1 (5.0-43.6)	14.8 ± 6.2 (5.5-37.5)	15.4 ± 7.3 (5.0-43.6)
<b>Gender</b>			
Female	43 (61.4)	84 (57.5)	127 (58.8)
Male	27 (38.6)	62 (42.5)	89 (41.2)
<b>DM complication</b>			
Neuropathy	10 (14.3)	44 (30.1)	54 (25.0)
Retinopathy	15 (21.4)	30 (20.5)	45 (20.8)
Cardiac disease	3 (4.3)	33 (22.6)	36 (16.7)

Nephropathy	4 (5.7)	7 (4.8)	11 (5.1)
Diabetic foot	0 (0.0)	1 (0.7)	1 (0.5)
Cerebrovascular disease	0 (0.0)	1 (0.7)	1 (0.5)
<b>DM treatment</b>			
Insulin	70 (100.0)	82 (56.2)	152 (70.4)
Training	67 (95.7)	112 (76.7)	179 (82.9)
Life style change	47 (67.1)	93 (63.7)	140 (64.8)
Diet	48 (68.6)	92 (63.0)	140 (64.8)
Oral anti-diabetic	4 (5.7)	131 (89.7)	135 (62.5)
Physical exercise	36 (51.4)	63 (43.2)	99 (45.8)
<b>Gastrointestinal symptoms</b>			
At least 1	11 (15.7)	14 (9.6)	25 (11.6)
None	59 (84.3)	132 (90.4)	191 (88.4)
Data are presented as mean ± standard deviation (minimum-maximum) or number (%), where appropriate. BMI, Body Mass Index; DM, Diabetes Mellitus.			

Totally, 31 (14.3%) patients had PEI in the entire study population. Mild-to-moderate PEI was observed in 12.0% of the patients and severe PEI was observed in 2.3% of the patients (Table 2).

**Table 2.** Pancreatic exocrine insufficiency in the study population.

	Type 1 DM (n=70)	Type 2 DM (n=146)	Entire group (n=216)
	n (%)	n (%)	n (%)
Normal exocrine function	59 (84.3)	126 (86.3)	185 (85.7)
Any PEI	11 (15.7)	20 (13.7)	31 (14.3)
Mild-to-moderate PEI	11 (15.7)	15 (10.3)	26 (12.0)
Severe PEI	-	5 (3.4)	5 (2.3)
DM, Diabetes Mellitus; PEI, Pancreatic Exocrine Insufficiency			

There was no significant difference between patients with or without PEI regarding the age, BMI, DM duration or insulin usage. The most frequent DM complication was neuropathy both in the patients with (35.5%) and without (23.1%) PEI, without a significant difference between them (p = 0.145). Of 31 patients with PEI, the rate of having at least one DM complication was 58.1% (n = 18); there was no significant difference between the patients with and without PEI regarding the presence of at least one DM complication (p = 0.052). The characteristics of the patients with and without PEI and entire study population and the results of intergroup comparisons are presented in Table 3.

**Table 3.** Characteristics of the patients with and without pancreatic exocrine insufficiency and entire study population and intergroup comparisons.

