

Does Pancreatic Elastase-1 in Stools Predict Steatorrhea in Type 1 Diabetes?

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A reduction of exocrine pancreas function frequently occurs in type 1 diabetes (1), and its detection has been made easy by measurement of fecal pancreatic elastase-1 (PE-1) (2,3). We recently observed that PE-1 correlates in these patients with poor blood glucose control, diabetes duration, and residual β -cell function (4). A possible consequence of severe pancreatic insufficiency is steatorrhea, defined as a daily fecal fat excretion (FFE) >6 (1) or >7 (5) g/day for subjects consuming 100 g of fat per day (1,5,6). Testing FFE requires multiple daily stool collections (6) and is not routinely feasible in asymptomatic subjects, being poorly accepted by patients and disliked by laboratory technicians. We considered here the hypothesis that low PE-1 identifies patients to be submitted to FFE measurement for steatorrhea detection.

RESEARCH DESIGN AND METHODS

— We studied, with the approval of the ethical committee of our institution and the subjects' informed consent, 66 consecutive type 1 diabetic subjects in regular follow-up at our diabetes clinic without history or symptoms of gastrointestinal disease and negative for anti-transglutaminase, anti-gliadin, and anti-endomysium antibodies checked to exclude celiac disease. Their clinical features were 32 men and 34 women aged (means \pm SD) 36.7 ± 12.1 years, age at diagnosis 22.7 ± 13.6 years, diabetes duration 13.9 ± 9.7 years, BMI 24.6 ± 3.7

kg/m², fasting C-peptide 0.21 ± 0.32 ng/ml (radioimmunoassay; Adaltis, Bologna, Italy), Diabetes Control and Complications Trial-aligned HbA_{1c} $8.4 \pm 1.4\%$ (high-performance liquid chromatography, Bio-Rad Variant II Total GHb Program; Bio-Rad Laboratories, Munchen, Germany; calibrated to the Diabetes Control and Complications Trial through the U.S. National Glycohemoglobin Standardized Protocol), and daily albumin excretion rate (AER) 35.3 ± 63.7 μ g/min (nephelometry; Beckman, Milan, Italy). A total of 49 subjects were normoalbuminuric, 15 were micro- and 2 macroalbuminuric, 45 presented no diabetic retinopathy, 14 had background and 7 preproliferative laser-treated retinopathy, 10 presented symptomatic neuropathy (5 autonomic, 3 sensorimotor, and 2 both autonomic and sensorimotor), 2 presented peripheral obstructive artery disease submitted to angioplasty, 1 had ischemic heart disease submitted to coronary angioplasty, and 1 had cerebrovascular disease with previous stroke. Patients, on steady metabolic control and body weight in the previous 6 months, were on a multiple insulin injection regimen and on a normocaloric diet (carbohydrates 55–60% and lipids 25–30% of calories and proteins 1 g/kg body wt). We measured serum amylase and lipase (Abbott Laboratory kits), FFE, and PE-1. PE-1 was determined in one stool specimen by enzyme-linked immunosorbent assay (ScheBo Pancreatic Elastase 1 ELISA kit; ScheBo-Tech, Giessen, Germany)

(normal values >200 μ g/g stools, intra- and interassay coefficients of variation 5.8 and 7.7%, respectively). In our laboratory, PE-1 presented a good longitudinal stability when measured in 50 type 1 diabetic patients at a 4-month interval (i.e., from 314 ± 150 to 300 ± 131 μ g/g stools, $P = \text{NS}$), the values at the two times being highly correlated ($r = 0.85$, $P = 0.0001$).

According to a standardized procedure (6), FFE was measured in patients receiving for 4 days a diet with a fat content of 100 g/day (reached with a fat supplementation), with a complete stool collection in the last 3 days for measurement of stool weight and fat concentration: average values of these collections were considered. FFE was evaluated by a method based on lipid reaction with sulfuric acid to form carbonium ions, which react with the vanillin phosphate ester to yield a colored complex that can be measured photometrically (7) (intra- and interassay coefficient of variation 5.9 and 8.7%, respectively), showing a good correlation ($r = 0.88$) with the method of van de Kamer et al. (8). Amylase and lipase were measured by Abbott Laboratory kits. Statistical evaluation was performed by Mann-Whitney nonparametric test for unpaired data, Wilcoxon test for paired data, linear and multiple regression analyses, Spearman rank correlation test, and χ^2 test utilizing the Stat View Software for the Macintosh. Data are means \pm SD.

RESULTS— Patients presented PE-1 315 ± 145 μ g/g stools (normal values >200 μ g/g stools), FFE 6 ± 3.2 g/day (normal values <7 g/day), serum amylase 55 ± 21.8 units/l (normal values 25–125 units/l), and serum lipase 25 ± 22.6 units/l (normal values 8–80 units/l). In particular, three patients presented amylase values lower than the normal range (i.e., 12–23 units/l) and none above, whereas four patients presented lipase values lower than the normal range (3–6 units/l) and three above (94–107 units/l). Figure 1A shows that PE-1 and FFE are negatively correlated ($r = -0.360$, $P = 0.0033$). The correlation has been confirmed with the Spearman rank correlation test ($\rho = -0.420$, $P = 0.0008$).

Of 66 patients, 19 (28.8%) presented

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Abbreviations: AER, albumin excretion rate; FFE, fecal fat excretion; PE-1, pancreatic elastase-1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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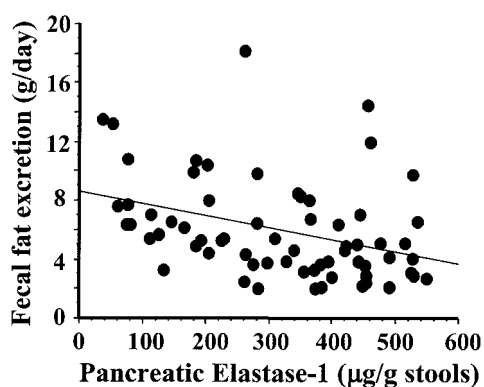


Figure 1—A: Linear regression plot of PE-1 in stools versus FFE in 66 type 1 diabetic subjects ($r = -0.360$, $P = 0.0033$).

