The easy way of evaluating exocrine pancreatic insufficiency in type 2 diabetes : listen to the patients' complaints and look in their eyes!

Z. Aksoz[1], T. Akkan[2], E. Beyan[1], M. Dagdeviren[2], A. Mete Yildirim[1], I. Karadag[1], O. Dogan[3], D.T. Ertugrul[2], M. Altay[2]

(1) University of Health Sciences, Kecioren Training and Research Hospital, Department of Internal Medicine ; (2) University of Health Sciences, Kecioren Training and Research Hospital, Department of Endocrinology and Metabolism ; (3) Ankara University Faculty of Medicine, Department of Medical Biochemistry, Ankara, Turqey.

Abstract

***Background and Study Aims* : The objective of this study is to determine the prevalence of exocrine pancreatic insufficiency (EPI) in diabetic patients, and to investigate whether there is a relationship between EPI and diabetes period, gastrointestinal complaints and other diabetic microvascular complications.**

***Patients and Methods* : A total of 93 participants, consisting of 57 type 2 diabetes patients and 36 healthy volunteers have been included in our cross-sectional study. Participants were questioned for abdominal complaints and weight loss. Fecal elastase-1 (FE-1) was determined in fecal spot samples received from participants. The relationship between EPI and blood glucose, HbA1c, and duration and complications of diabetes were investigated.**

***Results* : FE-1 levels were significantly lower in diabetic group compared to control group (p=0.007). The number of patients with FE-1 levels of <200µg/g were significantly higher in diabetic group (p=0.002). A statistically significant negative correlation was determined between FE-1 levels and the duration of diabetes (r= -0.453 p<0.001). FE-1 levels were significantly lower in patients with retinopathy (p= 0.014). In the post-hoc analysis, this difference was due to patients in the proliferative retinopathy group. A significant negative correlation was determined between the presence of retinopathy and FE-1 levels (r=-0.32, p=0.02). Abdominal pain and distension complaints were independent predictive factors that estimate EPI.**

***Conclusions* : An important part of type 2 diabetes patients has EPI and it should be considered in diabetes patients upon abdominal pain and distension. Determination of proliferative retinopathy in the eye examination may also suggest an idea on the possible presence of EPI.** (Acta gastroenterol. belg., **2020**, 83, **407-412**).

Key words : exocrine pancreatic insufficiency, abdominal distention, abdominal pain, diabetic retinopathy.

Introduction

Pancreas is a gland with endocrine and exocrine functions. Regulating blood sugar level is an endocrine function of pancreas, while regulating digestion and absorption of nutrients may be listed among the exocrine functions of pancreas. In exocrine pancreatic insufficiency (EPI), steatorrhea and malabsorption characterized with weight loss are experienced due to insufficient fat and protein digestion and absorption. Chronic pancreatitis, cystic fibrosis, pancreatic surgery due to acute necrotizing pancreatitis or Shwachman-Diamond syndrome, celiac disease, inflammatory bowel diseases, and other malabsorption syndromes may be listed among the main diseases that result in EPI (1-3).

EPI may be detected with direct and indirect tests. Indirect tests have been used more commonly in recent years due to their ease of application and they were confirmed with direct tests. FE-1 is a non-invasive, cheap and easily applicable test used for this purpose (4,5). Human pancreatic FE-1 enzyme is synthesized in acinar cells of pancreas. They are in zymogen granules in the pancreas. Elastase, passing into duodenum with the exocrine secretion of pancreas, is activated by trypsin in duodenum (6). It is excreted via feces without undergoing any change in its amount during intestinal passage. It was shown that the fact that FE-1 is connected to bile salts provided protection from proteolytic or catalytic breakdown during intestinal passage and ensured no breakdown (7). FE-1 stays in pancreatic fluid for approximately 5 hours. It can be said that FE-1 corresponds to the amount of enzymes synthesized by pancreas (8). FE-1 has become the gold standard test in recent years for the measurement of indirect pancreatic functions (9,10). Although the specificity for FE-1 in showing exocrine pancreas insufficiency is 90% and the sensitivity in serious insufficiency cases is 100%, its sensitivity falls to 65% for mild to moderate pancreatic insufficiency cases (4,5).

