Occult Pancreaticobiliary Reflux in Gallbladder Cancer and Benign Gallbladder Diseases

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Background and Objectives: It was proposed that occult pancreaticobiliary reflux (OPBR) was associated with precancerous mucosal changes in the gallbladder, hence the importance of this disorder. There are no published reports investigating the incidence of OPBR in patients operated on for the entire spectrum of benign gallbladder diseases and gallbladder cancer. Our aim was to determine the incidence of OPBR and measure the levels of active pancreatic enzymes (amylase and lipase) in gallbladder bile of patients undergoing cholecystectomy for benign and malignant gallbladder diseases.

Methods: One hundred eight patients with normal pancreaticobiliary junction evidenced by operative cholangiography were included in the study.

Results: According to gallbladder bile amylase and lipase levels, 84.2% and 89% patients respectively had OPBR. OPBR was present in all gallbladder cancer patients; in these patients the biliary levels of amylase and lipase were significantly higher than the levels found in patients with benign gallbladder pathology ($P < 0.0001$).

Conclusions: OPBR could lead to inflammatory changes of the biliary epithelium and progress towards the development of precancerous mucosal changes and gallbladder cancer. The reason why such high levels of pancreatic enzymes are regurgitated into the biliary tree of patients with gallbladder cancer should be clarified.

KEY WORDS: **gallbladder cancer; benign gallbladder diseases; occult pancreaticobiliary reflux; normal pancreaticobiliary junction**

INTRODUCTION

Pancreaticobiliary reflux, the reflux of pancreatic juice into the biliary tract, has been described in patients with anomalous pancreaticobiliary ductal junctions (APBDU) [1–3] and choledochal cysts [4–7], and is associated with malignant degeneration of biliary epithelium [1,2,7]. Occult pancreaticobiliary reflux (OPBR) in patients with APBDU and choledochal cysts, frequently related pathological processes, has been explained as a consequence of an anatomic anomaly of the pancreaticobiliary junction (PBJ) that allows the reflux of pancreatic juice into the bile duct and gallbladder [1–9].

In patients with normal PBJ a functional disorder of the sphincter of Oddi (SO) has been proposed as a possible cause for OPBR [10–15]. Some studies have been published concerning OPBR in patients with bile duct stones [13,16] and acute calculous cholecystitis [10,11,17]. Recently it was proposed that patients with normal PBJ and OPBR could develop precancerous changes of gallbladder mucosa [15,16,18]. However, to the best of our knowledge, there are no published reports investigating the incidence of OPBR in patients operated on for the entire spectrum of benign gallbladder diseases and gallbladder cancer.

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The aim of the present study was to determine the incidence of OPBR and the levels of active pancreatic enzymes (amylase and lipase) in gallbladder bile of patients undergoing cholecystectomy for benign gallbladder pathology and gallbladder cancer with a normal PBJ evidenced by operative cholangiography.

PATIENTS AND METHODS

The ethics committee of our institution approved the study. Every patient undergoing cholecystectomy signed a standard informed consent form that we used in our department for gallbladder surgery. On that form we detailed the surgery and procedures carried out during the operation including operative cholangiography, that we perform routinely, and eventual venous blood sampling. At our institution we operated on 350–400 elective cholecystectomies every year. For the purposes of this trial, we aimed to prospectively study 130 patients (32.5%–37% of the known population, $\alpha = 0.01$, error $= 0.1$, power 80%, 95% confidence intervals, statistical significance $P < 0.05$) operated on for elective cholecystectomy during the period of 1 year starting in July 2004. Patients were selected by randomization using the ''coin-toss'' method in the operating room before we started the surgery; consequently all included patients were blinded to the study. In all selected patients, bile and blood samples were taken and an operative cholangiography was performed. We included in the analysis only patients with normal PBJ and normal serum amylase and lipase levels. Of these 130 patients, 22 (17%) were excluded: 10 patients with small, shrunken and atrophic gallbladders with no bile content, 10 patients with concomitant acute pancreatitis (high amylase and lipase serum levels), 1 patient with a choledochal cyst type 1c according to Todani classification modified by Lenriot, et al. [4], and 1 patient with pancreaticobiliary APBDU according to Kimura et al. [19] classification. Consequently, a protocol comprising continuous and categorical variables was completed for 108 patients (83%). The male to female ratio was 1:4; there were 87 female (80%) and 21 male (20%) patients. Mean age was 50.4 ± 16.4 years (Table I).

