ORIGINAL ARTICLE

The relationship between bile reflux and common bile duct diameter after cholecystectomy: a clinical case–control study

La relación entre el reflujo biliar y el diámetro del conducto biliar común después de la colecistectomía: un estudio clínico de casos y controles

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Abstract

Objective: *The present study aims to investigate the relationship between bile reflux (BR) and diameter of the common bile duct (CBD) in patients after cholecystectomy.* **Materials and methods:** *In our case series analysis, according to the endoscopy results, the patients who underwent cholecystectomy were divided into two groups as those with BR and those non-BR. Age, sex, CBD diameter measured on ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and endoscopic biopsy results of the patients were statistically analyzed.* **Results:** *In a total of 188 patients included in the study, BR was detected in 93 patients, it was not observed in 95 patients. The CBD diameter of the patients was observed to be 7 mm or less in 70.9% (n = 66) in the BR group, and 23% (n = 22) in the non-BR group. The statistical analysis revealed that while there was a significant difference between the two groups in terms of CBD diameter and intestinal metaplasia, the results were similar in both groups in terms of inflammation, activity, atrophy, and Helicobacter pylori.* **Conclusion:** *We believe that CBD diameter may be a predictive factor in the detection of BR after cholecystectomy.*

Keywords: *Cholecystectomy. Common bile duct diameter. Bile reflux. Intestinal metaplasia. Helicobacter pylori.*

Resumen

Objetivo: *Investigar la relación entre el reflujo biliar y el diámetro del colédoco después de la colecistectomía.* **Método:** *Estudio retrospectivo en el que, de acuerdo con los resultados de la endoscopia, los pacientes que se sometieron a colecistectomía se dividieron en dos grupos: con reflujo biliar y sin reflujo biliar. Se analizaron estadísticamente la edad, el sexo, el diámetro del conducto biliar común medido por ultrasonografía, tomografía computarizada y colangiopancreatografía por resonancia magnética, y los resultados de la biopsia endoscópica.* **Resultados:** *En un total de 188 pacientes incluidos en el estudio, se detectó reflujo biliar en 93 pacientes y no se observó en 95 pacientes. Se vio que el diámetro del conducto biliar común de los pacientes era de 7 mm o menos en el 70.9% (n = 66) del grupo con reflujo biliar y en el 23% (n = 22) del grupo sin reflujo biliar. El análisis estadístico reveló que, si bien hubo una diferencia significativa entre los dos grupos en términos de diámetro del conducto biliar común y metaplasia intestinal, los resultados fueron similares en ambos grupos en términos de inflamación, actividad, atrofia y presencia de Helicobacter pylori.* **Conclusiones:** *Creemos que el diámetro del colédoco puede ser un factor predictivo en la detección de reflujo biliar después de la colecistectomía.*

Palabras clave: *Colecistectomía. Diámetro del conducto biliar común. Reflujo biliar. Metaplasia intestinal. Helicobacter pylori.*

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Introduction

Cholecystectomy is one of the most commonly performed surgeries worldwide. Complaints such as nausea, bilious vomiting, and dyspeptic symptoms occur in some patients after cholecystectomy. These findings are described as in post-cholecystectomy syndrome. It has been reported that 15-20% of patients after cholecystectomy had new-onset or ongoing symptoms[1].

It has been revealed by many studies that there is a physiological bile reflux (BR) in humans. Various studies have shown that the rate of BR can increase up to 60-78% in patients who have undergone cholecystectomy[2-4]. BR has harmful effects that start 2-6 months after cholecystectomy on gastric mucosa[4-6]. Moreover, there are some studies in the literature stating that histological changes caused by BR are a predisposing factor for gastric cancer[7,8].

The underlying causes of BR still remain unclear. The previous therapeutic biliary procedures and gastric diversion surgeries are proven reasons that increase BR. In addition, procedures defunctioning the sphincter of Oddi such as sphincterotomy, stent, and choledochoduodenostomy also increase the development of BR[3]. Since there is no pressure barrier in front of the bile released from the liver as a result of these procedures, it is not expected the common bile duct (CBD) to enlarge.

The upper limit of the CBD diameter is generally accepted to be 7 mm[9,10]. Different results have been obtained in various studies about changes in CBD diameter of patients after cholecystectomy. Some of these studies indicated that CBD diameter has significantly increased following cholecystectomy[11,12]. However, there are also studies in the literature reporting that CBD diameter does not increase significantly after cholecystectomy[13,14].

Most of the studies in the literature investigating the cause of BR have evaluated the findings after operations including sphincterotomy, stent, choledochoduodenostomy, and gastric diversion. Thus, we planned this case series analysis to reveal the relationship between CBD diameter and BR in patients who had cholecystectomy only.