	Patients with PEI (n=31)	Patients without PEI (n=185)	Entire Group (n=216)	p
Age	57.0 ± 15.8 (23.5-78.7)	53.2 ± 16.7 (18.5-85.7)	53.7 ± 16.6 (18.5-85.7)	0.230*
BMI (kg/m <sup>2</sup> )	28.4 ± 5.4 (21.5-43.6)	28.1 ± 5.3 (16.8-44.1)	28.1 ± 5.3 (16.8-44.1)	0.907*
DM duration	16.8 ± 7.8 (5.5-32.6)	15.2 ± 7.2 (5.0-43.6)	15.4 ± 7.3 (5.0-43.6)	0.345*
<b>Gender</b>				
Female	19 (61.3)	108 (58.4)	127 (58.8)	0.760
Male	12 (38.7)	77 (41.6)	89 (41.2)	
<b>DM complication</b>				
Neuropathy	11(35.5)	43 (23.1)	54 (25.0)	0.145
Retinopathy	7 (22.6)	38 (20.4)	45 (20.8)	0.796
Cardiac disease	6 (19.4)	30 (16.1)	36 (16.7)	0.664
Nephropathy	2 (6.5)	9 (4.8)	11 (5.1)	0.661**
Diabetic foot	0 (0.0)	1 (0.5)	1 (0.5)	1.000**
Cerebrovascular disease	0 (0.0)	1 (0.5)	1 (0.5)	1.000
<b>DM treatment</b>				
Insulin	26 (83.9)	126 (67.7)	152 (70.4)	0.873
Oral anti-diabetic	21 (67.7)	114 (61.3)	135 (62.5)	0.515
<b>Gastrointestinal symptoms</b>				
At least 1	2 (6.5)	23 (12.4)	25 (11.6)	0.335
None	29 (93.5)	162 (87.6)	191 (88.4)	
Data are presented as mean ± standard deviation (minimum-maximum) or number (%), where appropriate. Chi-square test was used unless otherwise stated; *Mann-Whitney U test; ** Fisher's exact test. BMI, Body Mass Index; DM, Diabetes Mellitus; PEI, Pancreatic Exocrine Insufficiency.				

## Laboratory Findings

The entire study population, as well as Type 1 and Type 2 DM patients, was grouped according to the presence and absence of PEI. The laboratory findings of these groups and the results of comparisons are presented in Table 4. There were no significant differences regarding any laboratory parameters between the patients with and without PEI in each group, except for vitamin D level in the patients with Type 1 DM ( $p = 0.010$ ).

Type 2 DM patients receiving and not receiving insulin therapy were grouped according to the presence and absence of PEI and were evaluated regarding laboratory findings. The laboratory findings

of these groups and the results of comparisons are presented in Table 5. The mean amylase level was significantly higher in Type 2 DM patients not receiving insulin therapy without PEI than in those receiving insulin therapy with PEI ( $p = 0.009$ ). The mean ALT level was significantly higher in Type 2 DM patients receiving insulin therapy with PEI than in those not receiving insulin therapy without PEI ( $p = 0.024$ ).

To evaluate the relationship between glycemic control and PEI, patients with DM Type 1 or 2 were divided into subgroups according to having HbA1c levels equal or higher than 7% and smaller than 7%. There was no correlation between these subgroups and PEI status in Type 1 and Type 2 DM patients (Table 6).

**Table 4.** Laboratory findings of Type 1 and Type 2 diabetes mellitus patients and entire study population grouped according to the presence of pancreatic exocrine insufficiency and results of comparisons.

	n	Type 1 DM			n	Type 2 DM		
		With PEI	Without PEI	p		With PEI	Without PEI	p
HbA1C (%)	70	8.5 ± 2.0 (6.3-13.8)	8.3 ± 1.6 (5.2-13.0)	0.981	145	7.5 ± 1.4 (6.0-11.4)	7.7 ± 1.3 (5.3-12.7)	0.457
C-Peptide (pmol/mL)	69	0.10 ± 0.22 (0.01-0.74)	0.23 ± 0.50 (0.01-2.24)	0.223	140	2.10 ± 1.57 (0.01-6.63)	2.48 ± 1.30 (0.01-6.25)	0.144
Amylase (IU/L)	65	63.6 ± 31.7 (8.7-130.0)	65.5 ± 31.2 (19.0-205.0)	0.920	145	68.7 ± 36.7 (9.8-20.0)	73.2 ± 35.5 (4.8-125.0)	0.424
Lipase (U/L)	65	29.6 ± 28.6 (6.2-105.0)	46.5 ± 52.7 (11.6-268.0)	0.122	144	34.8 ± 16.7 (7.2-63.4)	47.4 ± 41.9 (7.8-292.0)	0.244
AST (U/L)	70	18.9 ± 5.9 (10.0-29.0)	18.5 ± 8.4 (8.0-70.0)	0.512	145	21.7 ± 9.0 (12.0-44.0)	19.9 ± 6.1 (11.0-42.0)	0.638
ALT (U/L)	70	18.0 ± 8.9 (9.0-36.0)	19.5 ± 16.9 (7.0-128.0)	0.859	145	26.6 ± 24.9 (10.0-122.0)	24.0 ± 12.8 (9.0-85.0)	0.560
GGT (U/L)	69	16.6 ± 7.8 (9.0-36.0)	28.2 ± 65.3 (6.0-494.0)	0.693	142	28.4 ± 16.8 (8.0-75.0)	26.3 ± 16.4 (7.0-122.0)	0.571
Calcium (mg/dL)	68	9.4 ± 0.3 (8.9-9.7)	9.6 ± 0.4 (8.8-10.7)	0.100	145	9.7 ± 0.4 (8.8-10.5)	9.8 ± 0.5 (8.3-12.0)	0.472
Phosphorus (mg/dL)	68	3.8 ± 0.4 (3.2-4.5)	3.6 ± 0.6 (2.4-5.4)	0.079	146	3.5 ± 0.4 (2.7-4.2)	3.6 ± 0.6 (2.2-5.3)	0.749
Vitamin D (ng/mL)	60	19.8 ± 8.3 (9.6-31.0)	12.8 ± 9.0 (4.0-47.9)	<b>0.010</b>	133	17.4 ± 10.0 (5.1-34.5)	17.3 ± 10.4 (5.0-62.5)	0.963

