

Pancreatic Exocrine Insufficiency among Diabetic Patients

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ABSTRACT

Background: Various studies have defined the existence of pancreatic exocrine insufficiency (PEI) in diabetic patients. The concentration of faecal elastase-1 (FE-1) has long been used as a screening method for exocrine pancreatic activity, with good results when compared to direct methods. The prevalence of pancreatic exocrine insufficiency in Egyptian diabetic patients measured by FE-1 concentration is still unknown.

Objective: To investigate the prevalence of PEI in Egyptian diabetic patients, and to examine its relationship with the degree of glycemic control and other metabolic parameters.

Patients and Methods: In this cross-sectional study, 180 diabetic patients, were divided into two equal groups. Group I: patients with type 1 diabetes mellitus (T1D) and Group II: patients with type 2 diabetes mellitus (T2D). Other 90 healthy subjects were enrolled in the study as a control group (Group III). All participants were evaluated for PEI by measuring the FE-1 concentration through the enzyme-linked immunosorbent assay (ELISA) method. Patients having FE-1 concentration < 200 µg/g of stool were diagnosed with PEI.

Results: The prevalence of PEI was 35.6% in T1D, 31.3% in T2D, and 7.8% in the control group (P < 0.001). A significant negative correlation was observed between FE-1 levels and both FBS and HbA1c in diabetic patients. There was also a significant positive correlation between body mass index (BMI) and FE-1 concentration for T1D and T2D groups.

Conclusion: Significant PEI was observed in Egyptian T1D and T2D patients assessed by the FE-1 concentration test.

Keywords: Pancreatic exocrine insufficiency, Diabetes, FE-1, Faecal elastase-1 concentration.

INTRODUCTION

The pancreas is a mixed organ, with secretory and endocrine functions that interact and work together for the digestion, absorption and metabolism of nutrients⁽¹⁾. Pancreatic secretions have a significant effect on the digestion of nutrients, especially fats. Secretion of pancreatic enzymes is produced in the head, stomach and intestinal stages. Digestion of starch, protein, and fats occurs during the three main stages of digestion. The malabsorption process caused by insufficient (production, release or activation) of the pancreatic enzymes secreted from the pancreatic acinar cells or from enzymatic degradation of enzymes required for digestion such as amylase, lipase, and protease is known as pancreatic exocrine insufficiency (PEI). PEI occurs when the activity of pancreatic enzymes falls below 10%. Some of the manifestations which were found in those patients include steatorrhea, weight loss, and abdominal pain with bloating⁽²⁾. Furthermore, depending on the severity of malnutrition, more complex symptoms and signs may occur as a result of albumin deficiency and impaired absorption of fat-soluble vitamins⁽³⁾.

There were structural changes and indicators of damage in the pancreases of diabetic patients examined post-mortem, such as fibrosis, shrinkage, fatty accumulation, evidence of chronic inflammation,

and a reduction in size. Previous researches that used direct pancreatic function tests to evaluate the existence of pancreatic insufficiency found that nearly half of patients with type 1 and type 2 diabetes had impaired pancreatic function; however, these tests are not routinely used to diagnose PEI. In research that used indirect pancreatic function tests, similar findings were reported. PEI was observed in 51 percent of patients with type 1 diabetes and 32 percent of patients with type 2 diabetes⁽⁴⁾.

These findings are focused on FE-1 levels rather than the existence of symptoms. Exocrine pancreatic function is currently assessed using noninvasive stool tests, and FE-1 concentration estimate by ELISA has become a reliable and generally accepted diagnostic test for exocrine insufficiency^(5, 6). The FE-1 test has a good correlation with direct exocrine function tests, particularly in moderate to severe cases⁽⁷⁾. FE-1 is also a non-invasive and clear predictive clinical marker for pancreatic tumor prognosis after curative surgery⁽⁸⁾. Patients with FE-1 levels that are greater than (200 µg/g) are considered within normal, those having levels between (100 and 200 µg/g) are considered suffering of mild to moderate pancreatic insufficiency, and those having levels below



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(100 µg/g) are classified in severe pancreatic insufficiency category ⁽⁹⁾.