Even though diabetes is an endocrine disease of the pancreas, EPI has been reported in some studies (11). Its prevalence, symptoms and findings upon presentation, and its relation with the other complications of diabetes are not clear yet. Upon considering exocrine pancreatic insufficiency as a significant cause of morbidity, it is clear that extensive studies are required to be performed on diabetes patients in this subject.

The purpose of this study is to determine the prevalence of EPI in diabetic patients, and to investigate whether there is a relationship between EPI and diabetes period, gastrointestinal complaints and diabetic microvascular complications.

Material and Methods

Local ethics committee approval was obtained for the study. Oral and written consent was obtained from

Correspondence to : Tolga Akkan, MD, Department of Endocrinology and Metabolism, Kecioren Training and Research Hospital, University of Health Sciences, 06280, Ankara, Turkey
E-mail : tolgaakkan@outlook.com

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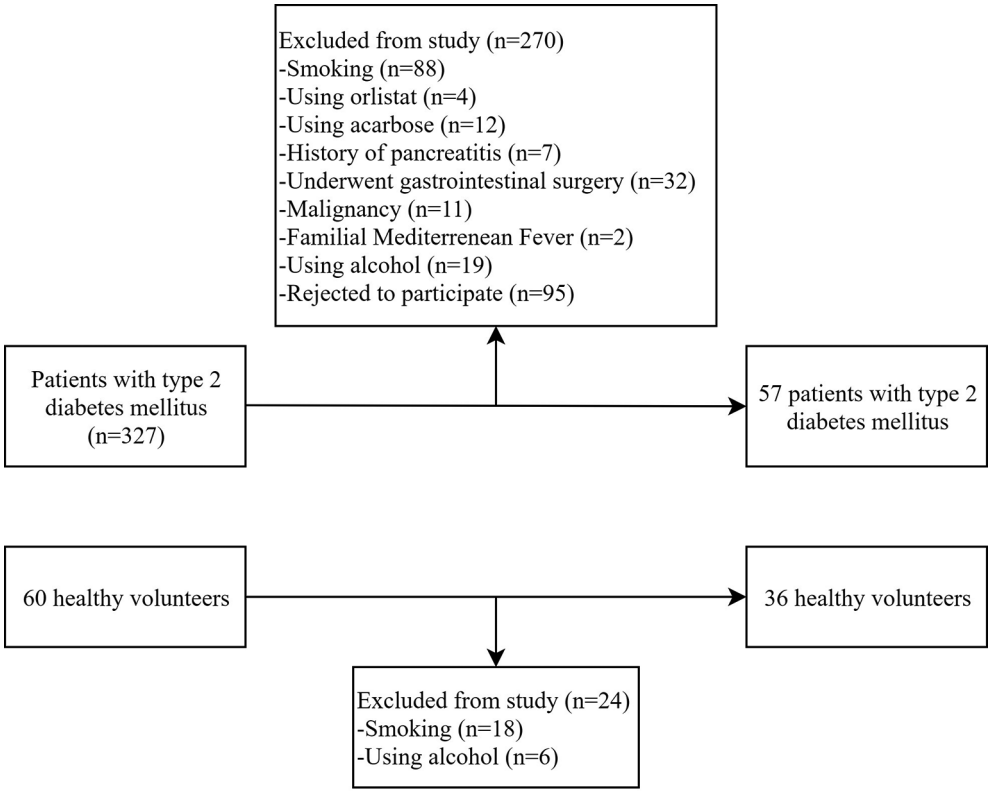

Figure 1.

all participants in the study. A total of 93 participants, consisting of 57 type 2 diabetes patients and 36 healthy volunteers have been included in our study. Patients who underwent gastrointestinal system surgery, chronic autoinflammatory disease (such as Behçet's disease and Familial Mediterranean Fever), chronic diarrhea, history of pancreatitis, any malignancy, inflammatory bowel disease or celiac disease, patients using orlistat or acarbose, patients who smoke or use alcohol, patients who experienced metformin associated gastrointestinal side effects, and patients under age 18 were not included in the study (Figure 1).

