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OBSERVATIONAL STUDY

Pancreatic exocrine insufficiency, diabetes mellitus and serum nutritional markers after acute pancreatitis

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Abstract

AIM: To investigate impairment and clinical significance of exocrine and endocrine pancreatic function in patients after acute pancreatitis (AP).

METHODS: Patients with AP were invited to participate in the study. Severity of AP was determined by the Atlanta classification and definitions revised in 2012. Pancreatic exocrine insufficiency (PEI) was diagnosed by the concentration of fecal elastase-1. An additional work-up, including laboratory testing of serum nutritional markers for determination of malnutrition, was offered to all patients with low levels of fecal elastase-1 FE. Hemoglobin A1c or oral glucose tolerance tests were also performed in patients without prior diabetes mellitus, and type 3c diabetes mellitus (T3cDM) was diagnosed according to American Diabetes Association criteria.

RESULTS: One hundred patients were included in the study: 75% (75/100) of patients had one attack of AP and 25% (25/100) had two or more attacks. The most common etiology was alcohol. Mild, moderately severe and severe AP were present in 67, 15 and 18% of patients, respectively. The mean time from attack of AP to inclusion in the study was 2.7 years. PEI was diagnosed in 21% (21/100) of patients and T3cDM in 14% (14/100) of patients. In all patients with PEI, at least one serologic nutritional marker was below the lower limit of normal. T3cDM was more frequently present in patients with severe AP (P = 0.031), but was also present in some patients with mild and moderately severe AP. PEI was present in all degrees of severity of AP. There were no statistically significantly differences according to gender, etiology and number of AP attacks.

CONCLUSION: As exocrine and endocrine pancreatic insufficiency can develop after AP, routine follow-up of patients is necessary, for which serum nutritional panel measurements can be useful.

Key words: Acute pancreatitis; Diabetes mellitus; Pancreatic exocrine insufficiency; Serum nutritional markers

Core tip: Endocrine and exocrine pancreatic insufficiency can develop after acute pancreatitis regardless of the severity, etiology, age, gender and number of attacks. In all patients with pancreatic exocrine insufficiency

(PEI), at least one serum nutritional marker was below the lower limit of normal regardless of the presence of classical clinical symptoms of PEI. Routine follow-up of patients with acute pancreatitis at least 24 mo after discharge from the hospital is necessary with special emphasis on diabetes detection. Measurement of serum nutritional markers regardless of the presence of other clinical symptoms of PEI can be of clinical importance.

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INTRODUCTION

Pancreatic exocrine insufficiency (PEI) and type 3c diabetes mellitus (T3cDM) can occur in patients after acute pancreatitis (AP). The data on the incidence of PEI and T3cDM and the clinical significance of both are controversial, ranging from sporadic cases to 78% of all patients having abnormal values[1-8]. The reasons for such differences in the results are attributable to the different methods used (direct and indirect), inclusion of different groups of patients (severe and mild AP) and different follow-up periods (early and late). Over the last 15 years, the fecal elastase-1 (FE) test became a suitable method for noninvasive diagnosis of PEI with high specificity and sensitivity, especially for the severe form of PEI (< 100 μg/g), and is now recommended as the first step in exocrine pancreatic function diagnostics[9,10].

Pancreatogenic diabetes due to pancreatic disease is classified as type 3c in the current classification of diabetes mellitus (diseases of the exocrine pancreas) and accounts for 5%-10% of the Western diabetic population[11,12]. Clinical and laboratory features of T3cDM differ from other types of diabetes[12], and it is often termed "brittle diabetes" due to the combination of persistent hyperglycemia (due to persistent hepatic glucose production) and exaggerated peripheral sensitivity to insulin[13]. Typically, hepatic insulin resistance predominates as a consequence of pancreatic polypeptide deficiency, while peripheral insulin sensitivity is enhanced because of relative hypoinsulinemia, resulting in problems with hypoglycemia in T3cDM[14]. Although T3cDM is associated with various benign and malignant diseases of the exocrine pancreas, the most common cause is chronic pancreatitis (CP), found in 78.5% of T3cDM cases[15]. In addition, both CP and diabetes are risk factors for the development of pancreatic carcinoma. Also, new-onset T3cDM occurs in 30% of pancreatic cancer patients[12,14]. Because of these specific features, it is important to correctly diagnose T3cDM, especially in view of the evidence showing that nearly half of the T3cDM patients are misdiagnosed as type 1 or 2[15]. There is also a misconception that the treatment of T3cDM is the same as for other forms of diabetes. The use of insulin, insulin secretagogues and incretin-based treatment should be used with caution in these types of patients owing to the high risk of pancreatic carcinoma[12,16-19]. On the other hand, therapy with metformin is associated with a significant reduction in cancer risk and should be preferred as a drug of choice due to its anti-diabetic and anti-neoplastic actions[12,16,19,20].