Methods

An ethical approval was obtained from the Clinical Studies Ethics Committee of Tokat Gaziosmanpasa University Faculty of Medicine (Ethics Committee Approval No: 21-KAEK-164). The data of 10,128 patients who underwent upper gastrointestinal system (GIS) endoscopy in the Medical Faculty Hospital of Tokat Gaziosmanpasa University between 2012 and 2020 were retrospectively reviewed. The patients proven to have had cholecystectomy during upper GIS endoscopy were included in the study. For this purpose, the pre-procedural radiological examination reports of the patients as well as their previous surgical history were examined. The patients whose pre-procedural radiological examination reports had the phrase “gallbladder not observed-operated” were included in the study. The endoscopy images of the patients were also examined, and the fact that the gastric mucosa was stained with bile and the presence of bile residues in the stomach during the procedure was evaluated as pathological BR. The patients’ age, sex, endoscopic biopsy results, and the CBD diameter measured from the widest section were recorded.

The patients with a history of therapeutic biliary procedures (sphincterotomy, stent, choledocoduodenostomy, and hepaticojejunostomy) before radiological examination, in which CBD diameter was measured were excluded from the study. In addition, those with signs of subtotal/total gastrectomy and gastric diversion, which remove or bypass the pylorus in their upper GIS endoscopy and surgical history, were also excluded from the study. The absence of sufficient data for quantitative measurement of CBD diameter was also an exclusion criteria. Through these criteria, the patients that were included and excluded have been shown in flow chart (Fig. 1).

In line with these criteria, a total of 189 patients were included in the study. The patients were categorized into two groups as BR group (those with BR,n = 93) and NBR group (those without BR, n = 96) according to endoscopy reports. As is generally accepted, CBD diameter measured above 7 mm was considered to be wide. The CBD diameter was measured from computed tomography (CT) images in 168 (89%) of 189 patients. It was measured by magnetic resonance cholangiopancreatography (MR/MR-CP) in 17 of the remaining 21 patients. All measurements were performed by a single author. The CBD diameter measured by abdominal ultrasonography (USG) reports was taken into account in only four patients. Endoscopic biopsy results were recorded as none, mild, moderate, and severe.

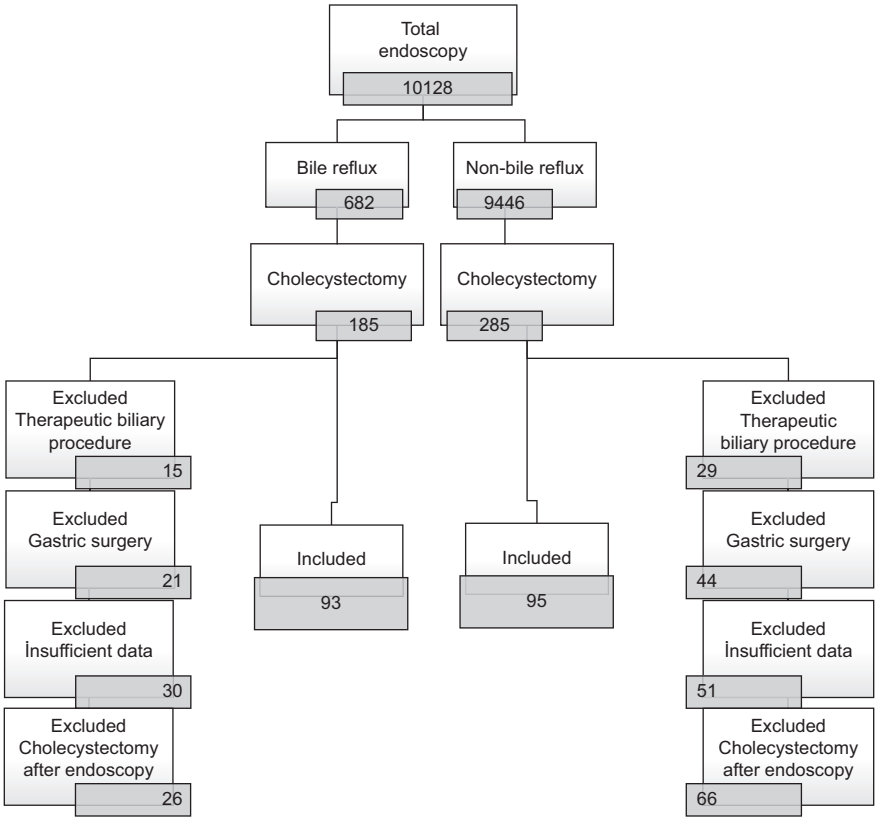

Figure 1. *Flow chart of patients.*

Statistical analysis

The data were recorded using the SPSS software (the Statistical Package for the Social Sciences, version 15). The student t-test was used to compare the difference between the two groups in terms of the mean age, sex, and the mean CBD diameter. The Pearson's Chi-square test was applied to determine the differences between the two groups in endoscopic biopsy results (inflammation, activity, atrophy, *Helicobacter pylori*, and intestinal metaplasia). $p < 0.05$ was regarded as statistically significant.