Detailed history was taken from the patients, and a physical examination was performed. For exocrine pancreas insufficiency, patients were questioned whether they had abdominal pain, distension, and steatorrhea, and whether they have involuntarily lost more than 10% of their weight in the last 6 months. We described steatorrhea to the participants as bulkier, pale, oily and foul-smelling feces. All of these questions defined as subjective symptoms so we did not perform any fecal excretion test or weight measurement in the last 6-month period. Body mass index was calculated for all patients and volunteers in the study. Patients, who underwent fundus examination for diabetic retinopathy evaluation with indirect ophthalmoscope by an ophthalmologist, have been divided in 3 groups consisting of those without retinopathy, patients with non-proliferative diabetic retinopathy and patients with proliferative diabetic retinopathy. For diabetic retinopathy evaluation ; creatinine clearance of patients was calculated with Modification of Diet in Renal Disease (MDRD) formula. Patients with creatinine clearance levels of <60mL/min/1.73m^2 and/or albuminuria >30mg/dl were assumed to have nephropathy, and patients with creatinine clearance levels of >60mL/min/1.73m^2 and albuminuria <30mg/dl were assumed to not have nephropathy.

In order to evaluate diabetic neuropathy, sensory neuropathy examination was performed with 10 g monofilament test. Also, they were evaluated according to whether they had numbing, burning, and pain in hands and/or feet. Patients who had these complaints and/or positive monofilament test results were assumed to have neuropathy, and patients with no symptoms and negative monofilament test results were assumed to not have neuropathy. Fasting blood sugar (FBS), HbA1c, plasma creatinine and microalbumin levels in spot urine have been recorded from patient files. Fecal spot samples were taken in the hospital and samples were stored by immediately freezing at -80 °C. After collecting samples, FE-1 was analyzed with double sandwich Enzyme-Linked Immuno Sorbent Assay and Bioserv Diagnostics GmbH Germany kit. Patients with FE-1 levels >200µg/g were assumed to be normal, between 100-200µg/g as mild to moderate pancreas insufficiency, and <100µg/g as severe pancreas insufficiency (12).

Serum creatinine was measured with kinetic Jaffe method by using Konelab 60i (Thermo Fisher Scientific Inc. MA, USA). Serum fasting blood sugar was measured with enzymatic method by using

Olympus AU680 (Beckmann Coulter, USA). HbA1c was analyzed with HPLC method by using automatic Tosoh G7 HbA1c Analyzer (Tosoh Corporation, Tokyo, Japan). Microalbumin was studied in Cobas Integra 400 autoanalyzer with turbidimetric method.

Statistical Method

The data obtained in this study was assessed by using SPSS 15.0 program. Kolmogorov-Smirnov test and histogram graphs of data were used to determine whether the data had normal distribution. Since the data did not have normal distribution, they were expressed in median (minimum-maximum). Categorical variables were presented in percentage values, and statistical analyses were performed with chi-square test and Fisher Exact test. The differences between groups were calculated with Mann-Whitney U test and Kruskal Wallis-H Test. In multivariate analysis, independent predictors of possible factors (relation with $p<0.25$) determined in previous analyses for the estimation of EPI were examined with logistic regression analysis. Hosmer-Lemeshow test was used for model compliance. Spearman's correlation test was used while studying the relations between variables. The significance level of $p<0.05$ was assumed to be a significant difference/relation while interpreting results. Bonferroni correction was performed in the comparison of more than two groups.

Results

A total of 93 subjects were included in our study. The subjects participating in the study were divided in two groups, which were the group of diabetic patients and the control group consisting of healthy volunteers. Two groups were similar with regard to age and gender, and body mass index was significantly lower in control group (Table 1). The prevalence of abdominal pain and steatorrhea was similar in both groups, but weight loss and distension complaints were significantly higher in diabetic group (Table 1).

Moreover, fasting blood sugar was significantly higher compared to control group (178mg/dl and 86mg/dl, respectively, p<0,001), and eGFR was significantly lower compared to control group in the diabetic group (80 ml/min/1,73m² and 99 ml/min/1,73m², respectively, p<0,001).

Median FE-1 value of the diabetic group was determined to be significantly lower than control group (203 µg/g and 297,5 µg/g, respectively, p=0.007). The rate of patients with FE-1 levels of <200µg/g were significantly higher in diabetic group (49.1% and 16.7%, respectively, p=0.002) (Table 1).