During surgery, before we initiated the dissection of the Calot triangle, 5 ml of bile was obtained from the gallbladder using a sterile syringe. Simultaneously, the anesthesiologist obtained a 5 ml sample of venous blood from a peripheral vein. Thus biliary and serum samples were obtained simultaneously and injected into two separate sterile tubes that were kept at room temperature (21–25°C) and delivered for processing and analysis within 2 hr. In all included patients, an intraoperative cholangiography was obtained to confirm a normal PBJ according to Kimura et al. [19] criteria. Amylase levels in bile and serum were measured by an enzymatic method using a Diasys Diagnostic Systems GMHB® calibrator (Holtzeim, Germany); the normal range of serum amylase with this system was 30–110 IU/L. Lipase levels in bile and serum were measured by a colorimetric method with the same calibrator, the normal range of serum lipase was 23–300 IU/L. The laboratory technicians running these assays were non-aware of the study and consequently blinded to the patients diagnosis. The patients were divided according to their surgical and pathological diagnosis as follows: (A) chronic calculous cholecystitis: 52 patients (48%), (B) acute calculous cholecystitis: 24 patients (22%), (C) cholelithiasis and choledocholithiasis: 17 patients (16%), (D) acalculous chronic cholecystitis: 8 patients (7%) (E) gallbladder carcinoma: 7 patients (6.5%).

Statistics

Categorical variables were expressed as proportions and continuous variables as mean, standard deviation, and range. Comparative analysis was performed with analysis of variance with the Bonferroni test for multiple comparisons and the Wilcoxon non-parametric test to compare amylase and lipase means. A P-value <0.05 was considered significant. The analysis was performed using the statistical software Stata® 8.0.

TABLE I. Demography According to Diagnosis

	Patients	Gender		Age
Group	n (%)	Female n (%)	Male n (%)	Mean SD ± (range)
(A) Chronic calculous cholecystitis	52 (48)	41 (79)	11 (21)	47 ± 14.8 (21–78)
(B) Acute calculous cholecystitis	24 (22)	19 (79)	5 (21)	51 ± 15.2 (27–86)
(C) Cholelithiasis and choledocholithiasis	17 (16)	14 (82)	3 (18)	59 ± 19.3 (19–91)
(D) Chronic acalculous cholecystitis	8 (7)	6 (75)	2 (25)	44 ± 14.2 (32–77)
(E) Gallbladder carcinoma	7 (6.5)	7 (100)	0	63 ± 5.8 (54–71)
Total	108 (100)	87 (80)	21 (20)	50.4 ± 16.4 (19–91)

SD: standard deviation.

RESULTS

Patients with gallbladder cancer were older (mean age 63 ± 5.8 years, range 54–71 years) than patients with other benign gallbladder diseases, however the widest range of age (19–91 years, mean age 59 ± 19.3) was found in patients with cholelithiasis and bile duct stones (Table I). According to gallbladder bile amylase and lipase levels, OPBR was present in 91 (84.2%) and 96 (89%) patients respectively (Table II). OPBR was present in all (100%) patients with gallbladder carcinoma, showing higher amylase and lipase levels than patients with benign gallbladder diseases (Figs. 1 and 2), biliary amylase and lipase levels in patients with gallbladder carcinoma, significantly ($P < 0.0001$) exceeded the levels of patients with benign biliary pathology. Patients with bile duct stones showed higher levels of gallbladder bile amylase and lipase than patients with other benign gallbladder diseases (Tables III and IV).

DISCUSSION

Biliary pancreatic enzymes levels are considered useful biochemical markers of pancreatic juice reflux into the biliary tree [10–15,20]. Biliary amylase and lipase levels have been extensively studied in patients with APBDU and choledochal cysts [1–3,7], also in patients with normal PBJ associated with bile duct stones [14], acute calculous cholecystitis [13,17] and in patients with normal PBJ associated with precancerous changes of gallbladder mucosa [12–16,18]. A strong correlation has been found between biliary amylase levels in the gallbladder and common bile duct when measured together during the same intervention; furthermore only patients with a dilated bile duct had higher bile duct amylase levels than gallbladder bile amylase levels [16]. In this study gallbladder bile amylase and lipase levels were determined to find out the incidence of OPBR and the levels of these pancreatic enzymes in patients operated on for benign and malignant gallbladder pathology. OPBR was found in 84.2% patients according to gallbladder bile amylase levels and 89% patients according to lipase, this incidence was similar to the incidence found in other studies [16,17].