Results

Of the 189 patients included in the study, one patient was observed to have a CBD diameter of 11 mm, which was measured by USG only. Due to the low sensitivity of USG in evaluating the mass and obstruction causes in the distal CBD, the patient was excluded from the study. All patients included in the study underwent upper GIS endoscopy at least 6 months after cholecystectomy. The CBD diameters were measured from radiologic images that were performed at least 6 months after cholecystectomy. While BR was detected in 93 patients (49.6%), it was not detected in 95 patients (50.6%).

Of the patients included in the study, 80.8% (n = 152) were women, 19.2% (n = 36) were men. The mean age was detected to be 58.64 SD 13.9 years in the BR group and 59.15 SD 12.2 years in the NBR group. While a significant difference was observed between the two groups in terms of sex ($p = 0.038$), the mean ages of groups were statistically similar ($p = 0.199$). The comparison of demographic and clinical characteristics is given in table 1. The CBD diameter was observed to be 7 mm or less in 70.9% (n = 66) of the patients in the BR group and in 23.1% (n = 22) of those in the NBR group. The mean CBD diameter was 6.94 SD 2.1 (3-13 mm) in the BR group, and 9.07 SD 2.3 (4-15 mm) in the NBR group. In our study, the CBD diameter was found to be statistically significantly higher in the NBR group ($p < 0.001$). The comparison of the two groups for biopsy results obtained during endoscopy revealed that intestinal metaplasia was significantly higher in the BR group ($p = 0.001$). On the other hand, no significant differences were observed in terms of inflammation ($p = 0.146$), activity ($p = 0.217$), *H. pylori* ($p = 0.311$), and atrophy ($p = 0.221$) (Table 2).

Table 1. Demographic and clinical characteristics of study patients

	Bile reflux	Non-bile reflux	p value
Population	93	95	
Mean age ± SD, years	59.15 ± 12.2	58.64 ± 13.9	NS
Sex (female/male)	78/15	74/21	0.038
Mean CBD diameter ± SD, mm	6.9 ± 2.1	9.07 ± 2.3	< 0.001
Range	3-13	4-15	
CBD diameter ≤ 7 mm (n)	66	22	< 0.001

CBD: common bile duct; n: population; SD: standard deviation.

Discussion

We investigated the relationship between CBD diameter and BR in patients with cholecystectomy in the present study. We observed that the CBD diameter was 7 mm or less in the group with BR. It was found that the CBD diameter was statistically significantly larger in the non-BR group compared to the BR group.

When the demographic characteristics of patients in both groups were compared, it was found that the mean age of both groups was statistically similar. On the other hand, a significant difference between groups was detected in terms of sex of the patients. However, we are of the opinion that this difference did not clinically affect the results of our study.

The comparison of endoscopic biopsy results revealed that severe intestinal metaplasia was observed in seven patients (13%) in the BR group, while it was not detected in any patients in the NBR group. Intestinal metaplasia was statistically higher in the BR group than in the NBR group. There were no significant differences between two groups in terms of inflammation, activity, atrophy, and *H. pylori.*

BR is defined as reflux of duodenal contents into the stomach, esophagus, or even larynx. The mechanism of BR formation is not clear. The motility of the stomach and duodenum and the prolongation of gastric emptying time are among the factors blamed. In addition, as shown in recent studies, BR is known to develop after operations involving gastric diversion[15,16]. Following the studies showing that BR increased as a result of therapeutic biliary procedures, including cholecystectomy, attention was turned to the sphincter of Oddi. After cholecystectomy, the reservoir function of the gallbladder is removed. The sphincter of Oddi is the first barrier in front of the bile. The bile released from the liver waits in the extrahepatic bile ducts. In cases where the pressure in the bile ducts exceeds the pressure of the sphincter or postprandial opening of the sphincter, bile passes to the duodenum with certain periods. This causes enlargement of the extrahepatic bile ducts. On the other hand, when the sphincter barrier is removed, enlargement of the bile ducts is not expected, since the bile continuously passes into the duodenum without waiting.

There are studies showing that post-operative BR occurs in patients who underwent cholecystectomy only[2,3]. In a study, in which 20 of the 131 patients included in the study underwent cholecystectomy only, BR was detected in 60% of the patients undergoing cholecystectomy alone[3]. Another study investigating BR before and after cholecystectomy revealed that there was an increase in BR in terms of both quantity and incidence after surgery in 66% of patients[2]. In our study, on the other hand, the incidence of BR after cholecystectomy was 49.6%.