Data are presented as mean ± standard deviation (minimum-maximum) or number (%), where appropriate.

DM, Diabetes Mellitus; PEI, Pancreatic Exocrine Insufficiency; HbA1c, Glycated Hemoglobin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase.

**Table 5.** Laboratory findings of Type 2 diabetes mellitus patients receiving and not receiving insulin therapy grouped according to the presence of pancreatic exocrine insufficiency and results of comparisons.

	n	Patients Receiving Insulin Therapy			n	Patients Not Receiving Insulin Therapy		
		With PEI	Without PEI	p		With PEI	Without PEI	p
HbA1c (%)	81	7.7 ± 1.5 (6-11.4)	8.1 ± 1.4 (5.8-12.7)	0.099	64	7.2 ± 1.2 (6.3-9.2)	7.2 ± 1 (5.3-9.5)	0.822
C-Peptide (pmol/mL)	80	1.6 ± 1 (0.01-3.9)	2.1 ± 1.3 (0.01-5.9)	0.247	60	4.1 ± 1.8 (2.6-6.6)	3 ± 1.1 (0.01-6.3)	0.134
Amylase (IU/L)	81	74.4 ± 41.1 (9.8-193)	71.5 ± 42.7 (20-279)	0.504	64	51.8 ± 5 (47-57)	75.1 ± 25.5 (4.8-145)	<b>0.009</b>
Lipase (U/L)	82	36.2 ± 18.9 (7.2-63.4)	43.2 ± 40.2 (7.8-292)	0.905	62	30.6 ± 7.2 (22.2-38.4)	52.3 ± 43.7 (12.8-286)	0.057
AST (U/L)	81	18.9 ± 4.8 (12-28)	19.7 ± 5.8 (11-34)	0.798	64	29.8 ± 13.9 (14-44)	20.1 ± 6.6 (11-42)	0.184
ALT (U/L)	82	17.5 ± 5.1 (10-26)	22.5 ± 10.7 (9-54)	0.560	63	53.6 ± 40.5 (22-122)	25.8 ± 14.9 (10-85)	<b>0.024</b>
GGT(U/L)	81	24.8 ± 12.6 (8-52)	26.4 ± 16.5 (7-122)	0.742	61	39 ± 24.4 (11-75)	26.2 ± 16.5 (10-86)	0.242
Calcium (mg/dL)	82	9.6 ± 0.5 (8.8-10.5)	9.7 ± 0.4 (8.8-10.6)	0.478	63	9.9 ± 0.2 (9.7-10.1)	9.9 ± 0.6 (8.3-12)	0.711
Phosphorus (mg/dL)	82	3.6 ± 0.4 (2.7-4.2)	3.6 ± 0.6 (2.2-4.7)	0.943	64	3.3 ± 0.4 (3-3.9)	3.5 ± 0.6 (2.3-5.3)	0.254
Vitamin D (ng/mL)	74	18 ± 10.9 (5.1-34.5)	14.5 ± 7.7 (5-39.3)	0.485	59	15.9 ± 8 (8-27.1)	20.5 ± 12.2 (5.4-62.5)	0.460

Data are presented as mean ± standard deviation (minimum-maximum) or number (%), where appropriate.  
PEI, Pancreatic Exocrine Insufficiency; HbA1c, Glycated Hemoglobin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase.

