Low Fecal Elastase 1 Levels Do Not Indicate Exocrine Pancreatic Insufficiency in Type-1 Diabetes Mellitus

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Objectives: On the basis of very low fecal elastase 1 and very high fecal fat estimations, it has been claimed that exocrine pancreatic insufficiency is frequent in diabetic patients, and that in up to 40% of the patients, pancreatic enzyme substitution would be indicated. Because this would affect millions of diabetic patients worldwide, we evaluated this suggestion by testing exocrine pancreatic function in type-1 diabetes using the criterion standard of exocrine pancreatic function tests, the secretin-cerulein test (SCT). The results of this test were then compared with those of fecal elastase 1 and fecal fat estimations.

Methods: Thirty-three patients with type-1 diabetes mellitus underwent an SCT, a fecal fat estimation, and 2 fecal elastase 1 tests (using both monoclonal and polyclonal antibodies) to evaluate their exocrine pancreatic function.

Results: The SCT results were abnormal in 11 of the 33 patients, who showed only mild to moderate exocrine pancreatic insufficiency, and the stimulated lipase secretion was never less than 10% of the level where pancreatic steatorrhea first occurs. The correlation between fecal elastase 1 and SCT showed much lower sensitivity, specificity, and positive and negative predictive values than did the correlation between SCT and fecal fat. Nonpancreatogenic steatorrhea was present in two thirds of the patients and was probably caused by bacterial overgrowth.

Conclusions: Neither low fecal elastase 1 nor raised fecal fat levels reliably indicate exocrine pancreatic insufficiency in type-1 diabetes and therefore should not be used as an indicator for expensive pancreatic enzyme substitution.

Key Words: fecal elastase 1, type-1 diabetes mellitus, exocrine pancreatic insufficiency

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The close proximity of the endocrine and exocrine regions of the pancreas has led to the suggestion that diseases of the one will influence the other part of the gland. For more than 40 years, several groups have studied exocrine pancreatic function in patients with insulin-dependent diabetes mellitus by means of the secretin test[1–3] and the secretin-pancreozymin test or modifications thereof.[4–8] It was found that exocrine pancreatic insufficiency is relatively frequent in insulin-dependent diabetes—in our own study from 1982, it occurred in 43% of the patients—but that it is not related to the age of the patient, the duration of diabetes mellitus, or its complications.[8] Exocrine pancreatic insufficiency was usually only mild to moderate, not requiring pancreatic enzyme substitution, and not progressing over time.[9,10]

After these studies, testing exocrine pancreatic function in diabetes mellitus lost scientific interest until 2 groups recently restudied the problem using fecal elastase 1 estimation, a new indirect pancreatic function test. This is a highly sensitive enzyme-linked immunosorbent assay for human duodenal and fecal elastase 1 that uses 2 specific monoclonal antibodies.[11] According to the manufacturers, fecal elastase 1 levels less than or equal to 200 μg/g stool indicate exocrine pancreatic insufficiency. Levels between 100 and 200 μg/g stool reflect mild to moderate, and those less than 100 μg/g stool severe functional impairment. The latter is an absolute indication for pancreatic enzyme substitution to compensate for loss of exocrine pancreatic function and to prevent the systemic effects of this insufficiency.

Using these parameters, Icks et al[12] and Hardt et al[13] reported mild to moderate insufficiency in 45.5% and 22.6% and severe insufficiency in 25.9% and 28.5%, respectively, of patients with type-1 diabetes. In type-2 diabetes, the corresponding data from both groups were 30.3% and 15.5% (mild to moderate) and 11.9% and 19.9% (severe).[13,14] In a subsequent study, Hardt et al[15] found steatorrhea (>7 g fecal fat/d) in 59.6% of patients with diabetes mellitus types 1 and 2, all of them with fecal elastase 1 concentrations less than or equal to 100 μg/g stool. Steatorrhea was clinically relevant, that is, greater than 10 g/d, in 39.6% of the patients. This amount of fecal fat excretion is usually regarded as an indication for pancreatic enzyme substitution to avoid the consequences of steatorrhea (eg, weight loss, osteoporosis, night blindness, etc).

