

# Common bile duct stones associated with pancreatobiliary reflux and disproportionate bile duct dilatation

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## Abstract

Occult pancreatobiliary reflux (PBR) in patients with a normal pancreatobiliary junction has been studied by various methods, but the exact etiology, mechanisms, and implications of this reflux have not yet been clarified. The aim of this study was to investigate the degree of PBR and patterns of biliary ductal dilatation in patients with acute calculous cholangitis by endoscopic retrograde cholangiopancreatography (ERCP).

We retrospectively evaluated the degree of PBR and pattern of bile duct dilatation in patients with acute calculous cholangitis due to distal CBD (common bile duct) stones (Group A) as compared with patients with malignant CBD obstruction due to distal CBD cancer (Group B). All related data were prospectively collected. Bile juice was aspirated at the proximal CBD for measurement of biliary amylase and lipase before the injection of contrast dye. The diameters of the CBD and the peripheral intrahepatic duct (IHD) were calculated after contrast dye injection. Patients with pancreatobiliary maljunction and/or gallstone pancreatitis were excluded from the study.

ERCP was performed on 33 patients with calculous cholangitis (Group A) and 12 patients with malignant CBD obstruction (Group B). Mean levels of bile amylase and lipase were significantly higher ( $P < .05$ ) in group A (1387 and 6737 U/l, respectively) versus those in group B (32 and 138 U/l, respectively). Thirty patients in group A (90.9%) showed disproportionate dilatation (i.e., CBD was and IHD was not dilated), whereas only 4 patients in group B (33%) showed disproportionate dilatation.

The results of this study suggest that patients with calculous cholangitis exhibit PBR that is associated with disproportionate bile duct dilatation.

**Abbreviations:** CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography, IHD = intrahepatic duct, PBM = pancreatobiliary maljunction, PBR = pancreatobiliary reflux.

**Keywords:** bile duct dilatation, bile duct stones, pancreatobiliary reflux

## 1. Introduction

The mechanisms and implications of pancreatobiliary reflux (PBR) are well established in patients with pancreatobiliary maljunction (PBM).<sup>[1,2]</sup> In these patients, the sphincter of Oddi loses its function at the junction of pancreatic and bile ducts, which results in frequent reflux of pancreatic juice into the bile duct and subsequent pathologic conditions in the biliary tract and gall bladder.<sup>[1-5]</sup> Recently, occult PBR in patients with anatomically normal pancreatobiliary junction has been fre-

quently recognized. However, the exact mechanisms and implications of this phenomenon are still unclear. Itokawa et al<sup>[6]</sup> reported that patients with advanced age, increased diameter of the common bile duct (CBD), and choledocholithiasis showed significantly higher values of pancreatic enzyme in bile juice, implying the possible presence of occult PBR. We observed that these patients exhibit a characteristic biliary ductal dilatation pattern and hypothesized that occult PBR could occur in patients with acute calculous cholangitis and that this reflux may affect choledochal wall dynamics.

CWH and HWK contributed equally to this study.

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## 2. Methods

### 2.1. Patients

A retrospective review was made of 248 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) in our institute from November 2014 to August 2015.

Among these patients, 33 patients with cholangitis due to distal CBD stones (Group A, acute calculous cholangitis) and 12 patients with malignant obstruction due to distal CBD cancer (Group B, malignant obstruction) were enrolled in our study. We chose patients with malignant obstruction of the distal CBD due to distal CBD cancer, who rarely exhibit PBR, as a control group because there is no consensus regarding the values of normal amylase and lipase levels in the bile duct. All 12 patients in group B were diagnosed with distal CBD cancer by histopathological evaluation. Among them, 7 patients were diagnosed after operation (e.g., Whipple's operation or pylorus preserving pancreatoduodec-

tomy), 3 patients were diagnosed by biopsy during ERCP and 2 patients were diagnosed by brush cytology. Patients who had a history of endoscopic sphincterotomy, endoscopic papillary balloon dilation, surgical sphincteroplasty, or pancreatobiliary maljunction and those who were diagnosed with gallstone pancreatitis before the procedure were excluded. Patients with sphincter of Oddi dysfunction were excluded on a clinical basis. The Institutional Review Board (IRB) of Gangnam Severance Hospital approved this study. We received a consent exemption from the IRB. Patients records and information was anonymized.