**Table 6.** Relationship of glycated hemoglobin level with pancreatic exocrine insufficiency in Type 1 and Type 2 diabetes mellitus patients and entire study population.

	Type 1 DM (n=56)			Type 2 DM (n=98)			Entire group (n=154)		
	HbA1c < 7.0%	HbA1c ≥ 7.0%	p	HbA1c < 7.0%	HbA1c ≥ 7.0%	p	HbA1c < 7.0%	HbA1c ≥ 7.0%	p
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
With PEI	2 (18.2)	9 (81.8)	1.000*	9 (45.0)	11 (55.0)	0.195	11 (35.5)	20 (64.5)	0.342
Without PEI	12(20.3)	47 (79.7)		38 (30.4)	87 (69.6)		50 (27.2)	134 (72.8)	

Chi-square test was used unless otherwise stated. \*Fisher's exact test.  
DM, Diabetes Mellitus; HbA1c, Glycated Hemoglobin; PEI, Pancreatic Exocrine Insufficiency.

Fecal elastase-1 level was not correlated with DM duration and levels of ALP, amylase, HbA1c, and lipase in Type 1 and Type 2 DM patients and entire study population. There was a positive correlation between FE-1 level and C-peptide level in Type 2 DM patients (p = 0.047, rho = 0.168). Univariate linear regression model revealed that amylase, lipase, and ALP levels and Type 2 DM were not significant predictors of FE-1 level. Univariate logistic regression model revealed that amylase, lipase, and ALP levels and Type 2 DM were not significant predictors of PEI.

## Discussion

During the previous decades, researchers have focused on PEI in DM in many studies and evaluated the pancreatic secretion after the injection of cholecystokinin-pancreozymin and secretin in early studies [26]. The results of these studies have revealed that the prevalence rates of PEI ranges between 43% to 80% [6, 8, 9, 27]. More recently, FE-1 has become a frequently used diagnostic method in the clinical practice to detect PEI. Studies utilizing this diagnostic method have also reported high prevalence of PEI in patients with DM, ranging between 5.4%- 56.7% which is slightly lower than the results of previous studies [1, 12, 26, 28-30].

The results of the present study revealed that PEI was not a rare condition among patients with DM, either Type 1 or Type 2. The overall prevalence of PEI in the study population was found to be 14.4% and almost 1 in 7 patients with DM appeared to have PEI. This result also confirmed that, in general daily practice, the awareness of Type 1 and Type 2 DM is well-established; however, Type 3c DM is rarely considered [31]. This finding is also consistent with the previous studies, which have shown that this particular subtype of diabetes is more common than that is thought and generally misdiagnosed [17, 20].

There are some mechanisms proposed to be responsible for the impaired exocrine function in DM, including insulin deficiency [32], diabetic microangiopathy [33] high levels of circulating glucagon and its suppressive effects [34], effects of different hormones like somatostatin or pancreatic polypeptide [35] and autoimmunity against both endocrine and exocrine pancreas [36]. Regardless of the mechanism, changes in the exocrine function of the pancreas are commonly seen in many diabetic patients. In the present study population, 14.4% of the patients had PEI (15.7% in Type 1 DM and 13.7% in Type 2 DM); this was a relatively small rate when compared with the results of the previous studies. In their study populations, the rates of PEI were found as 55% by Chey *et al.* [6] and 73% by Vacca *et al.* [7] More recently, Hardt *et al.* [1] found that fecal elastase test was abnormal in 57% of patients with Type 1 DM and 35% of patients with Type 2 DM. The results of the present study are in conflict with the previous studies with the relatively small rates, but in consistent with the recent studies. [11, 14, 37]. In a study included 544 Type 2 diabetic patients (age:  $63 \pm 8$  years) and 544 age- and gender-matched controls, Rahtmann *et al.* [11] reported that FE-1 concentrations were significantly lower in the patients than those of the controls and that low levels of FE-1 concentrations was present in 11.9% of the patients and 3.7% of the controls. In another study conducted by Larger *et al.* [14] on 667 patients (195 Type 1 DM and 472 Type 2 DM patients), 23% of the patients had an elastase 1 concentration  $<200 \mu\text{g/g}$ . Moreover, the study by Terzin *et al.* [37] reported lower elastase 1 concentrations in 16.8% of the patients with Type 2 DM patients ( $n = 101$ ).