This is a completely new finding and stands in contrast to all previous studies.[1–10] The prevalence of diabetic adults worldwide was estimated to be 4% in 1995 and to rise to 5.4% by the year 2025. That means that the number will rise from 135 million in 1995 to 300 million in the year 2025. In 1995, the 5 countries with the highest estimated number of diabetic adults were India (19.4 million), China (16.0 million), USA

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(13.9 million), Russian Federation (8.9 million), and Japan (6.3 million).[16] If, in keeping with these new findings,[12–14] 40% of all these diabetic patients also prove to have exocrine pancreatic insufficiency requiring enzyme substitution, this would certainly cause a very serious health care cost problem.

Because the results of these studies[12–14] diverged greatly from those of all previous reports—including our own,[8] in which the criterion standard for exocrine pancreatic function testing, the secretin-pancreozymin test, was used—we felt justified in reinvestigating more than 2 decades later exocrine pancreatic function in type-1 diabetes mellitus, this time using fecal elastase 1 estimations that we compared with the results of the secretin-cerulein test (SCT) and with various clinical and laboratory parameters.

MATERIALS AND METHODS

Patients

An evaluation of exocrine pancreatic function was initially offered to 93 consecutive patients with type-1 diabetes from the Clinic for Diabetes and Metabolic Diseases in Karlsburg, Germany. Of these, 30 patients were not interested in the examination, and another 5 were discouraged by their general practitioners from participating. Sixteen patients could not take part because of social problems, long travel distance from home to the hospital, and/or their reluctance to take time off from work for fear of jeopardizing their jobs. In 5 patients, severe concomitant disease (coronary heart disease, carcinoma) was discovered, and 4 were unable to swallow the endoscopy tube due because of motility problems. The remaining 33 patients underwent all test procedures. Upon comparison of the group of 60 patients not participating with the 33 patients participating in this study, it was found that participants were older (mean age, 47.7 vs 42.5 years; $P = 0.036$), more frequently had labile diabetes (44.8% vs 18.9%; $P = 0.015$), had a longer duration of diabetes (mean duration, 33.0 vs 24.3 years; $P = 0.0004$), and experienced more often neuropathy (46.8% vs 22.9%; $P = 0.018$) or nephropathy (68.8% vs 27.9%; $P = 0.003$) than nonparticipants. No significant differences between these groups were observed regarding sex, age at manifestation of diabetes, body mass index (BMI), hemoglobin A1c (HbA_{1C}), or retinopathy.

Seventeen of the tested patients were men, and 16 were women. Mean age was 47.9 ± 8.6 years (range, 37–63 years) in men and 47.5 ± 14.2 years (range, 21–65 years) in women. None of these patients had experienced previous attacks of acute pancreatitis, undergone gastric resection or any resective operation of the small or large intestine, or experienced hyperthyroidism or inflammatory bowel disease. Antibodies indicative of latent celiac disease were found in 5 patients; only one of them had previously been diagnosed with celiac disease.

Diabetes mellitus type-1 was diagnosed using the clinical history (age, weight loss, polyuria, polydipsia, ketosis) when the disease first manifested itself and an early need for insulin therapy. In some patients, with an atypical clinical history, the diagnosis was confirmed by the presence of diabetes-associated antibodies.

For the characterization of the quality of glucose control, the number of both mild and severe hypoglycemic events, the occurrence of diabetic ketoacidotic events, and the frequency of self-measured blood glucose levels outside the preprandial target range (5–7 mmol/L) were recorded. Glucose control was deemed stable in those patients who were generally normoglycemic and had only occasional mild hypoglycemic events. The diagnosis of labile diabetes was assigned to those with repeated hypoglycemic and ketotic events and a frequent need for both additional glucose intake and corrections of mealtime insulin doses.

Diagnosis of peripheral neuropathy was based on clinical symptoms and the results of clinical tests. Clinical examination included testing of Achilles' tendon reflexes, of vibration perception with a tuning fork, of temperature discrimination, and of pressure sensation using the 10-g Semmes-Weinstein monofilament.

To diagnose nephropathy, albumin and protein concentrations were measured in the urine (the first voided morning sample or a 24-hour urine collection). Blood specimens were taken to establish the level of serum creatinine. Incipient nephropathy was characterized by microalbuminuria (20–200 mg/L) and by normal creatinine clearance (>90 mL/min). For a diagnosis of manifest nephropathy, creatinine clearance had to be decreased and accompanied by either macroalbuminuria (>200 mg/L) or proteinuria.