In pancreatitis, the relationship between the extent of pancreatic necrosis and the severity of exocrine and endocrine pancreatic insufficiency has not been clearly demonstrated[2]. Clinical symptoms of PEI, such as abdominal pain, bloating, steatorrhea and weight loss, were traditionally the most important criteria for monitoring treatment success, but in recent years new studies have also demonstrated the importance of maldigestion, malnutrition and serum nutritional markers in PEI in the absence of the clinical symptoms[21,22].

The aims of the present study were: (1) to determine whether exocrine and endocrine pancreatic function are impaired in patients after AP; (2) to evaluate the relationship between exocrine and endocrine functions and the etiology and severity of AP; and (3) to assess the clinical significance of both exocrine and endocrine pancreatic insufficiency.

MATERIALS AND METHODS

Patients

Patients who experienced an AP attack were invited to participate in the study. All patients were Caucasians, over 18 years of age, and gave their informed consent prior to participating in the study. They were selected from the gastroenterology outpatient clinics of the general hospitals, which function as secondary level centers. Medical records of all patients were analyzed including demographics, laboratory tests, abdominal ultrasound, contrast-enhanced computed tomography, magnetic resonance imaging, and endoscopic ultrasound. FE and glycated hemoglobin or oral glucose tolerance tests were performed in patients without previous diabetic conditions.

Measurement of laboratory tests

FE measurements were performed using the enzyme-linked immunosorbent assay method and a commercial kit (ScheBo Biotech, Giessen, Germany). The results of FE are expressed in μg/g stool. FE levels > 200, 100-200 and < 100 μg/g were considered as normal exocrine pancreatic function, mild and severe PEI, respectively.

In patients with low FE (< 200 μg/g), further work-up was performed including the following laboratory serum measurements to determine malnutrition: iron, vitamin B12, folic acid, magnesium, and vitamins A, D, and E.

Table 1 Characteristics of patients with exocrine pancreatic insufficiency

Gender	Age (yr)	Etiology	No. of attacks	Severity of AP	FE (μg/g)	T3cDM
Male	30	Alcohol	1	Moderately Severe	7	No
Male	63	Alcohol	1	Moderately Severe	101	No
Male	59	Gallstone	1	Severe	19	Yes
Female	63	Gallstone	1	Severe	63	No
Male	52	Alcohol	1	Mild	46	No
Male	43	Alcohol	2	Moderately Severe	134	No
Male	66	Gallstone	2	Mild	5	Yes
Female	53	Alcohol	1	Mild	4	No
Male	47	Alcohol	2	Mild	156	No
Male	58	Unknown	8	Mild	176	Yes
Male	63	Alcohol	9	Mild	9	No
Male	59	Alcohol	2	Mild	37	No
Female	73	Gallstone	1	Mild	137	No
Male	64	Alcohol	1	Severe	151	Yes
Male	83	Gallstone	1	Mild	191	Yes
Male	63	Alcohol	2	Mild	163	No
Female	52	Drug-induced	1	Mild	94	No
Male	63	Unknown	1	Severe	89	No
Male	40	Alcohol	1	Severe	119	No
Male	53	Alcohol	1	Severe	198	Yes
Male	57	Alcohol	1	Severe	117	No

AP: Acute pancreatitis; FE: Fecal elastase-1; T3cDM: Type 3 diabetes mellitus.

Definitions

Pancreatic endocrine function (the occurrence of T3cDM) was determined by the American Diabetes Association criteria: glycated hemoglobin ⩾ 6.5% or two-hour plasma glucose ⩾ 11.1 mmol/L during oral glucose tolerance test in patients without a history of diabetes[11]. Severity and morphology of AP were determined by the Atlanta classification and definitions revised in 2012[23]. Pancreatic necrosis was determined by contrast-enhanced computed tomography according to the Balthazar's classification[24].

Ethics

The study was approved by the National Medical Ethics Committee number 133/01/11 on 28 January 2011.