The objective of our study was to evaluate the prevalence of PEI in Egyptian diabetic patients utilizing FE-1 concentration and to investigate its relation with the degree of glycemic control.

PATIENTS AND METHODS

This cross-sectional study was carried out on 180 diabetic patients (90 T1D = Group 1 and 90 T2D = Group 2) who were recruited from the Diabetes Clinic and Internal Medicine Department of Benha University Hospital, Egypt. Ninety healthy non-diabetic participants (Group III) were also enrolled and considered as a control group.

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

T1D and T2D were defined according to American Diabetes Association (ADA) ⁽¹⁰⁾ criteria. T1D was diagnosed if diabetes-associated antibodies were present, and patients were insulin-dependent at diagnosis. Patients having high C-peptide levels with BMI >25 Kg/m² and negative for antibodies were classified as T2D.

Exclusion criteria:

- Cases of fibrocalcific pancreatic diabetes.
- Evidence of pancreatic calcification on ultrasound/ abdominal X-ray.
- Alcohol abusers.
- Drug abusers.
- Pancreatic malabsorption.
- History of gastrointestinal surgery.
- Calcular cholecystitis or history of any other gallbladder disease.
- Patient having malignant tumors.
- Patients with known peptic ulcer or any known gastric diseases.

The following information was also obtained from each patient: Detailed history with special emphasis on diabetes duration, diabetes therapy, and presence of microvascular/ macrovascular complications.

Patients were classified to symptomatic or asymptomatic depending on the presence of the

following symptoms (diarrhea - flatulence – recurrent abdominal pain).

Patients were subjected to physical examination including BMI, biochemical parameters (FBS, HbA1c, hemoglobin, serum albumin, and serum calcium), abdominal ultrasound, and/or erect abdominal X-ray to exclude pancreatic calcification.

FE-1 level was measured by utilizing ELISA kits from BIOSERVE diagnostics GmbH, Germany. The microplates were coated with antibodies directed towards pancreatic elastase enzyme, which binds to the elastase in the sample of the patient. Another antibody labeled with biotin was then added which binds to the immobilized elastase. The next step was that the bound elastase-1 was visualized by adding a streptavidin labeled horseradish peroxidase. The peroxidase oxidizes the substrate TMB (3,3', 5,5'-tetramethylbenzidine). The oxidized TMP was estimated photometrically at 450 nm.

Normal values are above 200 mg/g, FE-1 <200 µg/g of stool was considered as diagnostic of pancreatic exocrine insufficiency. FE-1 <100 µg/g of stool was considered diagnostic of severe PEI.

Statistical analysis

Data were collected and analyzed using a statistical software program, SPSS (Statistical Package of the Social Services) version 16 for Microsoft windows. All the anthropometric and biochemical parameters were expressed as mean ± SD and were compared using ANOVA. Pearson's correlation was used to find the correlation between FE-1 and the various biochemical and anthropometric parameters. Chi-square test was used to compare the prevalence of PEI in the groups. P-value < 0.05 was considered significant.

RESULTS

Baseline characteristics of the studied groups revealed that the FE-1 of T1D and T2D were significantly lower as compared to the control group. Patients of T1D group were significantly younger than both T2D group and control group. Patients of T1D group had lower BMI than T2D group and control group.

FBS and HbA1c levels were significantly higher in T1D and T2D groups in comparison to the control group (p-value < <0.001). Serum albumin levels and serum calcium did not show significant difference between both T1D and T2D groups when compared to control group (Table 1).

Table (1): Comparison of anthropometric and biochemical parameters between the three groups.