**2.2. Estimation of pancreatobiliary reflux**

Occult PBR was confirmed by demonstrating elevated levels of amylase and lipase in bile during ERCP. After cannulation of the CBD, the operator located the catheter (TANDEM XL No 3570, Boston Scientific Corp.) at the proximal CBD level before contrast dye injection. Approximately 3–5 cc of yellowish bile was aspirated and sent to a laboratory for determination of the biliary amylase and lipase levels. Next, the 1:1 dilution contrast dye (Meglumine ioxitalamate, Telebrix 30M, France) was injected via the catheter and contrast images were obtained.

**2.3. Measuring the CBD and the peripheral intrahepatic duct (IHD) diameters**

The CBD and peripheral IHD diameters were measured using contrast imaging following the ERCP procedure. The 13-mm diameter width of the ERCP scope (TJF-240, Olympus video-endoscope, Tokyo, Japan) was taken into consideration for the calculation of the bile duct diameters. The CBD diameter was measured at its largest dilated level, and the peripheral IHD diameter was measured at the second bifurcation level. CBD and peripheral IHD dilatations were confirmed when the diameters were more than 11 and 4 mm, respectively.

**2.4. Statistical analysis**

The *t*-test was used for noncategorical variables in the intergroup comparisons of clinical characteristics. The accepted significance

**Table 1**  
Comparisons of age, amylase, and lipase level between group A (CBD stone group) and group B (malignant obstruction group).

Variables	Group A (N=33) (n, %)	Group B (N=12) (n, %)	P
Age, years, mean ±SD	53.4 ± 14.2	63.7 ± 13.5	.861
Gender			.517
Male	15 (45.5)	4 (33.3)	
Female	18 (54.5)	8 (66.7)	
Bile amylase, U/L, mean ±SD	1387.9 ± 2485.5	32.2 ± 39.2	.005
Bile lipase, U/L, mean ±SD	6737.4 ± 15118.0	138.8 ± 139.6	.028
Serum amylase, U/L, mean ±SD	52.4 ± 16.6	55.8 ± 35.1	.671
Serum lipase, U/L, mean ±SD	38.1 ± 19.1	34.4 ± 37.6	.697

CBD=common bile duct, SD=standard deviation.  
Amylase (normal values 25–97), lipase (normal values 6–46).

level was a *P* value of <.05. All statistical analyses were performed using the SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL).

