



# Does Blood Glucose Regulation in Adults with Type 2 Diabetes Affect Exocrine Pancreatic Functions?

## Tip 2 Diyabetli Erişkinlerde Kan Şekeri Regülasyonu Ekzokrin Pankreas Fonksiyonlarını Etkiler mi?

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### Abstract

**Objective:** The purpose of this study was to assess the possible effects of blood glucose regulation on pancreatic exocrine functions in type 2 diabetes mellitus (T2DM) patients with poor glycemic control. **Material and Methods:** This prospective clinical study was performed with 20 patients with poorly controlled T2DM (HbA1c >10%) and age- and sex-matched 20 healthy controls. At the beginning of the study, metabolic parameters and fecal elastase-1 (FE-1) levels, one of the markers of pancreatic exocrine insufficiency (PEI), were compared between the patient and control groups. In addition, after blood glucose regulation was achieved with at least three months of intensive insulin therapy in the patient group, FE-1 levels and metabolic parameters were compared with pre-treatment. PEI was defined as FE-1 levels lower than 200 µg/g. **Results:** FE-1 levels were significantly lower in the T2DM group than the control group (median values for patients=333.1 µg/g and controls=508.5 µg/g; p=0.013). PEI was detected in three patients (15%) but none in the control group. After intensive insulin therapy, T2DM patients FE-1 levels significantly increased compared to their pre-treatment (pre-treatment median: 333.15 (192.60) µg/g, post-treatment median: 415.40 (300.77) µg/g; p=0.044). The major factors impacting this increase were the duration of diabetes and the change in HbA1c levels. **Conclusions:** FE-1 levels in patients with poorly controlled T2DM were lower than the healthy control group, which significantly increased with blood glucose regulation.

**Keywords:** Type 2 diabetes mellitus;  
exocrine pancreatic  
insufficiency; pancreatic elastase 1

### Özet

**Amaç:** Bu çalışmada, glisemik kontrolü zayıf olan Tip 2 diabetes mellitus hastalarında kan şekeri regülasyonunun pankreas ekzokrin fonksiyonları üzerine etkisini değerlendirmek amaçlandı. **Gereç ve Yöntemler:** Bu prospektif klinik çalışma, kan şekeri regülasyonu bozuk (HbA1c >10) Tip 2 diyabetes mellituslu 20 hasta ile cinsiyet ve yaş uyumlu 20 sağlıklı kontrol grubundan oluşan bir popülasyonda gerçekleştirilmiştir. Çalışmanın başlangıcında pankreas ekzokrin yetmezliği belirteçlerinden biri olan fekal elastaz 1 (FE-1) düzeyleri ve metabolik parametreler hasta ve kontrol grubu arasında karşılaştırıldı. Ayrıca hasta grubunda en az 3 ay yoğun insülin tedavisi ile kan şekeri regülasyonu sağlandıktan sonra FE-1 düzeyleri ve metabolik parametreler tedavi öncesi ile karşılaştırıldı. Fekal elastaz 1 düzeylerinin 200 µg/g'ın altında olması pankreas ekzokrin yetmezliği olarak tanımlandı. **Bulgular:** Diyabetik hasta grubunda kontrol grubuna göre FE-1 düzeyleri anlamlı olarak daha düşük bulundu (Medyan: Hasta grubu=333,1 µg/g; Kontrol grubu= 508,5 µg/g; P=0,013). Hasta grubunda 3 (%15) hastada ekzokrin pankreas yetmezliği görüldüken kontrol grubunda ekzokrin pankreas yetmezliği görülmeydi. Hasta grubunda FE-1 düzeyleri kan şekeri regülasyonu öncesine göre anlamlı olarak arttı (tedavi öncesi medyan=333,15 (192,60) µg/g, tedavi sonrası medyan=415,40 (300,77) µg/g; P=0,044) ve bu artışa etki eden majör faktörler diyabet süresi ve HbA1c düzeyindeki değişimdi. **Sonuç:** Çalışmamızda kan şekeri regülasyonu bozuk Tip 2 diabetes mellitus hastalarında fekal elastaz 1 düzeyleri sağlıklı kontrol grubuna göre daha düşüktü ve bu hastalarda kan şekeri regülasyonunun sağlanması FE-1 düzeylerini anlamlı olarak artırdı.