FFE >7 g/day and 17 (25.8%) PE-1 ≤ 200 $\mu\text{g/g}$ stools, index of pancreatic insufficiency. Among 19 patients with FFE >7 g/day, 8 presented PE-1 ≤ 200 $\mu\text{g/g}$ stools (42.1%). Among 17 patients with PE-1 ≤ 200 $\mu\text{g/g}$ stools, 8 presented FFE >7 g/day (47.0%). An FFE >7 g/day was present in 5 of 7 patients with PE-1 ≤ 100 $\mu\text{g/g}$ stools, in 3 of 10 patients with PE-1 101–200 $\mu\text{g/g}$ stools, and in 11 of 49 patients with PE-1 >200 $\mu\text{g/g}$ stools (i.e., 71, 30, and 22%, respectively; $\chi^2 = 7.2$, $P = 0.028$). With the more strict cutoff point of >6 g/day (1), the percentages were 100, 50, and 30.6% for PE-1 values ≤ 100 , 101–200, and >200 $\mu\text{g/g}$ stools, respectively.

Using a multivariate analysis considering age, age at diagnosis, diabetes duration, BMI, HbA_{1c}, C-peptide, amylase, lipase, AER, stool weight, and PE-1, the parameters statistically associated with FFE were stool weight (standard coefficient 0.430, $P = 0.004$) and PE-1 (standard coefficient -0.290 , $P = 0.05$). Patients with steatorrhea denied abdominal pain or diarrhea.

As far as long-term diabetes complications are concerned 1) no correlation was found between AER and FFE; 2) two patients presented both steatorrhea and neuropathy; however, in both of them PE-1 was very low; 3) one patient presented both steatorrhea and peripheral obstructive artery disease, but he also presented low PE-1; and 4) one patient presented both steatorrhea and coronary artery disease, but he also presented low PE-1. Seven subjects with steatorrhea and low PE-1, who agreed to be treated for 2 months with pancreatic enzyme replacement, presented an FFE reduction from 11.1 ± 4.9 to 6.3 ± 1.7 ($P = 0.035$).

CONCLUSIONS— Steatorrhea accompanying diabetes has been attributed to 1) loss of exocrine pancreatic function

$>90\%$, 2) celiac disease, 3) abnormal bacterial proliferation in proximal small bowel, and 4) severe and uncontrolled diabetes per se (1). Patients falling in the first three categories respond, respectively, to pancreatic enzyme supplementation, gluten-free diet, and antibiotics, whereas patients falling in the fourth category present a poor therapeutic response (1). Treatment of steatorrhea is clinically useful; for instance, osteoporosis occurs in patients with pancreatic steatorrhea, owing to poor vitamin D absorption (9).

This study aimed to clarify whether PE-1 identifies patients that, although asymptomatic, may present steatorrhea and would deserve an FFE test. As far as we know, this is the first study evaluating the prevalence of steatorrhea in type 1 diabetic patients presenting a wide range of PE-1 concentrations.

The main messages of this study are that 1) $\sim 29\%$ of asymptomatic type 1 diabetic patients negative for autoantibodies associated with celiac disease present steatorrhea, 2) FFE inversely correlates to PE-1, and 3) steatorrhea occurs in $\sim 22\%$ of patients with normal PE-1. Our study therefore shows that PE-1 is associated with steatorrhea but to an extent too weak to justify measurement of FFE only in patients with low PE-1. Actually, in this case, more than half of patients with steatorrhea would be missed. Testing PE-1, on the other hand, helps to identify the pathogenetic involvement of exocrine pancreas. In our study, reduction of elevated FFE by means of pancreatic enzyme supplementation in patients with low PE-1 further supports the usefulness of PE-1 in identifying the pancreatic origin of steatorrhea. On the other hand, our study indicates that even when PE-1 is low, FFE should be measured before enzyme replacement prescription in agreement with a multicenter study carried out

in type 1 and 2 diabetic patients with PE-1 <100 $\mu\text{g/g}$ stools, which showed that not all of them present steatorrhea (6).

No clinical parameter, except for PE-1, seems to predict steatorrhea. A direct association with long-term diabetes complications is unlikely, since no correlation exists with AER, and patients with both steatorrhea and long-term complications also present exocrine pancreas failure indicated by low PE-1, not surprisingly owing to the common pathogenetic influence of diabetes duration and metabolic control (4). Further studies are needed to elucidate the pathogenesis of steatorrhea when it occurs in type 1 diabetic patients without exocrine pancreatic failure or celiac disease. As expected, stool weight correlates with FFE but cannot replace FFE measurement in the diagnosis of steatorrhea (10).

In conclusion, PE-1 is of limited usefulness to identify patients with steatorrhea but can be useful to identify those with steatorrhea of pancreatic origin, who present a rationale for pancreatic enzyme replacement. With this therapeutic purpose in mind, it could be proposed to measure FFE only in patients with a low PE-1, especially in those with a PE-1 <100 $\mu\text{g/g}$ stools. Since normal intestinal lipolysis is maintained by only 5–10% of the normally secreted lipolytic activity (5), steatorrhea is a consequence of very severe exocrine pancreas failure. Not surprisingly, it is clearly mirrored only by very low PE-1 concentrations. Further studies are needed to assess at which FFE value pancreatic enzyme supplementation should be started in type 1 diabetic patients.

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