	Group I (T1D) N=90	Group II (T2D) N=90	Group III Control N=90	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	31.7± 13.8	51.8± 15.6	43.5 ± 18.5	<0.001
FE-1 (µg/g)	262.5 ± 15	288.4± 16.9	385.5 ±160	<0.001
FBS (mg/dl)	179.7± 6.0	184.7 ± 6.3	89±5.2	<0.001
HbA1c (mmol/mol)	9.3 ± 1.8	9.1± 1.8	4.9±1.2	<0.001
BMI (kg/m ²)	21.4± 4.2	30.6 ± 4.7	27.6± 6.7	<0.001
Hb (g/dL)	12.8 ± 2.7	13.4 ± 2.01	13.51 ± 3.1	0.154
Serum albumin (g/dL)	3.98± 0.51	4.01± 0.3	4.1 ± 0.55	0.191
Serum calcium (mg/dL)	9.1±1.1	9.1 ± 0.7	9.1 ± 0.5	0.213

There was no statistical difference in the prevalence of PEI in T1D and T2D. The prevalence of PEI in control group was significantly lower than that of T1D and T2D (Table 2).

Table (2): Prevalence of PEI in the all studied groups.

FEC# (µg/g)	T1D N=90	T2D N=90	Control N=90	P value
<200	35.6%	31.1%	7.8%	<0.001
>200	64.4%	68.9%	92.2%	

FEC: Fecal Elastase Concentration (<200: PEI, >200: normal).

Prevalence of severe PEI:

Only 8.9% of patients with T1D and 6.7% of T2D patients had symptoms suggestive of PEI. The prevalence of severe PEI (i.e. FE-1 <100 µg/g of stool) in T1D was significantly higher than that of T2D (P < 0.01) (Figure 1).

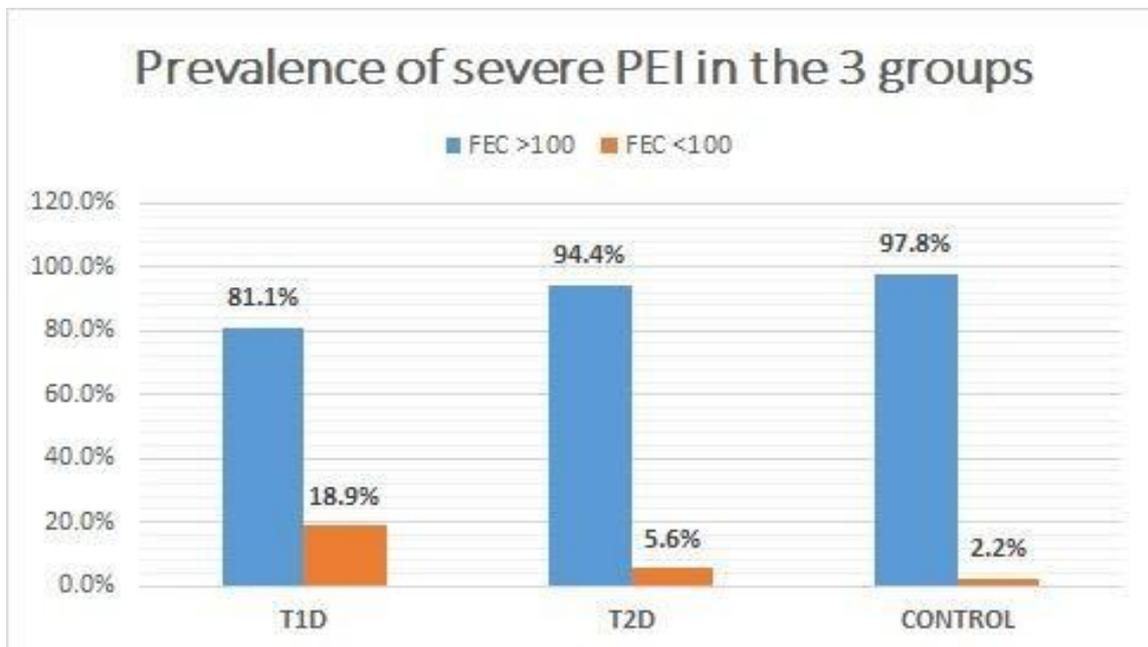


Figure (1): Prevalence of severe PEI (i.e. FEC <100 µg/g of stool).