Statistical analysis

Categorical data are presented as absolute numbers with relative frequencies. The normality of the numerical data distribution was checked using the Kolmogorov-Smirnov test and are described by mean ± SD. The χ^2 test was performed to test the significance in the distribution of gender, etiology, number of attacks, pancreatitis severity and morphology in patients with or without exocrine and endocrine pancreatic insufficiency. The Student's *t*-test was applied to test the difference in nutritional markers in patients with severe and mild to moderate PEI. A $P < 0.05$ was considered statistically significant. The statistical analyses were performed using the SPSS version 21 software package (IBM Corp., Armonk, NY, United States).

RESULTS

One hundred patients were included in the study: 65 male and 35 female, mean age 56.5 ± 13.9 years (range: 20-88 years). 75% (75/100) of the patients had one attack of AP and 25% (25/100) had two or more attacks. The most common etiology was alcohol (n = 42), followed by gallstones (n = 36), unexplained (n = 12), hypertriglyceridemia (n = 6), drug-induced (n = 3), and post-endoscopic retrograde cholangiopancreatography (n = 1). Mild, moderately severe and severe AP were present in 67, 15 and 18 patients, respectively. The mean time from the AP attack to inclusion in the study was 2.7 ± 4.3 years. In the majority (69/100) of patients, the time was one year, 2-5 years in 20% (20/100) of patients, and > 6 years in 11% (11/100). PEI was diagnosed in 21% (21/100) of patients and T3cDM in 14% (14/100) of patients.

The characteristics of patients with exocrine pancreatic insufficiency are summarized in Table 1. In the group with PEI, 17/21 (81%) were male and 4/21 (19%) were female, with a mean age of 57.2 ± 11.6 years (range: 30-83 years). The most common etiology was alcohol (13/21; 61.9%), followed by gallstones (5/21; 23.8%), unexplained (2/21; 9.5%) and drug-induced (1/21; 4.8%). Most patients with PEI had one attack of AP (14/21; 66.7%) and mild severity of AP (11/21; 52.4%). Imaging was performed in 14/21 (66.7%) patients with PEI; among them 71.4% (10/14) showed radiologic signs of CP. Laboratory testing was performed in 16/21 (76.2%) patients with PEI, and in all of them, at least one serologic nutritional marker was below the lower limit of normal (Table 2). In 6/21 (28.6%) patients with PEI, T3cDM was also found.

Bivariate statistical analysis was performed to determine differences between two groups of patients (PEI *vs* non-PEI, and T3cDM *vs* non-T3cDM). There were no statistically significant differences according to gender

Table 2 Nutritional parameters in patients with pancreatic exocrine insufficiency *n* (%)

Parameter	Valid cases (*n*)	Below lower limit of normal
Vitamin D	16	11 (68.8)
Vitamin A	16	1 (6.3)
Vitamin E	16	0
Vitamin B12	16	3 (18.8)
Folic acid	16	3 (18.8)
Iron	16	5 (31.2)
Magnesium	16	0

Reference values: folic acid, 7.0-39.7 nmol/L; iron, 10.7-28.6 μmol/L; magnesium, 0.65-1.05 mmol/L; vitamin A, 1.05-2.80 μmol/L; vitamin B12, 160-800 pg/mL; vitamin D, 65-165 nmol/L; vitamin E, 12-42 μmol/L.

(P = 0.085), etiology (P = 0.316), time from AP attack to inclusion in the study (P = 0.863) or number of AP attacks (P = 0.182). However, there was a statistically significant difference according to the severity of AP between patients with T3cDM and non-T3cDM (P = 0.031): patients with severe AP had a higher prevalence of T3cDM. There was no difference according to AP severity in patients with PEI (P = 0.115).

An enzyme replacement therapy was recommended for all patients with PEI. All patients with T3cDM were transferred to diabetic outpatient clinic.

DISCUSSION

The relationship between PEI and AP was a topic of many studies in the last 30 years. Mitchell *et al*[25] tested 30 patients with an N-benzoyl-l-tyrosyl-p-aminobenzoic acid test and showed that an attack of AP can impair exocrine pancreatic function for several months. Seidensticker *et al*[26] followed 38 patients for 34 mo after the first AP attack using endoscopic retrograde cholangiopancreatography, secretin-pancreozymin tests and fecal fat analysis, and found exocrine pancreatic impairment in half of the patients.