**Anahtar kelimeler:** Tip 2 diabetes mellitus;  
ekzokrin pankreas yetersizliği;  
pankreatik elastaz 1

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## Introduction

The pancreas is a retroperitoneal organ with exocrine and endocrine functions. It is postulated that pancreatic exocrine insufficiency (PEI) could occur in diabetic patients or vice versa due to the close anatomical and physiological relation between the pancreatic exocrine and endocrine components (1-3). The increased global prevalence of diabetes and PEI's coexistence has drawn attention in recent years. Diabetes mellitus can develop due to decreased numbers and functional capacity of islet cells in patients developing PEI secondary to diseases of the pancreas or pancreatic resection (2). Moreover, PEI can also develop in diabetic patients through several mechanisms, including changes in the regulatory effect of hormones secreted by the pancreatic islets on exocrine pancreatic functions, pancreatic fibrosis and atrophy due to diabetic microangiopathy, and impairment of entero-pancreatic reflexes due to diabetic neuropathy and gastroparesis (3,4). It was reported that acute hyperglycemia might play a role in PEI development by inhibiting exocrine pancreatic enzyme secretion and increasing the proliferation and activation of pancreatic stellate cells causing pancreatic fibrosis (3).

Traditionally, direct stimulation tests like the secretin stimulation test, an invasive test, are accepted as the gold standard for evaluating pancreatic exocrine functions. However, recently, pancreatic fecal elastase-1 (FE-1), a non-invasive procedure, is validated as the diagnostic test used progressively. FE-1 is secreted into the intestine among the pancreatic exocrine secretions and excreted unaltered in the stool. FE-1 measurement is relatively inexpensive, reliable, and easy to use (5).

Studies have reported inconsistent effects of pancreatic enzyme replacement therapy on blood glucose regulation in diabetes and PEI patients (6-9). However, to the best of our knowledge, no study has investigated glycemic control's effect on pancreatic exocrine functions in diabetic patients with poor glycemic control. Our study aimed to assess the impact of blood glucose regulation on pancreatic exocrine functions in type 2 diabetes mellitus (T2DM) patients with poor glycemic control.

## Material and Methods

### Patients and Study Design

This prospective study considered 28 patients with poor glycemic control (glycated hemoglobin, HbA1c >10) T2DM admitted to Karadeniz Technical University Medical Faculty Hospital Endocrinology Clinic between July 2017 to August 2018. The Control group consisted of age and sex that matched 20 healthy individuals selected among healthy volunteers presenting to the hospital's Family Medicine Clinic for screening purposes during June-August 2018. T2DM was diagnosed based on the American Diabetes Association criteria (10). Patients younger than 30 or older than 70, consuming more than 20 g alcohol a day, using Orlistat, Acarbose, or Gliptins, with a medical history of abdominal surgery or known pancreatic disorders, any other known reason for malabsorption, or with cancer, inflammatory bowel disease or autoimmune disease, and pregnant women were excluded from the study. None of the patients were receiving pancreatic enzyme replacement therapy. Detailed medical history was taken from patients eligible for the study and admitted to the hospital for blood glucose regulation following a thorough physical examination. Patients' metabolic parameters were assessed before the initiation of therapy. Stool specimens collected for quantifying FE-1 levels were stored at -80 °C for further analysis. Patients who previously received only oral anti-diabetic therapy were started on insulin therapy, adjusted for those who previously received such therapy. Fasting and postprandial blood glucose targets were <130 mg/dL and <180 mg/dL, respectively. Basal plus bolus insulin regimen was started at 0.5 units per kg patients who previously were on only oral anti-diabetic therapy. In patients receiving basal insulin previously, the insulin doses were adjusted to at least 0.5 units per kg body weight, and the bolus insulin regimen was initiated. Insulin doses were adjusted by doing two visits per week until the target blood glucose was reached. Subsequently, patients' metabolic parameters were re-investigated at clinical follow-ups at least three months, and stool specimens were again collected and stored

