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Original article

Prevalence of exocrine pancreatic insufficiency in type 2 diabetes mellitus with poor glycemic control

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ABSTRACT

Objectives: To evaluate the relationship between exocrine pancreatic insufficiency and the level of glycemic control in diabetes (DM).
Methods: Patients with type 2 DM treated in our clinic were prospectively recruited into the study. Pancreatic diabetes was excluded. Cases with HbA1c ≥7% formed Group A ($n = 59$), and with HbA1c <7% Group B ($n = 42$). The fecal level of pancreatic elastase (PE-1) was measured and morphological examinations of the pancreas were performed.
Results: The PE-1 level was significantly lower in Group A than in Group B (385.9 ± 171.1 μg/g, vs. 454.6 ± 147.3 μg/g, $p = 0.038$). The PE-1 level was not correlated with HbA1c ($r = -0.132$, $p = 0.187$), the duration of DM ($r = -0.046$, $p = 0.65$), age ($r = 0.010$, $p = 0.921$), BMI ($r = 0.203$, $p = 0.059$), or pancreatic steatosis ($r = 0.117$, $p = 0.244$). The size of the pancreas did not differ significantly between Groups A and B.
Conclusions: An exocrine pancreatic insufficiency demonstrated by fecal PE-1 determination is more frequent in type 2 DM patients with poor glycemic control. The impaired exocrine pancreatic function cannot be explained by an alteration in the size of the pancreas or by pancreatic steatosis.

Introduction

The exocrine and endocrine pancreata are closely linked both anatomically and physiologically. Pathological conditions in the exocrine tissue can cause an impairment of the endocrine function and vice versa [1]. An exocrine pancreatic insufficiency has been indicated by direct or indirect pancreatic function tests to be present in about 50% of type 1 and 30–50% of type 2 diabetes mellitus (DM) cases [2,3]. Steatorrhea was observed in about 60% of patients with diabetes mellitus and fecal elastase <100 μg/g, indicating relevant, severe damage of the exocrine function [4]. Pancreatic enzyme replacement therapy (PERT) in patients with diabetes mellitus and exocrine pancreatic insufficiency may improve glucose metabolism, nutritional parameters and incretin response [5]. However, the significance of an exocrine dysfunction in DM has recently been questioned [6], and no beneficial effect of PERT on the glucose metabolism was observed in patients with insulin treatment for diabetes mellitus, although a reduction in mild and moderate hypoglycemia was demonstrated [7].

Besides the exocrine function, the pancreas morphology has been revealed by ultrasonography (US), computer tomography (CT), endoscopic retrograde pancreatography or autopsy to be altered in many patients with DM [8–11]. Nonalcoholic fatty pancreas disease (NAFPD), defined as pancreatic fat accumulation, has been demonstrated to be associated with obesity, metabolic

Abbreviations: DM, diabetes mellitus; HbA1c, glycated hemoglobin; PE-1, pancreatic elastase; US, ultrasonography; CT, computer tomography; NAFPD, nonalcoholic fatty pancreas disease; ADA, American Diabetes Association; CP, chronic pancreatitis; BMI, body mass index; OR, odds ratio; PERT, pancreatic enzyme replacement therapy.

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syndrome and type 2 DM [12–14], and it has been suggested that NAFPD may cause an endocrine and exocrine pancreatic dysfunction [12].

An exocrine pancreatic insufficiency has not been accurately determined to date in relation to the level of glycemic control. The level of pancreatic elastase-1 (PE-1) has been reported to be lower [15] or not to differ [16] in patients with HbA1c >8% relative to those with HbA1c ≤8%. However, for the proper management of DM and to prevent microvascular complications, a goal should be to maintain HbA1c <7% [17].

The aim of the present prospective study was an evaluation of the possible relationship between type 2 DM with poor glycemic control (HbA1c ≥7.0%), an exocrine pancreatic insufficiency and alterations in pancreatic morphology.

Patients and methods

Patients

Consecutive patients with type 2 DM followed-up in the diabetes outpatient clinic of the First Department of Internal Medicine, University of Szeged were prospectively recruited into the study between April 1, 2012 and June 30, 2013. Fasting blood glucose and serum HbA1c level were measured at the time of recruitment. The patients were divided into two groups, depending on the serum level of HbA1c: Group A: patients with poor glycemic control (HbA1c ≥7%), and Group B: patients with good glycemic control (HbA1c <7%). The pancreatic exocrine function was evaluated via the measurement of fecal PE-1, and morphological examinations were performed on the pancreas.

The diagnosis of DM was made in accordance with the criteria of the American Diabetes Association (ADA) [17]. Chronic pancreatitis (CP) was diagnosed only when both the morphological and functional diagnostic criteria were fulfilled [18]. Cases with type 3c DM, i.e. diabetes secondary to exocrine pancreatic diseases, were excluded. The patients were not operated on the pancreas.

All patients provided their written informed consent to participation. The study protocol was in full accordance with the most recent revisions of the Helsinki Declaration and was approved by the ethics committee at the University of Szeged (200913).