TABLE II. Incidence of Patients With High Pancreatic Enzymatic Levels in Gallbladder Bile

	Patients	Amylase	Lipase
Group	n	n (%)	n (%)
(A) Chronic calculous cholecystitis	52	38 (73)	43 (82.6)
(B) Acute calculous cholecystitis	24	21 (87.5)	21 (87.5)
(C) Cholelithiasis and choledocholithiasis	17	17 (100)	17 (100)
(D) Acalculous cholecystitis	8	8 (100)	8 (100)
(E) Gallbladder carcinoma	7	7 (100)	7 (100)
Total	108	91 (84.2)	96 (89)

It has been suggested that OPBR in patients with normal PBJ and under physiologic conditions, could be the cause of the inflammatory changes in the biliary tree and consequent symptoms in patients with biliary diseases [10–17,20,21], as well as the cause of precancerous changes of gallbladder mucosa [12–16,18]. In this study elevated levels of gallbladder bile amylase and lipase were identified in all patients (100%) operated on for common bile duct stones, acalculous chronic cholecystitis and gallbladder cancer. Itokawa et al. [16] sampled common bile duct and gallbladder bile for amylase and found that patients with a dilated bile duct and choledocholithiasis had higher levels of amylase than the levels found in the gallbladder, however because gallbladder amylase is likely more relevant in gallbladder cancer, in this study common bile duct amylase and lipase were not determined and consequently we cannot support the findings reported by Itokawa. They also found out that patients with choledocholithiasis and gallbladder cancer were older than patients with other pancreaticobiliary diseases; these findings correspond with our own findings. Our choledocholithiasis and gallbladder cancer patients had higher levels of gallbladder bile amylase and lipase and were older (Table I) than patients with other benign gallbladder conditions (Tables III and IV). OPBR was also present in most patients operated on for other benign gallbladder diseases (Table II). These results support previously published findings [10–29] and additionally confirm that OPBR could play an important role in the development of biliary pathology and associated symptoms.

The only plausible explanation for OPBR in patients with normal PBJ is some form of functional disorder of the SO as previously proposed [8–15,20–22,30–37]. Two separate categories of SO dysfunction has been recognized based on distinct pathological mechanisms: SO stenosis and SO dyskinesia [27–29,31,36–38], SO dyskinesia is characterized by biliary-type pain in absence of any organic diseases in the pancreaticobiliary system related to disorders in the SO cyclic motility [28,29,31,37,38]. Intermittent spasm of the SO not related to the migrating myoelectric complex could be the cause of OPBR. There are also reports of SO dysfunction and pancreatic juice reflux in patients with choledochal cysts in whom the SO was found spastic and did not function as a normal sphincter allowing the free reflux of pancreatic juice into the biliary tree [1–3,10,11,15,19]. A similar mechanism in addition to SO dyskinesia or stenosis, could explain OPBR in patients with benign biliary pathology and gallbladder cancer [15,16,18,27,34–36]. In all patients enrolled on this study, intraoperative video-cholangiography showed