The ophthalmologic examination was performed by an experienced ophthalmologist. Diabetic retinopathy was classified as nonproliferative (microaneurysms, hard exudates, cotton wool spots, retinal hemorrhages), proliferative (new vessels, vitreous hemorrhages, diabetes-related blindness), or none.

Finally, HbA_{1C} (reference, <6.5%; HPLC, Diamat, Biorad, Munich, Germany) was determined and the presence of antibodies (transglutaminase–immunoglobulin A [IgA], gliadine-IgA and IgG), which would be expected in the case of concomitant celiac disease.

The ethical committee of the Ernst Moritz Arndt University, Greifswald, Germany, approved the study.

Methods

An SCT[17,18] and fecal weight and fat measurements[19] were performed in Lüneburg. Normal levels for SCT were: after secretin administration, fluid secretion greater than 67 mL/30 min, bicarbonate concentration greater than 70 mmol/l, bicarbonate output greater than 6.5 mmol/30 min; after cerulein administration, amylase output greater than

TABLE 1. Levels of FE-1 Versus SCT Results

SCT	FE-1, Monoclonal Test, n = 33		FE-1, Polyclonal Test, n = 33	
Results	Normal	Abnormal	Normal	Abnormal
Normal	13	9	17	5
Abnormal	5	6	7	4
Sensitivity	55%		36%	
Specificity	59%		77%	
PPV	40%		44%	
NPV	72%		71%	

FE-1 indicates fecal elastase 1.

TABLE 2. Results of SCT in the 11 Patients With an Abnormal Exocrine Pancreatic Function

No.	Volume, mL/30 min	Bicarbonate Concentration, mmol/L	Bicarbonate Output, mmol/30 min	Amylase Output, U/30 min	Lipase Output, U/30 min	Fecal Weight	Fecal Fat	Elastase 1 ScheboTech	Elastase 1 Bioserv
	Reference >67	Reference >70	Reference >6.5	Reference >12,000	Reference >21,000	Reference <200 g/d	Reference <7.0 g/d	>200 μg/g	>200 μg/g
1	104	124	**5.6**	79,749	**18,454**	148	5.5	500	500
2	68	**42.6**	**3**	43,356	25,514	**278**	**20.8**	**26**	**149**
3	250	**63**	13.6	161,485	47,415	190	**7.1**	280	426
4	**60**	**43.7**	**2**	78,780	26,715	**222**	**12.8**	400	500
5	**18**	**21.1**	**0.5**	17,044	**6640**	**418**	**8.2**	**155.3**	**161.**7
6	155	**65.7**	10.4	141,250	73,650	192	**23.5**	225	311.3
7	92	140	**5.3**	35,772	**15,960**	146	**10.4**	**96.7**	**112.7**
8	180	**58.2**	10.4	74,400	31,050	50	5.8	**146.7**	**191.3**
9	**60**	91.9	**2.7**	**4310**	**4765**	**321**	**11.2**	459.3	364.7
10	105	157	8.3	72,305	**18,097**	70	**9.7**	**148.7**	231.3
11	**66**	50.1	**3.5**	34,860	**18,884**	99	5.9	**155.7**	243.7

Data highlighted in bold indicates abnormal results.

12,000 U/30 min, lipase output greater than 21,000 U/30 min. Stools were collected for 3 days by the patient at home, and fecal fat analysis was done using the Van de Kamer method[19] (reference levels: fecal weight, <200 g/d; fecal fat, <7 g/d). Fecal elastase 1 was estimated in Karlsburg using 2 methods: (1) monoclonal antibodies (ScheboTech, Wettenberg, Germany); (2) polyclonal antibodies (Bioserv Diagnostics, Rostock, Germany). According to the manufacturers' instructions, exocrine pancreatic insufficiency is present when fecal elastase 1 levels are less than 200 μg pancreatic elastase 1/g stool.

The results of the SCT and fecal weight and fat estimations were unknown to those measuring fecal elastase 1, and vice versa.

Statistical Analysis

Continuous variables were compared using the Student *t* test, ordinal variables using the Kruskal-Wallis test, and categorical variables using Fisher exact test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for both fecal elastase 1 tests against the SCT and against fecal fat estimation. All tests were 2-sided.

