Pancreatic Exocrine Function in Patients with Chronic Liver Disease

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Summary: It is unclear whether patients with chronic liver disease have impaired pancreatic exocrine function. This study was designed to answer this question. Pancreatic exocrine function was evaluated with pancreatic function diagnostic (PFD) test in 16 patients with chronic hepatitis, 32 patients with liver cirrhosis, and 26 patients with cirrhosis and hepatocellular carcinoma (HCC) and in 26 control subjects. The values of PFD test were significantly lower in both patients with liver cirrhosis (70.5±10.7%, P<0.01) and patients with cirrhosis and HCC (68.5±11.2%, P<0.01) than in controls (77.8±6.5%). Although the value was also lower in patients with chronic hepatitis (71.8±11.4%) than in that in controls, the difference did not reach the level of significance. To evaluate potential effect of the impairment of para-amino-benzoic acid (PABA) absorption on the results of PFD test, we further performed a PABA absorption test in 16 patients with chronic liver disease who had abnormal PFD tests. There were no significant differences of the values of PABA test between control group and any patients groups. These results suggest that patients with chronic liver disease have an abnormal pancreatic exocrine function.

Key words pancreatic exocrine function, chronic liver disease, pancreatic function diagnostant

INTRODUCTION

The liver and pancreas have a close relation in anatomy and physiology. The pancreatic duct usually joins the common bile duct: pancreatic juice is therefore mixed with bile in the ampulla. Several gastrointestinal hormones, such as secretin, cholecystokinin-pancreozymin (CCK-PZ), gastrin, vasoactive intestinal polypeptide (VIP), and gastrointestinal polypeptide (GIP), are released from the duodenal mucosa in the postprandial condition [1]. These hormones stimulate the secretion of both bile and pancreatic juice [2-4]. CCK-PZ is well known to stimulate gallbladder contraction and the secretion of pancreatic enzymes.

Postmortem studies have shown a relatively high incidence of pancreatitis in patients with liver disease [5-7], suggesting that patients with chronic liver disease may also be susceptible to pancreatitis. However, to our knowledge, it remains unclear whether patients with chronic liver disease have impaired pancreatic exocrine function.

The aim of this study was to answer this question. For this purpose, we have examined pancreatic exocrine function in controls and patients with chronic liver disease.

MATERIALS AND METHODS

Study population

Pancreatic exocrine function was noninvasively evaluated with pancreatic function diagnostic (PFD) test (see later section) in 74 patients with chronic liver disease and 26 control subjects. The patients group consisted of 44 men and 30 women with mean age of 43.2±6.5 (mean ± S.D.) years. There were 16 patients with chronic hepatitis, 32 patients with liver cirrhosis, and 26 patients with cirrhosis and hepatocellular carcinoma (HCC). The diagnosis of liver...
disease was based on liver biopsy or on clinical grounds. The control group consisted of 16 men and 10 women with mean age of 40.1 ± 4.2 years.

CCK-PZ and secretin (PS) test (see later section) was further performed to evaluate pancreatic exocrine dysfunction in more detail in patients with chronic liver disease. For this purpose, we selected 8 patients with chronic liver disease who had abnormal PFD test (less than 70%). This group consisted of 5 men and 3 women with mean age of 42.1 ± 3.9 (mean ± S.D.) years. There were 2 patients with chronic hepatitis, 4 patients with liver cirrhosis, and 2 patients with cirrhosis and HCC.

Informed consent was obtained from each patient and the study protocol conformed to the 1975 Declaration of Helsinki.

Measurements of pancreatic exocrine function

**PFD test:** Drug treatment was discontinued for at least four days before the experiment day and the study was performed after overnight fast. In the study day, subjects were given 500 mg of N-benzoyl-tyrosyl-para-amino-benzoic acid (BT-PABA) with 250 ml of water, and then asked to collect urine for 6 hs. Urinary para-amino-benzoic acid (PABA) concentration was determined by a modification [8] of the previous method [9] and the total urinary PABA output was then determined. Then, the results of PFD test were reported as the ratio (%) of urinary PABA output to administered BT-PABA. To evaluate the possibility that impairment of PABA absorption had a role in producing abnormal PFD tests, we performed a PABA absorption test in 16 patients with chronic liver disease who had abnormal PFD tests (less than 70%). This test was performed in a separate day and the method was similar to the PFD test. In brief, 170 mg of PABA were administered and the total of urinary output of PABA was determined. Then, the results of the PABA absorption test were reported as the ratio (%) of urinary PABA output to administered PABA.