at -80 °C. Blood specimens from the control group collected at the time of presentation were also studied, and stool specimens were stored at -80°C for the study. The study was carried out based on the guidelines of the Declaration of Helsinki. Informed consent forms were obtained from the patient and control groups and approved by the Ethics Committee of Karadeniz Technical University (No:2017/126).

### Laboratory Examinations

Biochemical parameters such as fasting blood glucose, amylase, triglyceride, total cholesterol, C-reactive protein, alanine aminotransferase, blood urea, nitrogen, creatinine, albumin, total protein, calcium, phosphorus, magnesium were assayed using a Beckman Coulter AU 5800 autoanalyzer (Shizuoka, Japan) at the time of recruitment. Serum C-peptide levels were studied using the chemiluminescence immunoassay method on a Siemens Immulite 2000 XPI analyzer (Walpole, USA) and HbA1c levels using HPLC (Boronate affinity) on a Trinity Biotech Premier Hb9210 device (Kansas City, USA). Serum total 25 (OH)-vitamin D3 levels were studied using the chemiluminescence immunoassay method on a Beckman Coulter Unicel DXI 800 device (Minnesota, USA). At the end of the study, FE-1 levels in stools were quantified using a commercial kit to detect PEI's presence using enzyme-linked immunosorbent assay (Pancreatic Elastase ELISA, Bioserv Diagnostics GmbH, United Kingdom) and expressed as µg/g of stool. PEI was divided into three groups according to FE-1 levels (normal pancreatic exocrine function: FE-1 ≥200 µg/g stool, mild to moderate PEI: FE-1 ≥100 but <200 µg/g stool, or severe PEI: FE-1 <100 µg/g stool) (4).

### Statistical Analysis

All statistical analyses were performed on the Statistical Program for Social Sciences software (SPSS 23.0) for Windows (Chicago, IL, USA). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean±standard deviation, and non-normally distributed data as median

(IQR). Student's t-test, the paired samples test, and Wilcoxon, chi-square, and Mann-Whitney tests were applied to assess the significance of inter-group differences. Linear regression analysis was performed, taking into account the interactions between the variables. In the first model, the initial fecal elastase level was used as the dependent variable, and age, body mass index (BMI), initial HbA1c, 25 (OH)-Vitamin D3, magnesium, triglyceride, blood fasting glucose, and total cholesterol levels as independent variables. In the second model, fecal elastase differences were the dependent variable, whereas age, BMI, differences of HbA1c, 25 (OH)-Vitamin D3, triglyceride, fasting glucose, and duration of diabetes mellitus were independent variables. The Enter method was used in the analysis (11). Statistical significance was accepted as  $p < 0.05$ .

### Results

Five of the 28 participants included in the study subsequently dropped out due to non-compliance with treatment, and three due to failure to attend control examinations. Therefore, twenty patients with T2DM and 20 healthy controls were included in the analysis. The patient group consisted of 12 (60%) men and 8 (40%) women, and the control group of 9 (45%) men and 11 (55%) women. Mean age was  $50.7 \pm 10.0$  and  $52.1 \pm 9.3$  years in the patient and control groups, respectively. The patient and control groups were comparable in terms of age and gender. Demographic characteristics and laboratory parameters of participants are tabulated (Table 1). The mean follow-up duration of the patients in the study was 94.50 days (IQR:11.50). Five patients received only insulin therapy before the study, while 15 received combination therapy (oral antidiabetics and insulin). The median duration of diabetes was 5.00 years (IQR:4.75). At the beginning of the study, fasting blood glucose, HbA1c, and blood urea nitrogen levels were significantly higher in the patients than in the control group. In contrast, 25 (OH)-Vitamin D3, magnesium, and FE-1 levels were significantly lower (Table 1). In three (15%) patients, PEI was observed (one severe and two mild cases), but none from the control

Table 1. Baseline socio-demographic and laboratory findings among type 2 diabetic patients and healthy control groups.

