Unexplained Elevated Serum Pancreatic Enzymes: A Reason to Suspect Celiac Disease

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Background & Aims: **The frequency of elevated serum pancreatic enzymes in patients with celiac disease (CD) is unknown. The aim of this study was to evaluate the serum levels of pancreatic enzymes in CD patients.** ***Methods:*** **Serum pancreatic isoamylase and lipase levels were assayed in 90 adult and 112 pediatric consecutive CD patients at diagnosis and after 12 months of gluten-free diet (GFD). Serum elastase and trypsin levels were assayed in a subgroup of adult CD patients. Pancreatic ultrasonography was also performed.** ***Results:*** **Twenty-six adult (29%) and 29 pediatric (26%) CD patients exhibited elevated values of serum pancreatic amylase and/or lipase; trypsin was elevated in 69% and elastase in 19%. The frequency of elevated serum pancreatic enzymes observed was identical in the patients with "typical" and "atypical" CD symptoms and in the asymptomatic patients. Most of the elevated values were lower than 2-fold the threshold limits. Elevated pancreatic enzymes were not associated with alcohol consumption, drug use, presence of abdominal pain, or diabetes mellitus. Abdominal ultrasound scan showed no abnormal findings in the pancreatic region in any of the CD patients. After 12 months of GFD, pancreatic amylase was elevated in 3 cases and lipase in 2 cases; these patients had not strictly adhered to the GFD.** ***Conclusions:*** **We demonstrated a frequency of about 25% of elevated pancreatic enzymes values in CD patients, including subjects without gastrointestinal manifestations and apparently asymptomatic subjects. The finding of elevated serum amylase or lipase level, in the absence of signs of pancreatic disease, would appear to suggest a need to screen for celiac disease.**

Although celiac disease (CD) can be defined as an enteropathy dependent on gluten ingestion and the small bowel is the main "target organ" in CD, many other gastroenterologic[1–3] and extraintestinal[4–6] areas can be damaged.

As regards the exocrine pancreas, a deficiency in the duodenal output of pancreatic enzymes at diagnosis of CD has been shown,[7–11] but no studies have been performed to investigate the existence and frequency of abnormal serum pancreatic enzyme levels. The observation of some CD patients with elevated serum pancreatic enzymes without clinical evidence of pancreatic diseases induced us to evaluate the importance of this finding. In this study we assayed serum levels of pancreatic enzymes in adult and pediatric patients at CD diagnosis and after 1 year of gluten-free diet (GFD). These findings were correlated with the clinical manifestations of CD.

Patients and Methods

The study included 202 CD patients, 90 adult and 112 pediatric subjects, consecutively enrolled between January 2000 and December 2002 in 2 gastroenterology centers in Palermo. The adults (66 women, 24 men) had a mean age (standard deviation [SD]) of 31.1 (12.4) years, and the children (70 girls, 42 boys) had a mean age of 14.4 (10.1) months. In all cases CD was diagnosed on the basis of positive serum IgA anti-transglutaminase (anti-tTGs) and IgA anti-endomysium (EmA) antibodies associated with partial or total villous atrophy on duodenal histology at first observation and the subsequent normalization of anti-tTGs and EmAs and the disappearance of symptoms on GFD. The clinical manifestations of CD were classified as "typical" when they included chronic diarrhea, failure to thrive, anorexia, abdominal distention, and muscle wasting; other clinical manifestations were considered "atypical."[12] When CD diagnosis was made in subjects who were apparently asymptomatic, CD was classified as "silent." An accurate clinical history included information on alcohol consumption, drug use, history of chronic abdominal pain, or diabetes.

On CD diagnosis, routine hematochemical tests were performed, and serum amylase, pancreatic isoamylase, and lipase values were assayed. In 42 adult CD patients, serum trypsin and elastase values were also assayed. A subgroup of subjects

Abbreviations used in this paper: CD, celiac disease; EmA, anti-endomysium; GFD, gluten-free diet; SD, standard deviation; tTGs, transglutaminase.