A negative correlation was detected between FE-1 and HbA1c for patients with T1D and T2D (Figure 2).

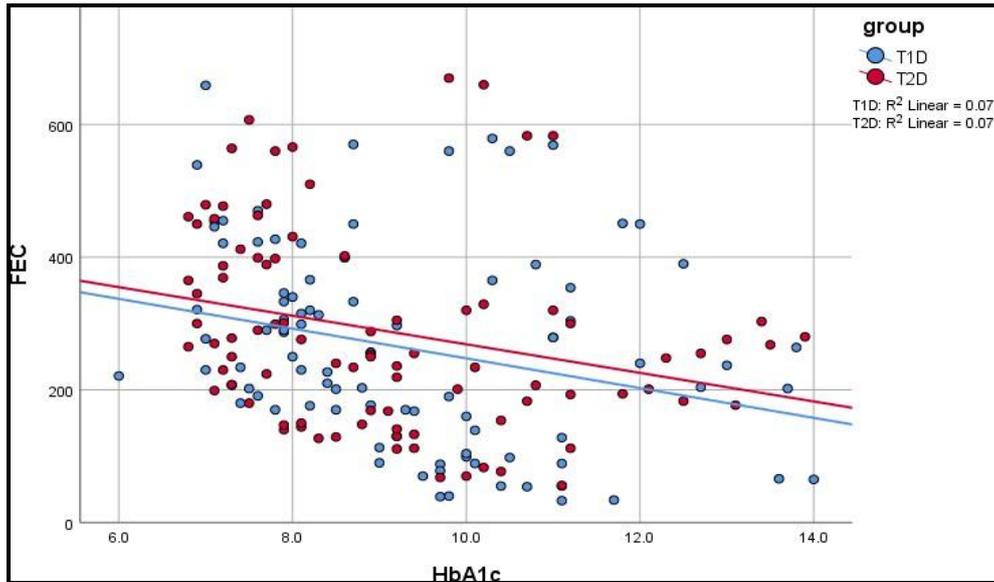


Figure (2): A scatterplot showing the correlation between HbA1c and FE-1, the correlation was negative ($R = -0.275$; $P < 0.001$).

There was also a negative correlation between FE-1 and FBS in the both groups ($R = -0.283$; $P < 0.001$). A significant negative correlation was observed between FE-1 and diabetes duration for patients with T1D ($R = -0.531$; $P < 0.001$) and for patients with T2D ($R = -0.433$; $P < 0.001$) (Figure 3).