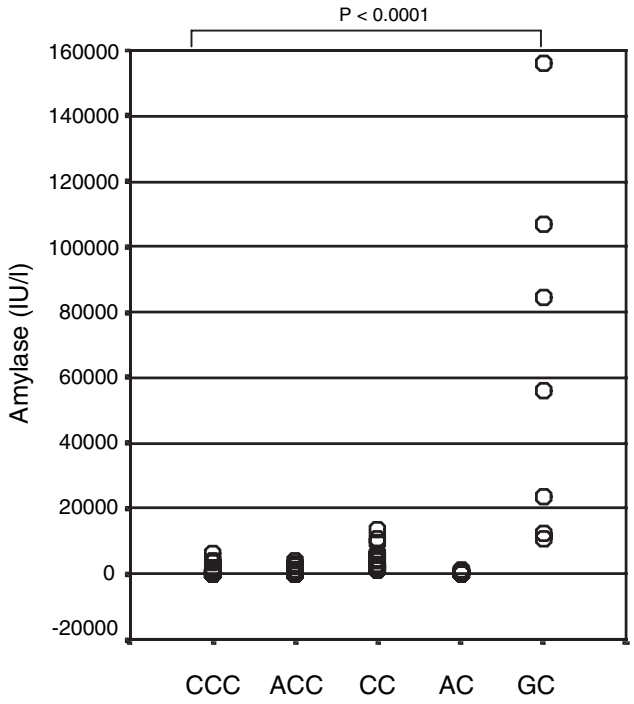

Fig. 1. Amylase levels in gallbladder bile. Amylase levels according to diagnosis: (1) Chronic calculous cholecystitis: 52 patients (48%). (2) Acute calculous cholecystitis: 24 patients (22%). (3) Cholelithiasis and choledocholithiasis: 17 patients (16%). (4) Acalculous chronic cholecystitis: 8 patients (7%). (5) Gallbladder carcinoma: 7 patients (6.5%). Patients with gallbladder carcinoma had significantly higher levels of gallbladder bile amylase than patients with other benign gallbladder diseases ($P = 0.000012$).

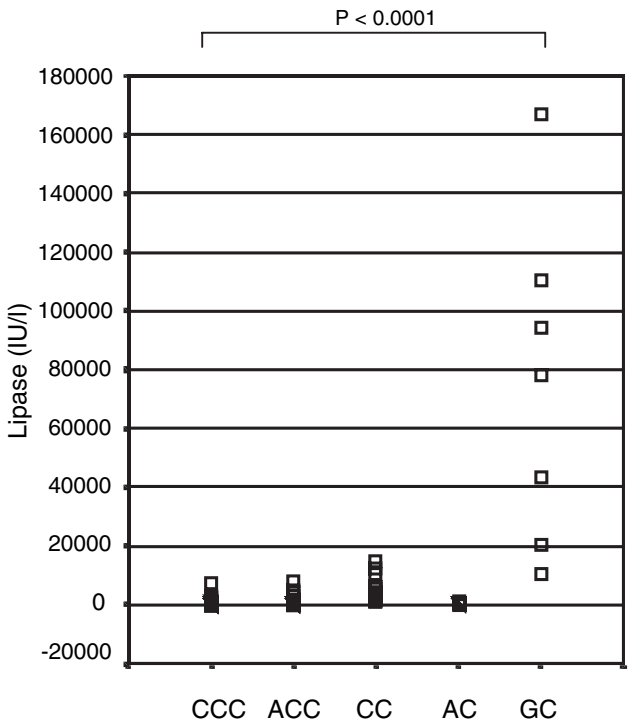

Fig. 2. Lipase levels in gallbladder bile. Lipase levels according to diagnosis: (1) Chronic calculous cholecystitis: 52 patients (48%). (2) Acute calculous cholecystitis: 24 patients (22%). (3) Cholelithiasis and choledocholithiasis: 17 patients (16%). (4) Acalculous chronic cholecystitis: 8 patients (7%). (5) Gallbladder carcinoma: 7 patients (6.5%). Gallbladder bile amylase levels were higher than the levels found in other benign gallbladder diseases ($P = 0.00005$).

normal flow of contrast into the duodenum, despite the fact that cholangiography did not rule out intermittent SO spasm, the cause of the findings in our patients could be SO dysfunction [28,29,37,38].

Whether biliary amylase levels and range are rarely, often or habitually elevated in patients without biliary pathology is currently unknown, the presence of OPBR in the majority of our patients with normal PBJ suggests that the source of active pancreatic enzymes identified in the gallbladder bile is SO dysfunction. As it was earlier proposed, this altered motility along with the intermittent or continuous reflux of pancreatic enzymes into the biliary tree, would gradually lead to inflammatory changes and lesions of the biliary mucosa [10–16], hepatic bile modification by the damaged gallbladder mucosa [33], and development of the whole spectrum of biliary pathology [11–17]. These pathophysiological processes could also explain the symptoms suffered by patients with biliary dyskinesia [28–32,34] and chronic acalculous cholecystitis [35,36]. In all eight patients

TABLE III. Serum and Gallbladder Bile Values for Amylase (IU/l)

Group	Serum (mean SD±)	Bile (mean SD±)	Bile (range)	P^*
(A) Chronic calculous cholecystitis	68 ± 23	478 ± 1,161	30–6,450	<0.001
(B) Acute calculous cholecystitis	76 ± 21	844 ± 1,200	20–25,340	<0.001
(C) Cholelithiasis and choledocholithiasis	70 ± 25	4,578 ± 3,669	1,130–13,760	<0.001
(D) Chronic acalculous cholecystitis	76 ± 32	463 ± 410	90–1,210	<0.001
(E) Gallbladder carcinoma	74 ± 20	64,318 ± 54,616**	10,580–156,000	<0.001
Total	71 ± 23	5341 ± 203,888	20–156,000	<0.001

SD: standard deviation
*Wilcoxon test ($P < 0.05$).
**Biliary amylase levels in gallbladder carcinoma (group E) versus groups A–D $P = 0.0001$.