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Table 1. Number and Percentage of Patients With Elevated Serum Pancreatic Enzymes on CD Diagnosis, Subdivided According to Age

	Number	Percentage	Range of -fold increase	Median of -fold increase
Adult CD				
Total amylase (n = 90)	20	22.2	1.1–3.1	1.5
Pancreatic amylase (n = 90)	18	20	1.1–2.1	1.3
Lipase (n = 90)	19	21.1	1.1–2.5	1.6
Elastase (n = 42)	8	19	1.1–3.5	1.2
Trypsin (n = 42)	29	69	1.1–2.9	1.7
Childhood CD				
Total amylase (n = 112)	25	22.3	1.1–2.5	1.4
Pancreatic amylase (n = 112)	23	20.5	1.1–2.0	1.4
Lipase (n = 112)	21	18.8	1.1–2.1	1.3

NOTE. The increase in serum pancreatic enzymes is shown as range and median of -fold increases over the upper normal limit.

with elevated serum amylase levels underwent macroamylasemia assay. All patients underwent abdominal ultrasonography, which was repeated after 6 and 12 months in the patients with 1 or more elevated pancreatic enzymes. Serum pancreatic amylase and lipase levels were re-evaluated in all patients after 11–13 (median, 12) months of GFD.

As controls for serum pancreatic enzymes levels, we studied 50 adult subjects (35 women, 15 men; mean age [SD], 30.4 [13.5] years) with blood hypertension and 40 children (28 girls, 12 boys; mean age [SD], 12.6 [21] months) with pharyngotonsillitis. All control subjects were negative for serum anti-tTGs and did not report alcohol abuse.

All subjects involved in the study, or their parents in the case of the pediatric patients, gave their informed consent. The study was approved by the Ethics Committee of the University Hospital of Palermo.

IgA anti-tTGs and EmA were assayed as previously described,[13,14] and duodenal histology was classified according to Oberhuber et al.[15] Amylase activity was measured with a chromogenic method (Alpha-amylase EPS; Boehringer Mannheim, Mannheim, Germany), pancreatic isoamylase was determined by an inhibitor method (Pancreatic Alpha-amylase EPS; Boehringer Mannheim), lipase by a turbidimetric method (Lipase; Boehringer Mannheim), trypsin by a radioimmunoassay method (Trypsik; Sorin Biomedica, Saluggia, Italy), and elastase by an enzyme-linked immunosorbent assay (Pancreatic Elastase 1; Schebo Biotech, Glessen, Germany). In the adult patients the reference ranges were based on the values provided by the kit manufacturers and were validated in our laboratory on a large series of healthy subjects: amylase, 10–160 IU/L; pancreatic isoamylase, 10–90 IU/L; lipase, 20–270 IU/L; trypsin, 8–38 ng/mL; elastase, 0.2–3.5 ng/mL. The upper normal limit for serum amylase and lipase in the pediatric patients varied according to age-dependent cutoffs; for each age class the cutoff was equal to the mean value + 2 SDs observed in our laboratory in healthy children of the same age range. Macroamylasemia was tested by measuring amylase on supernatants after precipitation of immune complexes with polyethylene glycol; a precipitation of >60% of amylase activity was diagnostic for macroamylasemia.

Statistical Analysis

The mean values and SD of the serum pancreatic enzymes were calculated. Frequency analysis was performed with Fisher exact test. Wilcoxon rank sum test was used to compare the pancreatic enzyme values at CD diagnosis and after 12 months of GFD. The Mann-Whitney *U* test was used to compare the pancreatic enzyme values in CD patients and in control subjects.

Results

At CD diagnosis 55 of the 202 patients (27.2%) had elevated serum amylase and/or lipase values. Both pancreatic amylase and lipase values were elevated in 26 patients, pancreatic amylase alone in 15 patients, and lipase alone in 14 patients. Table 1 shows the increases in the serum enzymes and the number of patients with elevated pancreatic enzymes, divided according to age. The frequency of elevated pancreatic enzymes was slightly higher in the adults (26 cases, 28.8%) than in the children (29 cases, 25.9 %). The increase in the pancreatic enzymes over the normal limit was not marked because most of the values were less than 2-fold above the threshold limits. In the 42 adult CD patients, who were also assayed for serum trypsin and elastase, these enzymes were higher than the upper normal limit in 69% and 19% of the cases, respectively.

None of the adult patients had a history of alcohol abuse (daily alcohol consumption < 40 mL in all cases), and no patients were receiving drugs that could determine pancreatic damage. Four adult and 5 pediatric CD patients were diabetic, and serum pancreatic enzymes were elevated in 1 of these adults and 1 of the children. Ten adults and 9 children had a history of recurrent abdominal pain; serum pancreatic enzymes were elevated in 3 of these adults and in 2 children. According to these results, elevated pancreatic enzymes were not associated