Sociodemographics & laboratory findings	Patient group (n=20)	Control group (n=20)	P value
Age (years)*	50.7±10.0	52.1±9.3	0.650
Sex (n, %)			
Female	8 (40)	11 (55)	0.527
Male	12 (60)	9 (45)	
BMI (kg/m <sup>2</sup> )**	31.5 (6.3)	29.1 (7.4)	0.200
Hemoglobin (g/dL)*	14.2±1.7	13.8±0.9	0.377
Fasting blood glucose (mg/dL)**	179.00 (145.00)	87.0 (13)	<0.001
HbA1c (%)*	11.5±1.3	5.6±0.3	<0.001
Total cholesterol (mg/dL)*	218.0±49.3	216.1±34.7	0.851
Triglycerides(mg/dL)**	143.5 (70.0)	112.0 (69.2)	0.072
25 OH Vitamin D3(µg/L)**	14.0 (6.9)	21.9 (12.0)	0.001
Albumin (g/L)**	4.15 (0.6)	4.2 (0.4)	0.162
Total Protein (g/L)*	7.0±0.5	7.3±0.5	0.147
Blood urea nitrogen (mg/dL)**	15.0 (9.2)	13.0 (2.0)	0.037
Creatine (mg/dL)**	0.7 (0.3)	0.8 (0.3)	0.850
Alanine aminotransferase (U/L)**	25.5 (30.7)	20.0 (9.0)	0.303
Amylase (U/L)**	59.5 (36.7)	81.0 (52.5)	0.106
Calcium (mg/dL)**	9.4 (0.8)	9.8 (0.7)	0.063
Phosphorus (mg/dL)**	3.6 (0.9)	3.1 (0.8)	0.183
Magnesium (mg/dL)**	1.9 (0.2)	2.1 (0.1)	0.003
C-reactive protein (mg/L)*	0.8±0.9	0.5±0.4	0.267
Fecal elastase 1(µg/g of stool)**	333.1 (192.60)	508.5 (130.13)	0.013

\*Mean±standard deviation; \*\*Median (interquartile range).

BMI: Body mass index; HbA1c: Glycated hemoglobin.

group. Analysis of the patient group revealed a significant decrease in fasting blood glucose, HbA1c, triglyceride, and alanine aminotransferase levels following at least three months of intensive insulin therapy compared to pre-treatment levels. In contrast, 25 (OH)-Vitamin D3, albumin, total protein, calcium, and FE-1 levels significantly increased (Table 2). Linear regression analysis was performed to examine the factors affecting the change in FE-1 levels after blood glucose regulation in the patient group. It was found that the significant factors were HbA1c levels and duration of diabetes mellitus ( $p=0.047$  and  $0.036$ , respectively, Table 3).

## Discussion

The present study investigated fecal elastase levels and various metabolic parameters in T2DM patients with poor glycemic control and a healthy control group to eval-

uate PEI. The study's analysis revealed significantly lower fecal elastase levels in the T2DM patients than the control group (case group, median: 333.1 µg/g; control group, median: 508.5 µg/g;  $p=0.013$ ). PEI was detected in 15% of the diabetic cases (prevalence of FE-1 <200 µg/g and <100 µg/g were 10% and 5%, respectively), but none in the control group.

Although in earlier studies employing invasive tests, meta-analysis evaluating the PEI prevalence in diabetic patients reported an average of 52.4% (18-100%), the mean prevalences of PEI using non-invasive tests was about 40% (26-74%) in type 1 diabetes patients and 27% (10-56%) in T2DM patients (3). Although patients with poor glycemic control were included in our study, PEI prevalence was lower than in other studies. In recent studies, a lower prevalence (between 9.2% and 13%) of PEI in diabetic patients was reported, concordant

Table 2. Laboratory findings and fecal elastase-1 levels in patients with Type 2 diabetes mellitus before and after insulin treatment.