RESULTS

Using monoclonal antibodies, fecal elastase 1 levels were normal in 18 (54.5%) and abnormal in 15 (45.5%) patients. In 13 of the 18 patients with a normal test result, the SCT was also normal but abnormal in the remaining 5 patients. In 9 of the 15 patients with an abnormal test result, the SCT was normal but also abnormal in 6 patients. Thus, normal and abnormal fecal elastase 1 test results were confirmed by the SCT in 19 (57.6%) and not confirmed in 14 (42.4%) patients (Table 1).

With polyclonal antibodies, fecal elastase 1 levels were normal in 24 (72.7%) and abnormal in 9 (27.3%) patients. In 17 of the 24 patients with a normal test result, the SCT was also normal but abnormal in the remaining 7 patients. In 5 of the 9 patients with an abnormal test result, the SCT was normal but abnormal in the remaining 4 patients. Thus, normal and abnormal fecal elastase 1 test results were confirmed by the SCT in 21 (63.6%) and not confirmed in 12 (36.4%) patients (Table 1).

Data for sensitivity, specificity, PPV, and NPV for fecal elastase 1 estimations using both tests for the prediction of the SCT result were low (Table 1).

Of the 11 (33.3%) patients with an abnormal SCT result, the ductular system (volume, secretion, bicarbonate output and concentration) was involved in 5, the acinar system (amylase and lipase output) in one, and both systems in 5 patients.

TABLE 3. Levels of FE-1 Versus Fecal Fat

Fecal Fat	FE-1, Monoclonal Test, n = 33		FE-1, Polyclonal Test, n = 33	
Results	Normal	Abnormal	Normal	Abnormal
Normal	5	6	8	3
Abnormal	13	9	16	6
Sensitivity	41%		27%	
Specificity	45%		73%	
PPV	60%		67%	
NPV	28%		33%	

TABLE 4. Correlation of FE-1 Levels With Increasing Fecal Fat Excretion

Parameters	FE-1, Monoclonal Test		FE-1, Polyclonal Test	
	Normal	Abnormal	Normal	Abnormal
Fecal Fat				
Normal (no steatorrhea; <7 g/d)	5	6	8	3
Abnormal (steatorrhea)				
Mild (>7–10 g/d)	4	3	6	1
Moderate (>10–15 g/d)	7	4	8	3
Severe (>15 g/d)	2	2	2	2
P (Kruskal-Wallis test)	0.57		0.58	

Within this same group, 8 patients had steatorrhea, of whom 4 had a normal lipase output. In the remaining 4 patients, lipase output was reduced but not less than the level of 10% of normal. Elastase 1 estimations were abnormal in 6 (monoclonal antibodies) and 4 patients (polyclonal antibodies), whereas the tests were normal in 5 and 7 patients, respectively. In only 1 patient was the level of elastase 1 (monoclonal antibodies) less than 100 μg/g stool (Table 2).

With the exception of the BMI, which was significantly higher in patients with normal SCT ($P = 0.02$), there was no significant correlation between the SCT results and sex, present age, age at onset of diabetes, duration of diabetes, alcohol intake, character of diabetes, HbA_{1C} levels, or complications like retinopathy, nephropathy, and neuropathy (data not shown).

Fecal fat excretion was abnormal in 22 (66.7%) and normal in 11 (33.3%) patients. There was a significant correlation between fecal fat concentration and fecal weight ($P = 0.0022$). Steatorrhea was mild to moderate (7–10 g/d) in 7 patients, of whom 3 had diarrhea; it was severe (>10 g/d) in 15, of whom 9 had diarrhea. All in all, 12 (54.5%) of 22 patients with steatorrhea were symptomatic, for example, had diarrhea. With the exception of the character of the diabetes, which was much more often labile in patients with steatorrhea ($P = 0.03$), there was no significant correlation between fecal fat excretion and sex, age at onset of diabetes, duration of diabetes, alcohol intake, HbA_{1C} levels, BMI, retinopathy, nephropathy, neuropathy, SCT results, or the presence or absence of celiac disease. Data for sensitivity and specificity, PPV, and NPV for fecal elastase 1 estimations using both tests predicting steatorrhea were low (Table 3). There was also no significant correlation between increased steatorrhea and fecal elastase 1 levels (Table 4).