TABLE IV. Serum and Gallbladder Bile Values for Lipase (IU/L)

Group	Serum (mean ± SD)	Bile (mean ± SD)	Bile (range)	P^*
(A) Chronic calculous cholecystitis	114 ± 83	524 ± 1,180	10–7,230	<0.001
(B) Acute calculous cholecystitis	160 ± 90	1,110 ± 1,875	30–24,950	<0.001
(C) Cholelithiasis and choledocholithiasis	119 ± 81	4,852 ± 4,063	940–14,560	<0.001
(D) Chronic acalculous cholecystitis	82 ± 28	447 ± 366	80–1,120	<0.001
(E) Gallbladder carcinoma	138 ± 68	74,986 ± 55,134**	20,570–167,030	<0.001
Total	124 ± 82	6,156 ± 22,541	10–167,030	<0.001

SD: standard deviation.
*Wilcoxon test ($P < 0.05$).
**Biliary lipase levels in gallbladder carcinoma (group E) versus groups A–D $P = 0.00005$.

(100%) operated on for chronic acalculous cholecystitis we found significantly ($P < 0.001$) elevated gallbladder bile amylase and lipase levels compared with their correspondent serum values which were normal (Tables III and IV). The histopathological report revealed non-specific inflammatory changes, mononuclear infiltration, Rokitansky–Aschoff sinuses and mucosa and gallbladder wall fibrosis, these findings being compatible with chronic cholecystitis, and consistent with previous reports [10–15,27,35,36]. Lack of gallbladder stones as well as chronic irritation of the gallbladder mucosa by intermittent or permanent waves of active pancreatic enzymes (amylase and lipase), is supporting evidence for their role as inflammatory agents in the development of chronic cholecystitis, which after some time may lead to malignant degeneration of the gallbladder epithelium [15,16,18].

The results of our study confirm that OPBR is present not only in patients with associated precancerous changes of the gallbladder epithelium [15,18] but also in patients with gallbladder cancer. An obstructed common bile duct was not present in any gallbladder cancer patients. One of these patients had macroscopic carcinoma and she did not present an obstructed biliary tract. The other six patients had carcinoma in situ found at histology by the pathologist. This finding suggests an important role of OPBR in the development of gallbladder cancer from the precancerous stage [15,18] to the established malignant carcinoma. In all our patients operated on with gallbladder cancer, of whom all were females and older than patients with benign gallbladder diseases (mean age 63 years, range 54–71), biliary lipase and amylase levels were significantly increased ($P < 0.001$) over the correspondent normal serum levels (Tables III and IV). However, an extremely high level of gallbladder bile amylase and lipase, ranging from 10,580 to 156,000 and from 20,570 to 167,030 IU/L respectively, was significantly higher ($P < 0.0001$) compared with the levels found in patients operated on for benign gallbladder diseases (groups A–D) (Figs. 1 and 2), there was not any relationship between tumor characteristics such as size or differentiation and amylase or lipase levels. This highly significant difference support the previously published observations concerning the regurgitation of pancreatic enzymes into the biliary tree that are associated with inflammatory changes and lesions of the biliary mucosa [10–16,18], hepatic bile modification by the gallbladder mucosa [33], precancerous mucosal changes [15,18] and development of gallbladder cancer. The results of this study suggest that it is necessary to find out why patients with normal PBJ associated to gallbladder cancer suffer the reflux of extremely high levels of pancreatic enzymes into the biliary tree.

CONCLUSIONS

According to gallbladder bile amylase and lipase levels the incidence of OPBR in patients operated on for the entire spectrum of gallbladder diseases was 84.2% and 89%, respectively. Reflux of pancreatic juice into the biliary tree is associated with inflammatory changes of the biliary epithelium, including the gallbladder, which could progress towards the development of biliary symptoms, biochemical alterations of the hepatic bile by the gallbladder epithelium, biliary sludge formation, precancerous mucosal changes, and finally gallbladder cancer. The reason why such extremely high levels of pancreatic enzymes are regurgitated into the biliary tree and gallbladder in patients with gallbladder cancer should be clarified by further research.

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