In the diabetic group, median fasting blood sugar level was 178 (92-416) mg/dl, median creatinine clearance was 80 (10-122) ml/min/1,73m², median HbA1c was 8.1% (5.2-14.5), median diabetes period was 12 (7-28) years, and median microalbumin level was 14.93 (1.7-612.9) mg/dl. All patients were using metformin as an oral anti-diabetic agent. Thirty-three patients were using insulin and metformin and 24 patients were using only oral anti-diabetics for the treatment of diabetes mellitus.

Upon dividing in sub-groups according to FE-1 levels, 29 (50.8%) patients had normal FE-1 value (above 200 µg/g) in the diabetic group, 13 patients (22.8%) had mild to moderate insufficiency (between 100-200 µg/g), and 15 patients (26.4%) had severe EPI (below 100 µg/g). In the healthy group, 30 subjects (83.3%) had normal FE-1 values, 5 subjects (13.8%) had mild to moderate insufficiency, and 1 subject (2.9%) had severe insufficiency (Table 2).

In the correlation analyses, a statistically significant negative correlation was determined between BMI, FBS and FE-1 level (r=-0,29, p=0,005 and r=-0,3, p=0,004, respectively).

Table 1. — **Comparison of diabetes patients with control group with regard to demographic data and exocrine pancreatic insufficiency**

	Diabetes Mellitus (n=57)	**Control (n=36)**	**p**
Gender (Female) - *%*	77.2	72.2	NS
Age - *years*	51 (27-59)	46.5 (31-63)	NS
BMI - *kg/m²*	30.3 (20.9-45.7)	26.2 (19.6-39)	**0.001**
Distension - *%*	58.5	19.4	**<0.001**
Abdominal pain - *%*	32.7	16.7	NS
Steatorrhea - *%*	13.2	11.1	NS
Weight loss - *%*	24.5	2.8	**0.006**
FBS (mg/dl)	178 (92-416)	86 (75-101)	**<0.001**
eGFR - *ml/min/1,73m²*	80 (10-122)	99 (51-131)	**<0.001**
FE-1 - µg/g	203 (9-596)	297.5 (12-641)	**0.007**
FE-1<200µg/g - *%*	49.2	16.7	**0.002**

Abbreviations : BMI : body mass index, FBS : fasting blood sugar, eGFR : estimated glomerular filtration rate, FE-1 : fecal elastase 1, NS : not significant.

Table 2. — **Comparison of groups according to FE-1 levels for exocrine pancreatic insufficiency and its severity**

Exocrine pancreatic insufficiency (FE-1 level µg/g)	Diabetes Mellitus (n=57)	Control (n=36)	p
No EPI (>200) %	50.8	83.3	**0.04**
EPI (<200) %	49.2	16.7	**0.002**
Mild - Moderate (100-200) %	22.8	13.8	NS
Severe (<100) %	26.4	2.9	**0.009**

Abbreviations : EPI : exocrine pancreatic insufficiency, FE-1 : fecal elastase 1, NS : not significant.

A statistically significant negative correlation was determined between FE-1 level and the duration of diabetes (r= -0.453 p<0.001).

Upon examining all of the participants, FE-1 level was significantly lower in participants with abdominal pain compared to those who hadn't, and it was also significantly lower in participants with distension compared to those who didn't have distension (175µg/g and 296µg/g, respectively, p<0.001; 192µg/g and 337µg/g, p<0.001). No significant difference was determined in FE-1 levels according to steatorrhea and weight loss status.

There was no significant relationship between the treatment used in diabetic group (oral antidiabetics or insulin) and FE-1 level. FE-1 levels of patients with diabetes period of 10 years and above was significantly lower compared to those with a diabetes period below 10 years (192µg/g and 508µg/g, respectively, p=0,007).

Upon examining FE-1 values according to the presence of microvascular complications of diabetes, median FE-1 value was 215 µg/g (29-596) for the group without retinopathy, median FE-1 value was 246 µg/g (9-559) in the group with non-proliferative diabetic retinopathy (15 patients, 26.3%), and median FE-1 value was 86 µg/g (9-169) in the proliferative diabetic retinopathy (7 patients, %12.2). A statistically significant difference was determined between patients who did not have retinopathy, and patients with non-proliferative and proliferative diabetic retinopathy (p= 0.014). It was observed in the post hoc analysis that this difference is due to patients in the proliferative retinopathy group. A significant negative correlation was determined between the presence of retinopathy and FE-1 levels upon performing correlation analysis (r=-0.32, p=0.02). There was no significant difference between FE-1 levels of patients with or without diabetic nephropathy or neuropathy.