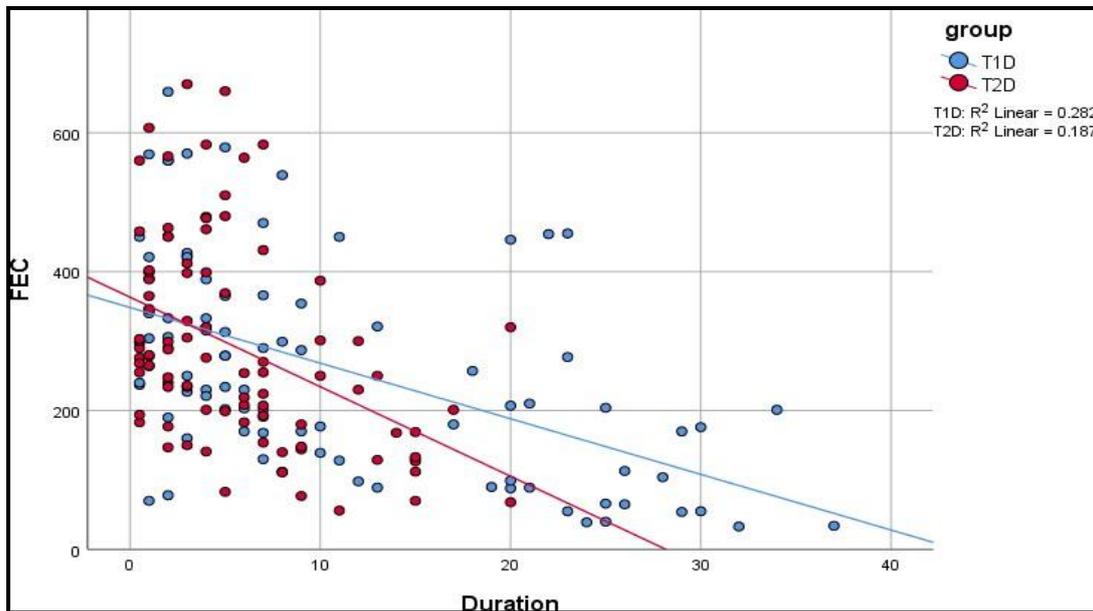


Figure (3): A scatterplot showing the correlation between FE-1 and Diabetes duration.

There was positive correlation between FE-1 and BMI for patients with T1D ($R = 0.446$; $P < 0.001$) and for patients with T2D ($R = 0.210$; $P = 0.047$) with no significant correlation between BMI and FE-1 for the control group ($R = 0.087$; $P = 0.415$) (Figure 4).

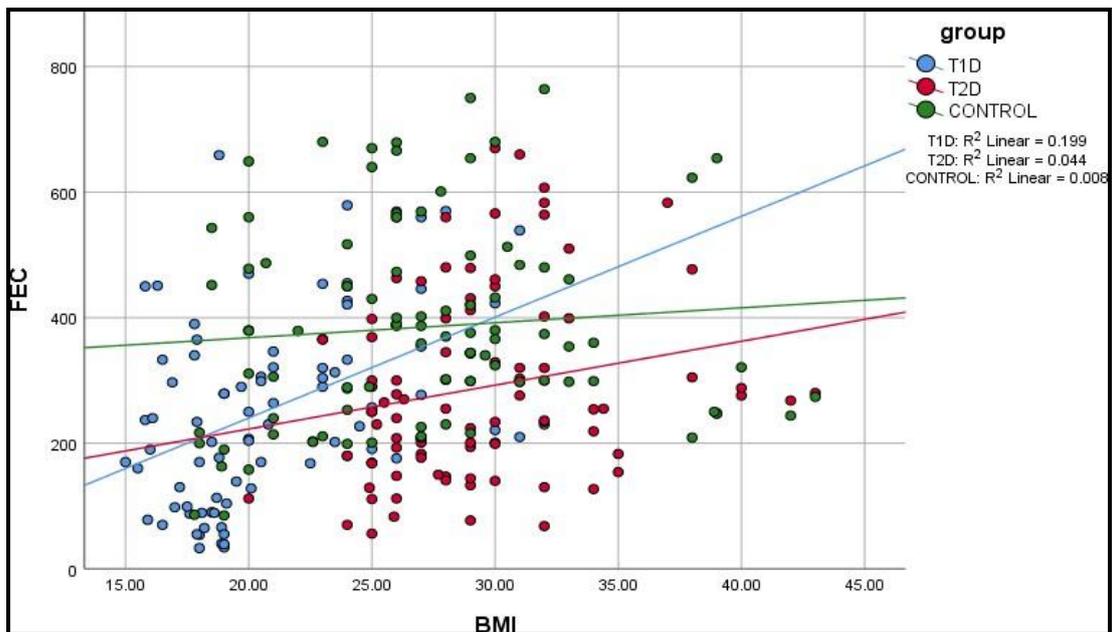


Figure (4): A scatterplot showing the correlation between BMI and FE-1.