Other invasive and noninvasive methods were also used for the determination of PEI. Glasbrenner *et al*[27] used a fluorescein dilaurate test and fecal chymotrypsin in a group of 29 patients after the first episode of AP, and confirmed abnormal findings in 79% patients on days 2-3 and in 10% of patients on days 28-30 after the attack. Bozkurt *et al*[8] performed a follow-up study on 53 patients after the first attack of necrotizing pancreatitis using a Lundh test meal for diagnosis of PEI. In the first 4-12 wk after recovery, 26% of patients had a marked decrease in pancreatic function and 74% had a mild to moderate decrease. PEI persisted after 18 mo of follow-up in 13% of the patients. In studies with longer follow-ups (5-7 years), both exocrine and endocrine impairment were found in a high percentage of patients (Table 3) and a correlation with the extent of necrosis and PEI was found.

In the last 25 years, noninvasive methods have become a gold standard for PEI detection[9,28-30]. In the largest study performed so far with FE as a diagnostic method, Pezzilli *et al*[4] included 75 patients with AP in the early recovery phase (on the day of re-feeding) and found 12% of patients had PEI (9.3% with mild and 2.7% with severe AP). The present study addresses the highest number of patients suffering from an AP attack so far and includes all etiologies and severities of AP. Based on the above-mentioned results, we expected to find PEI more often in patients with severe AP and in those recovering after alcohol-induced AP. Surprisingly, we found a significantly lower prevalence of PEI (21/100), which was frequently of mild severity and occurring after one attack of AP. On the other hand, PEI was also confirmed in patients with AP due to other etiologies, with one or more attacks of AP, and in those recovering from mild and moderately severe AP. There was no difference in gender, etiology, or time from, severity or number of AP attacks between patients with and without PEI. One explanation for the lower than expected PEI prevalence could be a decreased sensitivity of the FE test in mild and moderate PEI, which was predominant in our cohort. The ^{13}C breath test is a useful diagnostic tool for PEI, but as with secretin magnetic retrograde cholangiopancreatography, is not currently widely available, and could be even more useful for a definitive determination of pancreatic morphology and exocrine function in this group of patients. However, these methods, along with the quantitative stool fat analysis, are not currently a part of a routine diagnostic procedure in Slovenia, leaving FE as the only diagnostic method for PEI.

The clinical significance of PEI was also assessed in this study by using a complete laboratory serum nutritional panel. At least one serologic nutritional marker was below the lower limit of normal in all of these patients, which also confirms the importance of maldigestion, malnutrition and serum nutritional markers in PEI in the absence of the clinical symptoms[21,22]. We performed a nutritional evaluation only in patients with low FE, which is a limitation of the study. It would be interesting to evaluate nutritional status in all patients, which could be even more accurate for than FE for PEI. The commonest findings were vitamin D, iron and folic acid deficiencies. Previous studies show the importance and clinical significance of serum nutritional status in patients with CP[21,22], which was observed in the majority of our patients with PEI. However, we have also demonstrated low serologic nutritional markers in patients without radiologic signs of CP, suggesting that late complications of AP could be present even in the absence of CP. In addition, the majority of patients with PEI had a mild episode of AP, which is an unexpected finding (it is generally accepted that the probability of PEI depends on extent of necrosis due to the loss of functional parenchyma). Unfortunately, data about smoking are lacking, which is another important limitation of the study. Nevertheless, the number of patients (four) in this group was too small for definite

Table 3 Prevalence of exocrine and endocrine pancreatic insufficiency after acute pancreatitis