Another critical point in the present study was that the diagnostic method was based on the fecal elastase test and the impaired results suggested the deteriorated digestive pathways in these patients. In a large-scale population based study by Bytzer *et al.* [38] on 15,000 adults, it was reported that gastrointestinal symptoms were observed with an increased prevalence in patients with diabetes and poor glycemic control. In the present study, at least one gastrointestinal symptom was present in 11.6% of the patients. When the diagnostic subgroups were considered, 15.7% of Type 1 DM patients and 9.6% of Type 2 DM patients had gastrointestinal symptoms. When the presence of gastrointestinal symptoms was compared according to the presence of PEI, there was no statistically significant difference between the groups. This finding was contradictory to the results of the previous studies by Nunes *et al.* [29], Icks *et al.* [28], and Rathmann *et al.* [11], which all reported that deteriorations in exocrine functions also impaired digestive functions in DM. However, this finding also supported some previous reports, which stated the controversies in the clinical presentation of PEI [26].

The duration of DM and the treatment with insulin are known as significant contributors to the changes in levels of digestive enzymes, such as amylase, in diabetes. Previous studies have shown that enzyme levels are significantly decreased in most diabetic cases with a long duration of disease and insulin treatment [39]. In the present study, there were no significant differences regarding enzyme levels between the patients with and without PEI neither in Type 1 nor in Type 2 diabetes. However, in the Type 2 DM patients not receiving insulin therapy, serum amylase level was significantly lower in the patients with PEI than in those without PEI. This finding did not support the previous evidence about insulin usage [29]. Layer *et al.* [40] reported on this issue that despite the decreased enzyme levels, there were no clinical evidence of pancreatic exocrine disease in these patients; however, according to our results, PEI was present in the patients with decreased amylase levels. Nevertheless, we could not define an effect of disease duration on the presence of PEI. The patients had similar duration of diabetes in both groups with and without PEI.

Presence of obesity and increased BMI are significant factors in the prognosis of DM. In the present study population, BMI was higher in the patients with Type 2 DM but not found to be differed between the patients with and without PEI. This was also mentioned by the previous studies and excess body weight defined as a BMI of  $>25 \text{ kg/m}^2$  was not reported to be effective on fecal elastase levels. [29] However, regardless of BMI, poor glycemic control has been associated with decreased exocrine functions of pancreas [11, 37].

Although some recent studies showed that PEI have been seen more frequently in the patients with poor glycemic control ( $\text{HbA1c} \geq 7\%$ ) than in the patients with good glycemic control ( $\text{HbA1c} < 7\%$ ) [11, 37], we did not find a correlation between PEI and glycemic control. Larger *et al.* had also indicated the similar results as we found [14]. According to these findings, the relationship between poor glycemic control and PEI is still contradictory and needs more studies to evaluate.

Vitamin D is a fat-soluble vitamin and its deficiency is expected more common in patients with PEI than without PEI. According to our results, the prevalence of vitamin D deficiency does not differ between diabetics with PEI and without PEI. It may be the reason of high prevalence of vitamin D deficiency in Turkey [41].

In conclusion, this is one of the very few studies about the prevalence and characteristics of PEI in patients with diabetes in Turkey. Although the prevalence rate of PEI in DM in our study was not found as high as in the previous studies, PEI was not a rare condition both in Type 1 and Type 2 DM; and these patient population has to be considered as Type 3c DM. Generally, the demographic and clinical characteristics were similar in the patients with and without PEI and the clinical presentation was inconclusive in these patients regarding exocrine pancreas functions. Although these findings should be supported by further, large-scale, prospective, randomized and controlled studies, our results contribute to the current evidence as new data from a less-studied population.

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