**PS test:** In the study day, after overnight fasting, a Dreiling tube was placed in the duodenum under fluoroscopic visualization. The duodenal content was aspirated and collected on ice after intravenous administration of CCK-PZ and secretin (1 Unit/kg of each). The volume, the maximal bicarbonate concentration and the total output of amylase were determined. Bicarbonate was determined by the standard Van Slyke procedure. Amylase was determined by the method of Somogyi [9].

**Data analysis**

The results are reported as mean ± S.D. The unpaired Student’s t-test was used for statistical analysis. Significance was established at P<0.05.

**RESULTS**

The results of the PFD test are illustrated in Fig. 1. The values of the PFD test were significantly lower in both patients with liver cirrhosis (P<0.01) and patients with cirrhosis and HCC (P<0.01) than in controls. Although the value was also lower in patients with chronic hepatitis than in controls, the difference did not reach the level of significance. In contrast, as shown in Fig. 2, there were no significant differences of the values in PABA test between control group and any patients groups.

When the value of the PFD test was compared with that of the PABA test in 16 patients with chronic liver disease, the value of the PABA test was significantly higher than that of the PFD test. It should be also emphasized that all patients had a higher PABA test value in comparison with PFD test value (Fig. 3).

The results of the PS test are illustrated in Fig. 4. As stated under Methods, this test was performed in 8 patients with values of the PFD test below 70%. The main findings were hypersecretion of water and decreased total output of amylase, as shown in Fig. 4. The dotted rectangles indicate the normal range.

![Fig. 1. Individual values of PFD test in controls and patients with chronic liver diseases.](image-url)
Fig. 2. Individual values of PABA test in controls and patients with chronic liver diseases.

Fig. 3. Individual values of PFD test and PABA test in 16 patients with chronic liver diseases.

Fig. 4. Individual values of PS test in 8 patients with chronic liver diseases.
DISCUSSION

The PS test has been used to evaluate pancreatic exocrine function. Although this method can provide important informations about pancreatic exocrine function, this method is invasive. For this reason, the PS test does not satisfy the clinical needs in some instances. In contrast, the PFD test is an noninvasive tool to evaluate pancreatic exocrine function. As shown in this study, one can estimate pancreatic exocrine function from the ratio of urinary PABA output to administered BT-PABA.

An important finding of this study is that patients with chronic liver disease had abnormal results of PFD tests. Indeed, patients with cirrhosis with or without HCC had lower values of PFD test in comparison with controls. Although these findings suggest that patients with chronic liver disease have pancreatic exocrine dysfunction, a cautious interpretation is required. Indeed, a major limitation of the PFD test, leading to an overestimate of pancreatic exocrine dysfunction, is the possibility of malabsorption of PABA [10]. However, it has been shown that the simultaneous performance of PABA test and PFD test allows to overcome this drawback [11]. Based on the latter study, it was suggested that pancreatic exocrine dysfunction should be considered present only if the difference of PABA test and PFD test is greater than 14%. In the present study, we therefore performed the PABA absorption test in 16 patients with chronic liver disease who had abnormal PFD tests (less than 70%) and found that the values of PABA test were significantly higher than those of PFD test. It is likely therefore that the contribution of malabsorption of PABA to the observed lower values of PFD tests in these patients is very small.

The PS test showed that the volume of duodenal juice was elevated in liver cirrhosis. The reasons for pancreatic hypersecretion of water in liver cirrhosis are not clear, but possible explanations are reduced inactivation of secretin in cirrhotic liver, increased pressure in the portal system with resultant increased flow of pancreatic juice and bile, and association of pancreatic hypersecretion with mild pancreatitis [12, 13]. Concerning the last possibility, it has been shown that acute pancreatitis is present in about 30% of autopsy cases of patients with liver disease [7,14, 15]. In another study, pancreatic fibrosis was seen in 20% of cases of acute hepatitis and 80% of cases of cirrhosis [16,17]. In the present study, we have clearly shown that patients with chronic liver disease, particularly patients with cirrhosis, have abnormal pancreatic exocrine function. These previous and current observations suggest that patients with chronic liver disease have functional and structural abnormalities of the pancreas.

The pathogenesis of pancreatic dysfunction in patients with chronic liver disease is not known. Two possible mechanisms may be considered. First, the hemodynamic alteration of the pancreatic circulation due to portal hypertension. This may be supported by the current finding that the values of the PFD test were lower in advanced liver disease than in early stages of liver disease. Second, viral infection, since a potential role of hepatitis B virus infection in the pathogenesis of acute pancreatitis has been shown [6]. Exact definition may be a subject for future study.

In conclusion, our results suggest that patients with chronic liver disease have an abnormal pancreatic exocrine function. This finding may have an important clinical implication in the management of chronic liver disease.

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