An HbA_{1C} value of greater than 9% (an indicator of severe and uncontrolled diabetes) was only measured in 2 patients. One had an abnormal SCT, an abnormal fecal elastase 1 estimation (both tests), and steatorrhea. The other had a normal SCT and a normal fecal fat excretion, but an abnormal fecal elastase 1 value (both tests). Finally, with the exception of nephropathy, which was significantly more frequent in patients with decreased elastase 1 levels ($P = 0.002$), there was no significant correlation between fecal elastase 1 levels and sex, age at onset of diabetes, duration of diabetes, alcohol intake, character of diabetes, HbA_{1C} levels, BMI, retinopathy, neuropathy, SCT results, or the presence or absence of celiac disease (data not shown).

DISCUSSION

Although the patients in our study came from a referral center for diabetes and may not have been representative for diabetic patients in the general population, we believe that this has no impact on the comparison of the direct with indirect pancreatic function test results.

The prevalence of exocrine pancreatic insufficiency in this study (33%) is in the same range as in our report from 20 years ago (43%).[8]

Again, we found no correlation of exocrine pancreatic insufficiency with the age of the patients, the duration of the disease, the quality of diabetes control, or the complications. Such a correlation, however, had been found previously for type-1 but not for type-2 diabetes using fecal elastase 1 estimations.[12,14]

The pattern of exocrine pancreatic insufficiency in our diabetic patients is of particular interest as not only the acinar but also the ductular system is involved, and in some cases, both. This differs from the pattern of exocrine pancreatic insufficiency in chronic pancreatitis, where the functional impairment increases over the years from mild (reduction of enzyme output only; acinar system) to moderate (as before, plus reduction of bicarbonate concentration; acinar and ductular system) and then to severe (as before, plus steatorrhea).[17,20] In contrast to this progression, exocrine pancreatic insufficiency in diabetes mellitus does not increase with time.[9,10]

Fecal elastase 1 estimations proved poor predictors for exocrine pancreatic insufficiency. It may be argued that we did not measure elastase 1 in duodenal fluid during the SCT for comparison, but previous studies have shown that fecal elastase 1 levels correlate strongly with pancreatic bicarbonate, amylase, trypsin, and lipase secretion.[21,22]

The incidence of steatorrhea in diabetes mellitus is surprisingly high. Intraluminal maldigestion, mucosal malabsorption, or lymphatic obstruction may produce steatorrhea.[23] Intraluminal maldigestion usually results from pancreatic exocrine insufficiency. In the 4 patients with reduced lipase output and steatorrhea, lipase secretion was not less than 10% of normal, which is when pancreatic steatorrhea usually manifests itself.[24,25] Thus, the steatorrhea in these 4 and the other 18 patients was not pancreatogenic. Further causes of intraluminal maldigestion resulting in steatorrhea are bacterial overgrowth and cirrhosis or biliary obstruction. Mucosal malabsorption is generally caused by celiac sprue. Postmucosal lymphatic obstruction is caused by the rare congenital condition, intestinal lymphangiectasia, or acquired lymphatic obstruction.[23] In our study, there was no correlation between steatorrhea and celiac disease, and patients with overt inflammatory bowel disease and hyperthyroidism had been excluded. In addition, there were no signs or symptoms of the rare causes mentioned previously. Therefore, in these patients, the most likely explanation for steatorrhea in type-1 diabetes mellitus was bacterial overgrowth.

Open questions, such as why exocrine pancreatic function is correlated with the BMI, why steatorrhea is more frequent in labile diabetes, why fecal elastase 1 is more often abnormal in patients with diabetic nephropathy, and how steatorrhea originates in type 1 diabetes mellitus, will require future prospective studies for answers.

This study may be criticized for 3 reasons. First, the number of patients evaluated may—at first glance—seem relatively small, but it should be taken into account that these patients were tested with the criterion standard, the SCT, which was not used in previous investigations.[12–14] Second, the group of patients with longer disease duration and a higher incidence of some, but not all, complications may be considered to have been more severely ill, thus rendering our result of impaired exocrine pancreatic function in 33% less valid for other patients with milder type-1 diabetes mellitus.

However, previous studies have shown that exocrine pancreatic insufficiency in insulin-dependent diabetes is not correlated to the age of the patient, and the duration of the disease or its complications.[8] Third, we have not given a final explanation for the occurrence of steatorrhea in patients with type-1 diabetes mellitus, and it still has to be tested whether steatorrhea in these patients is caused by bacterial overgrowth.

However, the primary purpose of our study was to investigate the value of fecal elastase 1 estimations in diabetic patients, and for the time being, neither a low fecal elastase 1 level nor steatorrhea reliably diagnoses exocrine pancreatic insufficiency in type-1 diabetes mellitus, and both are, therefore, not indications for pancreatic enzyme substitution. This may also be true in type-2 diabetes.