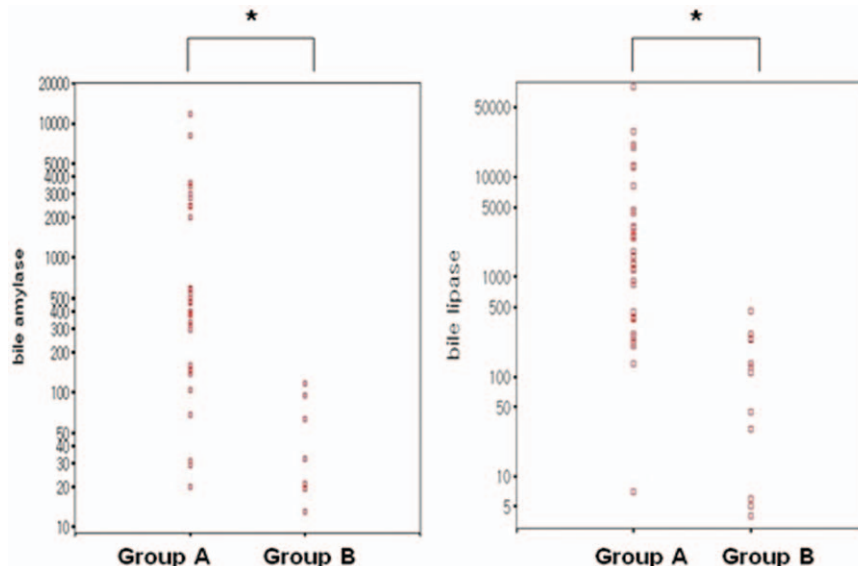
**3. Results**

**3.1. Degree of PBR**

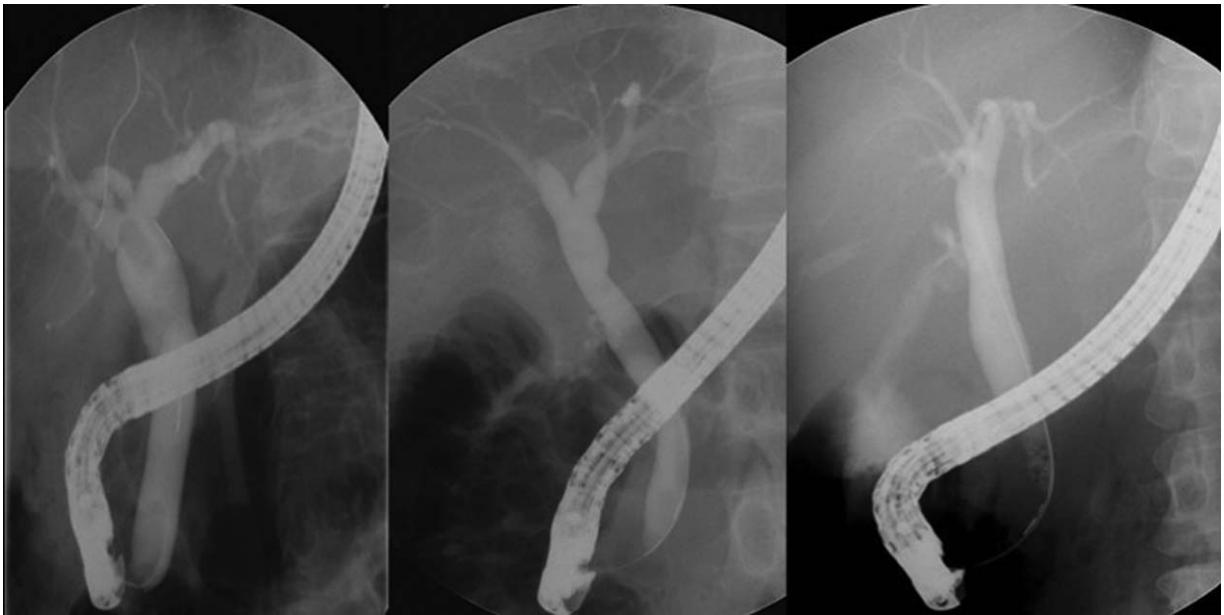
The mean levels of bile amylase and lipase were significantly higher (*P* < .05) in group A (1387 and 6737 U/L, respectively) versus those in group B (32 and 138 U/L, respectively) (Table 1). This result suggests that occult PBR may be present in group A (Fig. 1). There were no statistical differences in age, serum amylase, and serum lipase between the 2 groups (Table 1). Normal values for levels of serum amylase and lipase in our institute are 97 U/L and 54 U/L, respectively.

**3.2. Ductal dilatation pattern**

In group A, a disproportionate dilatation pattern was seen in which 30 of 33 patients (90.9%) showed CBD dilatation without an increase in peripheral IHD diameter (Fig. 2). In group B,



**Figure 1.** Comparison of biliary amylase and lipase levels between group A (CBD stone group) and group B (malignant obstruction group). Group A shows significantly higher levels of biliary amylase and lipase levels than group B. \**P* < .05. CBD = common bile duct.



**Figure 2.** ERCP findings for the CBD stone group (group A) show marked dilatation of the extrahepatic duct in contrast to disproportionate lack of dilatation of the intrahepatic duct (not dilated IHD). CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography, IHD = intrahepatic duct.

however, a disproportionate dilatation pattern was seen in only 4 of 12 patients (33.3%), and the remaining 8 patients showed a proportionate dilatation pattern in which both the CBD and the peripheral IHD were dilated (Fig. 3).

#### 4. Discussion

The exact mechanism of ductal dilatation in acute calculous cholangitis is still unknown. In our study, group A (acute calculous cholangitis) patients had PBR and exhibited disproportionate ductal dilatation. This combination is a meaningful result because it is the first evidence to suggest an effect of PBR as

one of the mechanisms of disproportionate ductal dilatation and because it will help us further understand the dynamic of the choledochal wall.

Recently, the presence of occult PBR has been frequently reported in patients with normal pancreatobiliary junction.<sup>[3,7,8]</sup> Sai et al,<sup>[9]</sup> using secretin-stimulated magnetic resonance cholangiopancreatography, reported that occult PBR was observed in 5.7% of patients with a normal pancreatobiliary junction. A multicenter trial in Japan also showed that among patients with a normal pancreatobiliary junction, 5.5% (23 of 420) had elevated amylase levels in bile juice after ERCP.<sup>[10]</sup> Although the clinical significance of occult



**Figure 3.** ERCP findings for the CBD malignant obstruction group (group B) showing proportional dilatation of both the extrahepatic duct and the intrahepatic duct. CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography.