DISCUSSION

Exocrine pancreatic function which is assessed by ELISA concentrations of FE-1 has become a widely accepted diagnostic test for exocrine insufficiency^(5,6).

The prevalence of PEI in T1D noted in our study was comparable to the results from other studies. In patients with T1D, a study by **Rathmann et al.**⁽¹¹⁾ estimated the prevalence of PEI by using FEC in 1020 diabetic patients (323 T1D and 697 T2D) and found that 51% of T1D were detected to have PEI. In a different study by **Larger et al.**⁽¹²⁾ involving 195 T1D patients, 34% were found to have PEI. In other researches, the percentages of PEI in diabetic patients type 1 using FEC were from 20 % to 74%⁽¹²⁻¹⁷⁾. However, another study by **Vujasinovic et al.**⁽¹⁸⁾ was different and showed a very low prevalence of PEI of 6% in T1D.

In diabetic patient type 2, a research by **Groger et al.**⁽¹⁹⁾ found a prevalence of 35%. In another larger study by **Rathmann et al.**⁽¹¹⁾, in 544 T2D patients, 30% were found to have PEI. In the study done by **Larger et al.**⁽¹²⁾, of the 472 diabetic patient type 2, the percentage of PEI was 18%. In other studies, the prevalence of PEI in T2D ranged from 28 to 36%^(13,14,20,21). In a meta-analysis of prospective, observational studies that used FE-1 estimation to determine PEI in patients with diabetes, one in three patients with DM showed signs of abnormal exocrine function⁽²²⁾.

In our study, FEC was inversely correlated with HbA1c and FBS. In the series by **Hardt et al.**⁽⁴⁾, also negative correlation was detected between FEC and HbA1c. **Terzin et al.**⁽²³⁾ had shown that people with higher HbA1c had a lower FEC value. Other studies also have reported a significant inverse

correlation between PEI and HbA1c, though some failed to show any association^(4,11-13,17).

In our study, FEC was positively correlated with BMI for patients with T1D and T2D however there was non-significant correlation for the control group. There are conflicting reports on the association between FEC and BMI. Whereas a less series showed a relation between FEC and BMI, a few studies failed to reveal any association^(12,14,15,24).

There are five significant speculations proposed to clarify the reason for PEI in diabetic patients. The theory number one is that pancreatic islet cell hormones have regulatory functions for exocrine tissue properties, and that the balance between stimulating-inhibitory islet cell hormones changes in diabetic patients^(4,25). The second hypothesis is that insulin has a trophic effect pancreatic acinar cells, and that decreased insulin level can cause atrophy of the pancreatic acini^(25,26). The third theory is that it is linked to a decreased entero-pancreatic reflex and exocrine pancreatic functions as a result of autonomic neuropathy and gastroparesis as a diabetic complication^(4, 24). Autoimmunity is the fourth hypothesis, in which antibodies directed against the islet cells can cross-react with acinar cells, or antibodies against exocrine pancreatic tissue (such as anti-cytokeratin antibodies) may cause pancreatic insufficiency^(27,28). The fifth theory is that the impairment of blood flow to the pancreas secondary to microvascular abnormalities, and fibrosis occurs, resulting in exocrine pancreatic insufficiency^(16,29). Another theory proposed by **Chey et al.**⁽³⁰⁾, who said that diabetes is secondary to underlying pancreatic exocrine dysfunction, but this theory is not generally accepted. More research is needed to evaluate the main reasons for the increased incidence of PEI in diabetic

patients. PEI's effect on glycemic control and other parameters would also need to be investigated. Also the effect of enzyme replacements in diabetics with PEI needs more studies.

CONCLUSION

PEI is frequent in both type 1 and type 2 Egyptian diabetic patients. The presence of PEI was correlated with lower BMI, higher HbA1c, and longer duration of diabetes.

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Conflicts of interest: Not Available.

Data Availability: The data used and analyzed in this study are available through the corresponding author on reasonable request.

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