How do our results affect clinical practice? Clinicians may be reassured that although exocrine pancreatic insufficiency is not infrequent in diabetes mellitus, it neither presents a severe clinical problem nor requires expensive pancreatic enzyme substitution. Furthermore, clinicians may be advised not to use low fecal elastase 1 levels or raised fecal fat excretion in diabetic patients as an indicator for such enzyme substitution. Keeping this in mind will help avoid overprescription in millions of patients with diabetes mellitus.

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REFERENCES

1. Pollard HM, Miller L, Brewer WA. The external secretion of the pancreas and diabetes mellitus. *Am J Dig Dis*. 1943;10:20–23.
2. Dreiling DA. Studies in pancreatic function. IV. The use of the secretin test in the diagnosis of tumors in and about the pancreas. *Gastroenterology*. 1951;18:184–196.
3. Vacca JB, Henke WJ, Knight WA Jr. The exocrine pancreas in diabetes mellitus. *Ann Intern Med*. 1964;61:242–247.
4. Bartelheimer H, Ritter U. Das exkretorische Pankreas bei Diabetikern. *Med Klin*. 1960;55:700–703.
5. Chey WY, Shay H, Shuman CR. External pancreatic secretion in diabetes mellitus. *Ann Intern Med*. 1963;59:812–821.
6. Ritter U. Die exkretorische Pankreassekretion bei Diabetes mellitus. *Dtsch Med Wochenschr*. 1965;90:1063–1064.
7. Domschke W, Tympner F, Domschke S, et al. Exocrine pancreatic function in juvenile diabetics. *Am J Dig Dis*. 1975;20:309–312.
8. Lankisch PG, Manthey G, Otto J, et al. Exocrine pancreatic function in insulin-dependent diabetes mellitus. *Digestion*. 1982;25:211–216.
9. Stöckmann F, Gleichmann D, Otto J, et al. Follow-up of exocrine pancreatic function in type-I diabetes mellitus [abstract]. *Pancreas*. 1991;6:720.
10. Creutzfeldt W, Gleichmann D, Otto J, et al. Follow-up of exocrine pancreatic function in type-1 diabetes mellitus. *Digestion*. 2005;72: 71–75.
11. Scheefers-Borchel U, Scheefers H, Arnold R, et al. Pankreatische Elastase 1: Parameter für die chronische und akute Pankreatitis. *Lab Med*. 1992;16:427–432.
12. Icks A, Haastert B, Giani G, et al. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol*. 2001;39:823–830.
13. Hardt PD, Hauenschild A, Nalop J, et al. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. *Pancreatology*. 2003;3:395–402.
14. Rathmann W, Haastert B, Icks A, et al. Low faecal elastase 1 concentrations in type 2 diabetes mellitus. *Scand J Gastroenterol*. 2001; 36:1056–1061.
15. Hardt PD, Hauenschild A, Jaeger C, et al. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. A prospective multicenter study. *Dig Dis Sci*. 2003;48:1688–1692.
16. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025. Prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414–1431.
17. Lankisch PG, Schreiber A, Otto J. Pancreolauryl test. Evaluation of a tubeless pancreatic function test in comparison with other indirect and direct tests for exocrine pancreatic function. *Dig Dis Sci*. 1983; 28:490–493.
18. Lankisch PG, Schmidt I, König H, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. *Gut*. 1998;42:551–554.
19. Van de Kamer JH, ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. *J Biol Chem*. 1949;177: 347–355.
20. Lankisch PG, Löhr-Happe A, Otto J, et al. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. *Digestion*. 1993;54:148–155.
21. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut*. 1996; 39:580–586.
22. Katschinski M, Schirra J, Bross A, et al. Duodenal secretion and fecal excretion of pancreatic elastase-1 in healthy humans and patients with chronic pancreatitis. *Pancreas*. 1997;15:191–200.
23. Ahlquist DA, Camilleri M. Diarrhea and constipation. In: Kasper DL, Fauci AS, Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill, Med Publ Div; 2005: 224–233.
24. DiMagno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med*. 1973;288:813–815.
25. Lankisch PG, Lembcke B, Wemken G, et al. Functional reserve capacity of the exocrine pancreas. *Digestion*. 1986;35:175–181.