Ref.	Year	Follow-up	*n*	Etiology	Methods	Exocrine insufficiency	Endocrine insufficiency
Glasbrenner *et al*[27]	1992	Acute phase and after 1 mo	29 oedematous AP	Alcohol, gallstone	FDL serum test, fecal chymotrypsin	FDL abnormal: 79% in acute phase and 10% after 1 mo chymotrypsin abnormal: 69% in acute phase and 3% after 1 mo	Has not been determined
Seidensticker *et al*[26]	1995	34 mo	38	Alcohol, gallstone, unexplained	SPT, fecal fat analysis, ERCP	50% had one or more abnormal tests	Has not been determined
Bozkurt *et al*[8]	1995	4 wk-18 mo	53 all severe AP	Alcohol, gallstone	Lundh test meal with measurement of duodenal secretion and enzyme activity	6%-84% of all patients; 6%-26% marked and 74%-81% moderate	Has not been determined
Tsiotos *et al*[7]	1998	5 yr	44 severe AP	Alcohol, gallstone, post-ERCP, hereditary	Fecal fat excretion, fasting plasma glucose	25%	36.4%
Appelros *et al*[6]	2001	Mean 7 yr	26 all severe AP	Alcohol, gallstone, post-ERCP, hyperlipidemia, unexplained	Triolein test, fasting plasma glucose, HbA1c	69.2% with pathologic triolein test	43%
Boreham *et al*[2]	2003	Acute phase and after 3 mo	23 16 mild, 7 severe AP	Alcohol, gallstone, post-ERCP, hyperlipidemia, unexplained	Fecal elastase-1, fasting plasma glucose	34.8% of all patients; 26.1% after severe and 8.7% after mild AP	17.4% of all patients; 13.0% after severe and 4.4% after mild AP
Connor *et al*[3]	2005	29 mo	63 after necrosectomy	Alcohol, gallstone	Clinical symptoms of steatorrhea, OGTT	25%	33%
Symersky *et al*[1]	2006	4.6 yr	34 22 mild, 12 severe AP	Gallstone, post-ERCP	PABA test, OGTT, PP secretion, fecal fat analysis	64.7% of all patients; 29.4% after severe and 35.3% after mild AP	35%
Pezzilli *et al*[4]	2009	Acute phase (on the day of refeeding)	75 60 mild, 15 severe AP	Alcohol, gallstone, hyperlipidemia	Fecal elastase-1	12% of all patients; 2.7% after severe and 9.3% after mild AP	Has not been determined
Gupta *et al*[5]	2009	Mean 31 mo	30 21 with necrosis	Alcohol, gallstone, unexplained	Fecal fat excretion, urinary D-xylose excretion, OGTT	40%	40%
Present study	2013	Mean 2.7 yr	100 17 with necrosis	Alchohol, gallstone, hyperlipidemia, unexplained, drug-induced,	Fecal elastase-1, OGTT	21%	14%

AP: Acute pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; FDL: Fluorescein dilaurate; HbA1c: Glycated hemoglobin; OGTT: Oral glucose tolerance test; PABA: 4-aminobenzoic acid; PP: Pancreatic polypeptide; SPT: Secretin-pancreozymin test.

conclusions.

CP could also explain the occurrence of T3cDM, which was used to evaluate endocrine pancreatic function in patients who have suffered an AP attack. We found T3cDM after AP in 14% of the patients, and patients with severe AP had a higher prevalence of T3cDM, but there were no differences in gender, age, time from AP attack to inclusion in the study and number of AP attacks in patients with T3cDM. Due to specific features of T3cDM and a high risk of pancreatic cancer in patients with chronic pancreatitis and T3cDM, we transferred all our T3cDM patients to a diabetes outpatients clinic for further diagnostics and treatment.

In conclusion, our study confirmed that exocrine and endocrine pancreatic insufficiency can develop after AP regardless of its severity, etiology, age and gender, suggesting that routine follow-up of patients with AP after discharge from the hospital is necessary. Most of the patients with PEI had radiologic or endoscopic signs of CP, but PEI was also present in small amount of patients after the first attack of mild AP without signs of CP. Measurement of the serum nutritional panel regardless of the presence of clinical symptoms of PEI can be of clinical importance. Further studies on this topic are necessary, especially in patients after the first attack of AP with the use of more accurate diagnostic procedures in combination of serum nutritional markers.

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COMMENTS

Background

Pancreatic exocrine insufficiency (PEI) and type 3c diabetes mellitus (T3cDM) can occur in patients after acute pancreatitis (AP). The data on the incidence of

PEI and T3cDM and the clinical significance of both are controversial.

Research frontiers

Although the relationship between PEI, T3cDM and AP has been a topic of many studies over the last 30 years, the results are limited due to small patient samples and the methodologies used.

Innovations and breakthroughs

Noninvasive methods, such as fecal elastase-1 concentrations, have currently become a gold standard for PEI detection. Combined with the results of the serum nutritional panel, they allow the timely detection of maldigestion and malnutrition in patients to prevent further complications even in the absence of clinical symptoms. Due to the specific features and a high risk of pancreatic cancer, it is also of great importance to diagnose and properly treat T3cDM.

Applications

The results of this study suggest that routine follow-up of patients with AP after discharge from the hospital is necessary to improve the final outcome after an attack of AP.

Terminology

Acute pancreatitis is a sudden inflammation of the pancreas. PEI is the lack of pancreatic digestive enzymes with the consequent inability to properly digest food. Fecal elastase-1 is a pancreatic digestive enzyme that breaks down elastin and other proteins. T3cDM is diabetes secondary to pancreatic diseases.

Peer review

This is an excellent paper in which exocrine and endocrine pancreatic insufficiency were observed after AP.

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