Methods

Fecal PE-1 was determined through the use of monoclonal antibodies (ScheBo Biotech AG, Giessen, Germany). PE-1 concentrations >200 μg/g in the stools indicated a normal exocrine pancreatic function, concentrations between 100 and 200 μg/g indicated a mild exocrine pancreatic insufficiency, and concentrations <100 μg/g denoted a severe exocrine pancreatic insufficiency [19].

Abdominal US and CT were performed to detect the characteristic morphological features of CP. US was applied for the detection of pancreatic steatosis. The liver, or the kidney if the liver was hyperechogenic, was used as reference point; echogenicity of the pancreas higher than that of the liver or kidney parenchyma was an indicator of pancreatic steatosis [20]. The thickness of the pancreas was measured by US just across the spine [8,21]. All US examinations were carried out by the same gastroenterologist, who was blind to the other results on the patients.

Statistical analysis

The experimental data were analyzed statistically with the independent-samples *t*-test, the Mann–Whitney *U* test, the chi-square test. The linear association between two variables was compared by Pearson-correlation analysis. p values <0.05 were accepted as being statistically significant. Statistical data are expressed as means ± standard deviation (SPSS 13.0 for Windows).

Results

A total of 106 type 2 diabetic patients were recruited between April 1, 2012 and June 30, 2013. Five patients were excluded, because morphological examinations revealed the characteristic features (calcifications and dilation of the main pancreatic duct) of advanced CP, all of them with poor glycemic control and with a decreased PE-1 concentration. Consequently, 101 type 2 diabetic patients were included into the study: 59 (25 male, 34 female, mean age: 63.6 ± 10.4 y, range: 42–89 y) in Group A and 42 (22 male, 20 female, mean age: 57.1 ± 11.2 y, range: 30–83 y) in Group B. 2. Two patients had autoimmune disorders, both suffered from rheumatoid arthritis, one in Group A and one in Group B. In group A 12 patients were on oral antidiabetic therapy, while the other 47 patients received insulin treatment. The same in Group B were 23 and 15, respectively, and the rest 4 patients were on diet only. The range of HbA1c was 7.0–11.6% in Group A and 5–6.9% in Group B. The BMI of the patients were comparable in the two groups ($p = 0.278$). However, the mean age was significantly higher ($p < 0.008$), and the duration of DM was significantly longer ($p < 0.006$) in Group A as compared to Group B (Table 1).

The fecal PE-1 concentration in Group A was normal in 45 patients (76.3%), while 11 (18.6%) exhibited a mild and 3 (5.1%) a severe exocrine pancreatic insufficiency. In Group B, the PE-1 concentration was normal in 39 subjects (92.9%), while 3 (7.1%) displayed a mild exocrine pancreatic insufficiency, and none a severe insufficiency. The prevalence of abnormal PE-1 concentration was significantly different between Group A and B (23.7% vs. 7.1%; $p = 0.033$). The PE-1 level was decreased in overall 16.8% of the cases. There were no significant differences in BMI between the patients with a decreased or a normal PE-1 concentration within Group A or B (Table 1).

The PE-1 level was significantly lower in Group A than in Group B (385.9 ± 171.1 μg/g vs. 454.6 ± 147.3 μg/g, $p < 0.04$, odds ratio [OR] = 4.0). The PE-1 level was not correlated with HbA1c ($r = -0.132$, $p = 0.187$), the duration of DM ($r = -0.046$, $p = 0.65$), age ($r = 0.010$, $p = 0.921$), or BMI ($r = 0.203$, $p = 0.059$) (Fig. 1).

US revealed pancreatic steatosis in 35 patients: 19 in Group A and 16 in Group B. Pancreatic steatosis was less frequent in Group A (32.2%) than in Group B (38.1%) (OR = 0.77), but it was more common in patients with an abnormal PE-1 concentration as compared with those with a normal PE-1 concentration (OR = 1.4)

Table 1
Clinical characteristics of the patients.

	Group A	Group B	*p*
No. of patients	59	42	–
Male/female	25/34	22/20	–
Mean age (y)	63.6 ± 10.4	57.1 ± 11.2	$p < 0.008$
Duration of DM (mean ± SD) (y)	13.2 ± 8.9	8.3 ± 7.9	$p < 0.006$
BMI (mean ± SD)	29.74 ± 5.65	28.43 ± 5.23	$p = 0.278$
Mean BMI of patients with decreased PE-1 (mean ± SD)	29.99 ± 4.58	32.29 ± 5.29	$p = 0.658$
Treatment of diabetes (oral antidiabetics/insulin/diet only)	12/47/0	23/15/4	–
Fasting plasma glucose (mean ± SD) (mmol/l)	10.56 ± 3.64	7.03 ± 1.65	$p < 0.001$
Mean HbA1c (range) (%)	8.3 (7–11.6)	6.2 (5–6.9)	$p < 0.001$

Data are reported as means with ranges in parentheses or as means ± SD.
DM: diabetes mellitus.
BMI: body mass index.
PE-1: pancreatic elastase-1.