As a result of BR, a number of changes occur in the gastric and esophageal mucosa. Endoscopies performed after a certain period of cholecystectomy revealed the development of gastritis due to BR[4,5]. In a multicenter study including 2283 patients, it was shown that especially high-concentration BR caused significantly more intestinal metaplasia than the other groups[17]. The study examining gastric and esophageal biopsies indicated that antral intestinal metaplasia was detected in 10% of the patients, while the presence of intestinal metaplasia was found in the gastroesophageal junction in 33% of patients[18]. There are studies in the literature showing that gastric, esophageal, and even laryngopharyngeal malignancies develop as a result of mucosal changes due to BR[7,19,20]. BR has been determined to be an independent factor in the development of precancerous lesions and gastric cancer[21].

While age and the conditions causing obstruction have been shown among the factors that increase CBD diameter, there are studies revealing that cholecystectomy also increased CBD diameter. In a study conducted in individuals without biliary pathology, it was shown that CBD diameter increases with age, especially in advanced age[22]. In a study that examined the diameter of CBD in similar age groups, it was found that in 80% of patients with cholecystectomy, the diameter of CBD was 6 mm and above at proximal, while this ratio was 28% in the group that did not undergo cholecystectomy[11]. In our study, the CBD diameter was found to be 6 mm and above in 83% of

Table 2. Endoscopic biopsy results of patients

	Non n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total* n (%)	p value
Inflammation bile reflux	1 (1%)	25 (33%)	41 (55%)	8 (11%)	75 (100%)	NS
Non-bile reflux	0 (0%)	20 (48%)	14 (34%)	7 (18%)	41 (100%)	
Activity bile reflux	36 (48%)	20 (27%)	16 (22%)	2 (3%)	74 (100%)	NS
Non-bile reflux	20 (49%)	9 (22%)	7 (17%)	5 (12%)	41 (100%)	
Atrophybile reflux	54 (77%)	10 (14%)	5 (7%)	1 (2%)	70 (100%)	NS
Non-bile reflux	32 (78%)	9 (22%)	0 (0%)	0 (0%)	41 (100%)	
H. pylori bile reflux	60 (77%)	5 (6%)	10 (13%)	3 (4%)	78 (100%)	NS
Non-bile reflux	37 (80%)	4 (8%)	2 (4%)	4 (8%)	47 (100%)	
IM bile reflux	39 (70%)	3 (6%)	6 (11%)	7 (13%)	55 (100%)	0.001
Non-bile reflux	25 (70%)	8 (22%)	3 (8%)	0 (0%)	36 (100%)	

*Endoscopic biopsies were taken from 124 of 188 patients.
IM: intestinal metaplasia; *H. pylori: Helicobacter pylori.*

patients with cholecystectomy. However, in our study, we accepted CBD diameter above 7 mm to be wide, as is generally regarded. We detected that the CBD diameter of 34 patients (18%) was above 10 mm. Of these patients, the CBD diameter was measured by only CT in 28 patients, CT and MR/MR-CP in two patients, only MR/MR-CP in three patients, and only USG in one patient. It is known that CT and MR/MR-CP are superior to USG in the diagnosis of extrahepatic biliary tract diseases[23-25]. In addition, USG is a person-specific examination method. Therefore, this patient, whose CBD diameter was measured by USG, was excluded from the study. We found that 17 of the patients with a CBD diameter of above 10 mm were over 65 years of age and five patients were 80 years of age or older. On the other hand, we did not observe any biliary pathology or elevated liver function tests on CT and MR/MR-CP performed in patients with very large CBD diameters. In our study, the facts that the two groups were similar in terms of age and that most of the CBD diameters (99%) were measured by CT and MR/MR-CP strengthen the results of our study.

There are some limitations in our study due to its retrospective nature. In the patient records, we observed that the CBD diameters of some patients could not be measured quantitatively; thus, we excluded these patients from the study. In this case, the number of the patients included in the study reduced. In addition, the Oddi sphincter pressure of the patients included in the study was not measured. The fact that no biopsy was taken in some patients during endoscopy is also another limitation of the study. In the literature review, we have not come across a study investigating the relationship between CBD diameter and BR. We believe that the issue will be better clarified with prospective and larger population studies.

We observed in our study that BR was less common in cholecystectomy patients with increased CBD diameter. At the same time, we revealed that BR was significantly higher in the patients whose CBD diameter was found 7 mm or below. For this reason, we recommend that patients whose CBD diameter is detected to be 7 mm or below after cholecystectomy be closely monitored for BR. We anticipate that these patients can be protected from malignancies, in which BR plays a predisposing role with appropriate treatment.

Conclusion

We are of the opinion that CBD diameter found 7 mm or below after cholecystectomy may be a predictive factor in the detection of BR. However, we think that this issue should be further investigated with prospective, larger population studies.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the Relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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