	Baseline	After the third month	p value
Hemoglobin (g/dL)*	14.2±1.6	14.1±1.5	0.523
Fasting blood glucose (mg/dL)**	179.0 (145.0)	121.0 (72.0)	0.003
C peptide (µg/L)**	2.3 (2.2)	1.6 (1.4)	0.076
HbA1c (%)*	11.5±1.3	7.1±1.0	<0.001
Total cholesterol (mg/dL)*	218±49.3	209±52.6	0.252
Triglycerides (mg/dL)**	143.5 (70.0)	99.0 (80.2)	0.003
25 OH Vitamin D3(µg/L)**	14.0 (6.9)	15.6 (9.4)	0.033
Prothrombin time (sec)	11.6±1.2	11.6±1.0	0.694
INR*	1.0±0.1	1.0±0.9	0.659
Albumin (g/L)**	4.1 (0.6)	4.3 (0.6)	0.020
Total Protein (g/L)*	7.0±0.5	7.3±0.4	0.009
Blood urea nitrogen (mg/dL) *	15.0 (9.2)	14.0 (6.7)	0.061
Creatine (mg/dL)**	0.7 (0.3)	0.7 (0.2)	0.615
Alanine aminotransferase (U/L)**	25.5 (30.7)	16.0 (17.7)	0.014
Amylase (U/L)**	59.5 (36.7)	63.0 (40.0)	0.057
Calcium (mg/dL)**	9.4 (0.8)	9.6 (0.6)	0.036
Phosphorus (mg/dL)**	3.5 (0.9)	3.4 (0.8)	0.723
Magnesium (mg/dL)**	1.9 (0.2)	2.0 (0.2)	0.355
C-reactive protein (mg/L)*	0.8±0.9	0.8±1.1	0.834
Fecal elastase 1 (µg/g of stools)**	333.1 (192.6)	415.4 (300.8)	0.044

\* Mean±standard deviation, \*\*Median (IQR).

HbA1c: Glycated hemoglobin.

Table 3. Linear regression analysis of factors affecting differences in fecal elastase in patients with type 2 diabetes mellitus.

Model	Coefficients <sup>a</sup>			
	Unstandardized coefficients		95.0% confidence interval for B	
	B	p value	Lower bound	Upper bound
(Constant)	152.55	0.600	-464.68	769.78
Difference at HbA1c	-59.34	0.047	-117.63	-1.04
Duration of diabetes mellitus	15.90	0.036	1.26	30.53
Age (years)	-0.07	0.982	-6.92	6.77
Body Mass Index (kg/m <sup>2</sup> )	-12.41	0.101	-27.62	2.80
Difference in fasting glucose	-0.55	0.084	-1.17	0.08
Difference in 25 OH Vitamin D3	-0.33	0.956	-13.10	12.44
Difference in triglycerides	0.52	0.224	-0.36	1.40

a. Dependent Variable: Difference in fecal elastase

to our study (9,12). Vujasinovic et al. reported a low prevalence of PEI (5.4%) in a study of 150 patients with type-1 and type-2 diabetes, which was attributed to the exclusion of alcohol use and other causes of

malabsorption (13). The inconsistencies between studies may be due to differences in patient selection and diagnostic methods. Patients with pancreatogenic diabetes (Type 3c) emerging secondary to pancre-



atic diseases such as chronic pancreatitis were generally not excluded from older studies, reporting higher PEI prevalence. However, patients with pancreatic disease were generally excluded from subsequent studies.