PBR is still unclear, pancreatic enzymes are thought to affect the epithelium of the bile duct and gallbladder, which could subsequently lead to carcinogenesis.<sup>[8,10–12]</sup>

In this study, we observed that the levels of bile amylase and bile lipase were elevated in patients with acute calculous cholangitis. Because it is not easy to obtain bile juice from the normal population, normal ranges of bile amylase and lipase are not clearly known. The plasma level of pancreatic enzyme is commonly used by many researchers as a reference for detecting PBR without PBM.<sup>[7]</sup> In our study, we analyzed the bile amylase and lipase levels in patients with calculous cholangitis and compared the results to those in patients with malignant distal CBD obstruction because reflux is less likely to occur in these patients.

Several studies have suggested theories regarding the mechanism of occult PBR in calculous cholangitis with normal pancreatobiliary junction.<sup>[6,8,13,14]</sup> Some researchers hypothesized that papillitis due to stones causes dysfunction of the sphincter of Oddi, which then leads to reflux of pancreatic juice.<sup>[14]</sup> In contrast, others suggested that reflux of pancreatic juice causes chronic inflammation of the gallbladder, which subsequently results in gallstone formation.<sup>[5,8,13,15,16]</sup> Although, it is unclear whether the stones causes PBR or vice versa, our observation of PBR in patients with acute calculous cholangitis is compatible with the results of others that conducted studies on occult PBR in patients with a normal pancreatobiliary junction.<sup>[6,14]</sup> However, there is still no definitive knowledge of exactly what this occult PBR means clinically.

Our results on the pattern of ductal dilatation differentiate our study from others. Patients with acute calculous cholangitis show a disproportionate ductal dilatation pattern in which CBD is more dilated than normal, whereas the peripheral bile duct shows no dilatation. In contrast, patients with distal CBD malignant obstruction show a proportionate dilatation pattern in which both CBD and peripheral IHD are dilated. Although this phenomenon is seen frequently in radiologic images, the exact mechanism is still unknown.

Because the extrahepatic bile duct histologically contains profound elastic fibers with scarce smooth muscle components, a change in the size of bile duct occurs rapidly during obstruction. Such a mechanism of acute dilation of the bile duct could be explained by the passive phenomenon determined by the intraductal pressure and the volume of bile flow.<sup>[17–20]</sup> However, from what we can deduce from this study, the mechanism of disproportionate dilatation pattern in acute calculous cholangitis may be affected by not only hydrostatic pressure but also by chemical injury of the bile duct caused by pancreatic enzymes.

Bile duct damage caused by chemical irritation of PBR is well studied in patients with congenital choledochal cysts.<sup>[21–25]</sup> Numerous studies support the hypothesis first suggested by Babbit<sup>[25]</sup> that the reflux of pancreatic juice due to an anomalous pancreatobiliary junction weakens the choledochal wall. For example, Kato et al<sup>[23]</sup> performed an animal study evaluating the effect of pancreatic juice on the bile duct wall after pancreaticocholecystostomy and observed that cylindrical dilation of the common bile duct, inflammatory change of submucosal layer, and damage of intercellular junction of biliary epithelium occurred in the early stage of the disease.

As seen in our study, unlike distal CBD obstruction due to malignancy, both CBD and peripheral IHD are dilated solely by the hydrostatic pressure created by the true obstruction of the distal CBD. In contrast, our results indicate that hydrostatic pressure as well as chemical irritation by PBR may have relatively

more of an effect on the distal CBD, resulting in a disproportionate dilatation pattern in patients with calculous cholangitis.

Several studies have evaluated the bile duct damage induced by reflux of pancreatic enzymes in patients with normal pancreatobiliary junction.<sup>[8,10,13,26]</sup> Vracko and Wiechel<sup>[27]</sup> divided 63 patients with gallstones into a group with and a group without bile duct stones. They found that trypsin, a marker of pancreatic juice reflux, was increased within the gall bladder and that the width of the cystic duct was increased in the group with bile duct stones. These authors explained that chronic inflammation of the cystic duct caused by pancreatic juice reflux resulted in an increase of cystic duct width, which then led to an easier migration of the gallstones into the bile duct.

Our study has some limitations. We could not confirm bile duct damage induced by chemical irritation of PBR with histopathological evidence. Therefore, further studies are needed to elucidate the direct relationship between ductal dilatation and chemical irritation caused by PBR. Furthermore, additional clinical workups, such as histological examination or enzymatic assay, are needed to reveal the nature of the substances (whether it is pancreatic juice, biliary juice, or other inflammatory substances) that cause irritation.

In conclusion, patients suffering from acute calculous cholangitis with a normal pancreatobiliary junction exhibit pancreatobiliary reflux and dilatation that was more prominent in the CBD than in the peripheral IHD. These results suggest that not only mechanical obstruction of the stone but also chemical irritations produced by PBR are responsible for the disproportionate bile duct dilatation.

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