In the logistic regression analysis model of patient and control groups which aims to investigate the independent factors estimating EPI, it has been detected that abdominal pain and distension complaints are independent predictive factors estimating EPI (OR=5.96 (1.52-23.31), p=0.01 and OR=4.05 (1.25-13.09), p=0.01, respectively). It was detected that age, gender, BMI, steatorrhea and weight loss were not independent predictive factors (Table 3). In the logistic regression analysis model of only the diabetic patient group in which we aim to investigate independent predictive factors used to estimate EPI, we have determined that HbA1c, FBS, neuropathy, retinopathy and nephropathy were not independent predictive factors estimating EPI.

Table 3. — **Logistic regression analysis performed to assume EPI**

Risk factor	RR (95% CI)	p
Gender	1,75 (0.51-5,97)	NS
Age	1.02 (0.96-1.09)	NS
BMI	1.01 (0.91-1.12)	NS
Steatorrhea	0.4 (0.08-1.95)	NS
Weight loss	0.62 (0.13-2.99)	NS
Abdominal pain	5.96 (1.52-23.31)	**0.01**
Distension	4.05 (1.25-13.09)	**0.01**

Abbreviations : RR : estimated relative risk denoted with odds ratio, CI : Confidence Interval, BMI : body mass index, NS : not significant.

Discussion

In our study, we have determined that diabetes is a risk factor for EPI, and this condition was associated with the duration of diabetes, there was a significant relationship between exocrine insufficiency and proliferative retinopathy, and that abdominal pain and distension complaints were independent predictive factors estimating EPI.

Although endocrine pancreatic insufficiency is known in diabetic patients, it was reported that there may also be EPI (8). It is not yet clear why diabetic patients are observed to have EPI. Some hypotheses have been suggested for this subject. The first one of these hypotheses is endocrine and exocrine pancreas are close neighbors from an anatomic and functional aspect, and show a common functionality (13). The second one is: Insulin shows a tropic effect on pancreatic acinar cells, and pancreatic acinar atrophy may be developed in insulin insufficiency (14,15). The third one is: Pancreatic islet cell hormones have a regulating effect on exocrine cell functions, and islet cell hormones shows differences in diabetic patients (15-17). Fourth hypothesis is : antibodies against exocrine pancreatic tissue (such as anti-cytokeratin antibodies) may cause pancreatic insufficiency (18-20). Fifth hypothesis is : EPI may be a

complication of DM, or DM may be accompanying decreased exocrine functions and autonomic neuropathy enteropancreatic reflex which is developed in diabetic patients (21,22). The last hypothesis is : microvascular complications may be associated with EPI (23).

In the studies performed, EPI in healthy individuals has been reported in various prevalence levels between 3.8%-18.1% (24,25). In our study, the prevalence of EPI was determined as 16.7% in healthy control group. The relatively high rate of healthy group suggests that this may be associated with social and environmental factors. Still, age may pose a factor in these results. This is due to the fact that we have determined a negative correlation between age and FE-1 level in control group. Herzig and colleagues have also detected that FE-1 level decreases physiologically in healthy individuals above age 60 (26). In studies performed on diabetes patients, the prevalence of EPI has been reported by Vujasinovic et al. as 5.4%, Terzin et al. as 16.8%, and by Hardt et al. as 40.7% (11,27,28). Similar to our study, FE-1 level was determined to be significantly lower in diabetes patients in studies performed by Vesterhus, Yilmaztepe, Nunes and colleagues (8,24,25). EPI has been detected as 49.2% in the diabetic group of our study, which is higher than previous studies. This suggests that a significant part of patients has EPI.