The relationship between glycemic control levels and PEI in diabetic patients is still not understood. Some studies have reported lower FE-1 levels in diabetic patients with poor glycemic control than patients with good glycemic control (14-16), while others have reported no difference (17,18). PEI rate increases with the rise in blood glucose regulation impairment. In our study, blood glucose regulation in patients with poorly controlled diabetes mellitus was performed employing intensive insulin therapy lasting at least three months. Significantly increased FE-1 levels was obtained in these patients compared to pre-treatment levels (pre-treatment median 333.1 (192.6) µg/g, post-treatment median: 415.4 (300.8) µg/g;  $p=0.044$ ) (Table 2).

To the best of our knowledge, the present study is the first to reveal the effect of glycemic control in poorly controlled T2DM patients on pancreatic exocrine functions. Blood glucose regulation in diabetic patients with uncontrolled blood glucose improves acute and chronic complications associated with hyperglycemia and improves pancreatic exocrine functions. Pancreatic exocrine enzymes are responsible for absorbing fat and fat-soluble vitamins and proteins (19). Regulation of exocrine functions in patients with PEI, independent of the etiology, significantly increases the absorption of fat and fat-soluble fats and proteins and alleviates clinical symptoms such as bloating and abdominal discomfort (19,20). Improvement of exocrine functions in diabetic patients can also help establish blood glucose regulation by improving the digestion and absorption of these foods (6,7,21,22). In our study, significant improvements in 25 (OH)-Vitamin D3, total protein, albumin, and calcium values were observed in patients' after intensive insulin treatment. Improvement in exocrine pancreatic functions and diabetes regulation may have a role in these nutritional markers' progress.

However, there are some limitations in this study. In particular, the sample size was small as our study investigated T2DM patients with poor glycemic control ( $HbA1c >10$ ), resulting in low statistical power. Another limitation was that other nutritional markers, such as vitamin A and E for PEI, could not be studied. Also, in some patients, the pancreatic structure could not be evaluated using ultrasonography or other imaging techniques. Pancreatogenic diabetes (type 3c) emerging secondary to pancreatic diseases such as chronic pancreatitis is sometimes misdiagnosed as T2DM (10). However, none of our patients had a history of alcohol use, and thus we considered that all our patients had Type 2 diabetes.

In conclusion, in this study, FE-1 levels were lower in T2DM patients with poor glycemic control than in the healthy control group. Although our patients consisted of poor glycemic control, PEI prevalence was lower than in previous studies. The establishment of blood glucose regulation with intensive insulin therapy significantly increased FE-1 levels, and the main factors affecting these changes were the duration of diabetes and shift in  $HbA1c$ . Therefore, blood glucose regulation is crucial for micro and macrovascular complications and improved pancreatic exocrine functions. Thus, this study has some implications for better understanding the pathogenesis and treating pancreatic inflammation and chronic pancreatitis.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authorship Contributions

Idea/Concept: Sami Fidan, Savaş Volkan Kiiioğlu, Halil Önder Ersöz, Orhan Özgür; Design: Sami Fidan, Savaş Volkan Kiiioğlu, Celal Kurtuluş Buruk, Elif Ateş, Arif Mansur Coşar; Control/Supervision: Sami Fidan, Savaş Volkan Kiiioğlu, Arif Mansur Coşar, Halil Önder Ersöz, Orhan Özgür; Data Collection and/or Processing: Sami Fidan, Savaş Volkan Kiiioğlu, Celal Kurtuluş Buruk, Elif Ateş, Arif Mansur Coşar; Analysis and/or Interpretation: Sami Fidan, Savaş Volkan Kiiioğlu, Halil Önder Ersöz, Orhan Özgür; Literature Review: Sami Fidan, Savaş Volkan Kiiioğlu, Celal Kurtuluş Buruk, Elif Ateş; Writing the Article: Sami Fidan, Savaş Volkan Kiiioğlu, Celal Kurtuluş Buruk, Elif Ateş, Arif Mansur Coşar, Halil Önder Ersöz; Critical Review: Sami Fidan, Savaş Volkan Kiiioğlu, Arif Mansur Coşar, Orhan Özgür; Materials: Sami Fidan, Savaş Volkan Kiiioğlu, Celal Kurtuluş Buruk.

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