Endocrine and exocrine pancreas are close neighbors from an anatomic and functional aspect, and show a common functionality (13). For example, it has been suggested that the fibrosis observed in chronic calcified pancreatitis disrupts the functions of islet cells by causing vascular damage, and thus causes endocrine insufficiency (29). Endocrine pathologies may also cause exocrine insufficiency. It is known that exocrine pancreatic functions may be disrupted as a result of the destruction of acinar cells due to glucotoxicity in patients with poor glycemic control (27). Based on this hypothesis, lower FE-1 levels may be expected in individuals with high HbA1c and fasting blood sugar. Studies on this subject have determined quite contradicting results. While there are studies that have determined a statistically significant association between HbA1c and FE-1 levels (22,27), there are also studies that did not find a significant relation (25,30). In our study, a significant negative correlation has been determined between FE-1 level, and both FBS and diabetes period. It is well-known that the incidence of microangiopathy increases with increasing diabetes period. It has been suggested that diabetic microangiopathic process disrupts exocrine pancreas perfusion, and causes exocrine pancreatic ischemia, and even fibrosis (27). However, data from studies performed on DM period and FE-1 level is quite incompatible. While there are studies showing there is a relationship between DM period and FE-1 level, there are also studies suggesting the opposite (22,25,27,31). There is a limited number of studies investigating the relationship between neuropathy, retinopathy and nephropathy in diabetes, and EPI. In studies performed by Larger et al. and Mancilla et al., no statistically significant relationship was determined between both diabetic nephropathy and retinopathy, and FE-1 level (30,32). In a study performed by Kumar et al., 75% of 16 type 2 diabetes patients with retinopathy had severe EPI, and 19% had mild EPI. A significant relationship was determined between FE-1 level and retinopathy in this study (33). No relationship has determined in our study between diabetic nephropathy and neuropathy, and FE-1 level. Nevertheless, FE-1 level of patients with diabetic retinopathy was determined to be significantly lower than those without retinopathy. We have determined that this low level was mostly due to patients with proliferative retinopathy. Furthermore, a significant negative correlation has been determined between the presence of retinopathy and FE-1 levels. Besides, all of 7 patients with proliferative retinopathy had severe EPI. The presence of such a remarkable relationship between diabetic retinopathy and Fe-1 levels shows a confirmatory characteristic for microangiopathic destruction hypothesis which was suggested for EPI pathogenesis. Over the years, angiopathy is developed due to diabetes, and formation of arterial lesions, pancreatic fibrosis and exocrine atrophy arises. The negative correlation between diabetes period and FE-1 level determined in our study also supports this.

Gastrointestinal system symptoms are observed more commonly is DM patients compared to healthy population (11). We have questioned possible symptoms in exocrine insufficiency, such as abdominal pain, distension, steatorrhea and weight loss; and we have compared these symptoms with FE-1 levels. In the study performed by Hardt et al., a statistically significant relationship was determined between clinical symptoms and FE-1(34). However, there was a statistically negative relationship between abdominal pain and distension, and FE-1 level in our study. It was also determined that abdominal pain and distension complaints are independent predictive factors that estimate EPI. Nonetheless, there was no significant relationship between steatorrhea and weight loss, and FE-1. For this reason, we think that EPI should also be examined in diabetic patients describing abdominal pain and distension.

There are some limitations of our study. The first one is the fact that results cannot be generalized for all diabetes patients since only type 2 diabetes patients were included in the study. The second one is the small number of proliferative retinopathy patients in our study. Although all of them were determined to have severe EPI, more extensive studies are required in order to state that all patients with proliferative retinopathy must have EPI. The third one is the fact that no histopathological examination or biomarker study was performed in our study in order to determine a causal relationship between EPI formation and retinopathy development. The fourth one is that we described steatorrhea as a subjective symptom and we did not perform objective method such as quantitative fat excretion. And the last one is the fact that we could not determine the type of chronological relationship between

EPI formation process and retinopathy development since our study has a cross-sectional design.

In conclusion, approximately half of diabetic patients in our study were determined to have EPI. We suggest that this must be considered particularly in patients describing abdominal pain and distension. We could only determine a relationship between EPI and retinopathy among all microvascular complications. For this reason, we think that more extensive studies are required in order to state that microvascular destruction may play a role in the etiology.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics

Ethical approval was obtained from the ethical committee of Kecioren Training and Research Hospital. Informed consents were obtained from the all participants for publication of this study.

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