Biliary manometry, bacterial characteristics, bile composition, and histologic changes fifteen to seventeem years after endoscopic sphincterotomy

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Biliary manometry, bacterial characteristics, bile composition, and histologic changes fifteen to seventeen years after endoscopic sphincterotomy

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Aim: **To evaluate the function of the biliary sphincter 15 to 17 years after endoscopic sphincterotomy and to investigate if loss of sphincter function is associated with bacterial colonization, changes in bile composition, or inflammation of the biliary system.**
Methods: **Eight patients who had undergone endoscopic sphincterotomy for bile duct stones 15 to 17 years previously underwent ERCP with biliary manometry, bile sampling, and biopsy. Manometry was performed using a perfused triple-lumen manometry catheter and a station pull-through technique. Bile samples were cultured and analyzed for biliary lipids, bile salts, bacterial β-glucuronidase, and phospholipase A_2. Biopsy specimens were taken from the proximal common hepatic duct for histologic examination.**
Results: **Manometry demonstrated absent basal sphincter pressure and no choledochoduodenal pressure gradient in all patients. Phasic contractions were observed in two patients. Cholangiography showed stones in one patient. Positive cultures were obtained in three patients, including the patient with stones. All bile samples showed a high content of biliary lipids and cholesterol. Some samples contained considerable amounts of hydrophobic bile salts. Five samples contained very high levels of phospholipase A_2 activity. Significant bacterial β-glucuronidase activity was found in one patient, the patient with stones. Biopsy specimens of the proximal common hepatic duct in three patients showed chronic inflammation with fibrosis and reactive epithelial changes.**
Conclusions: **After endoscopic sphincterotomy for bile duct stones, the function of the biliary sphincter is permanently lost. This is associated with bacterial colonization, presence of cytotoxic components in the bile, and chronic inflammation of the biliary system. (Gastrointest Endosc 1997;45:400-5.)**

Endoscopic sphincterotomy and stone removal is considered the treatment of choice in patients with bile duct stones. This approach is highly effective, with complete stone extraction established in 85% to 90% of cases.[1] Recent prospective studies concerning early complications of endoscopic sphincterotomy have shown that the procedure is safe, with early complications occurring in 10% of patients.[2] In only 1% to 2% of patients these complications are graded as severe.[2] The long-term sequelae of endoscopic sphincterotomy, however, are still largely unknown.

Manometric follow-up studies have shown that the function of the biliary sphincter is absent up to 2 years after endoscopic sphincterotomy[3] and it is hypothesized that this loss of function is permanent. If this is the case, long-term duodenobiliary reflux and bacterial contamination of the bile ducts might be hazardous.[4, 5] Late complications might include recurrence of

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bile duct stones due to deconjugation of bilirubin by bacterial enzymes,[6] inflammatory changes of the biliary system,[7, 8] recurrent ascending cholangitis,[9] and even malignant degeneration.[10, 11] An important premise is that the function of the biliary sphincter does not recover after endoscopic sphincterotomy. However, no long-term manometric evaluation of sphincter function is available.

The aim of this study was to evaluate the function of the biliary sphincter 15 to 17 years after endoscopic sphincterotomy and to investigate if loss of sphincter function is associated with bacterial colonization, changes in bile composition, and/or inflammation of the biliary system.

PATIENTS AND METHODS

Patients

Recently, we reported the results of a retrospective study of long-term complications after endoscopic sphincterotomy for removal of bile duct stones.[12] For this study we retrospectively identified all patients who had undergone endoscopic sphincterotomy and successful stone removal between January 1976 through December 1980. A total of 100 patients were identified. Information concerning long-term complications after endoscopic sphincterotomy was obtained from general practitioners and patients by telephone. Furthermore, patients completed a postal questionnaire and a blood sample was obtained for liver function tests. The complications that occurred during the follow-up period (median length of follow-up was 15 years) were previously reported in this journal.[12] At the time of follow-up (March 1994), 8 patients had had recent abdominal symptoms and/or cholestatic liver function tests. This study reports the findings at ERCP in these 8 patients.

There were seven women and one man with a mean age of 57 years (range 43 to 70 years). All patients had undergone cholecystectomy. Indications for ERCP were cholestasis and colicky pain (n = 3), cholestasis only (n = 3), and nonspecific abdominal pain (n = 2). None of the patients had had any biliary interventions or complications during the follow-up period since sphincterotomy and cholecystectomy. None of the patients were receiving antimicrobacterial drugs or acid-lowering drugs that might have affected their bacterial counts.

Endoscopic procedure

The patients underwent ERCP using the Olympus TJF-100 side-viewing therapeutic duodenoscope after being sedated with intravenous midazolam[13] (5 mg). Antispasmolytics such as butylscopalamine and narcotic analgesics were not used during the procedure. After the endoscope had been positioned into the duodenum, the bile duct was cannulated with a sterilized catheter and a bile sample was collected. The position of the metal-tipped catheter was confirmed with fluoroscopy, without the use of radiographic contrast agents.

The first 4 ml sample was immediately sent to the laboratory and stored at –20° C until analysis. Subsequently, 1 ml of bile was collected in a sterile test tube, immediately transported to the microbiology laboratory, and processed within 2 hours of collection.

After the bile samples were obtained and before injection of contrast into the bile duct, biliary manometry was performed. Bile duct and sphincter pressures were measured using a perfused triple-lumen manometry catheter (Wilson-Cook Medical Inc, Winston-Salem, N.C.). Continuous recording of intraluminal duodenal pressure was also obtained, using a second single-lumen catheter passed through the working channel of the endoscope and positioned with its recording orifice 2 cm distal to the sphincterotomy opening. During pressure recording the four manometry channels were perfused with bubble-free saline solution (0.3 ml/minute) using a low-compliance pneumohydraulic capillary perfusion system with its reservoir pressure set at 760 mm Hg. At the start of the manometry recording, the triple-lumen catheter was advanced into the bile duct and stationed there for 1 to 2 minutes to measure the basal bile duct pressure. The catheter was subsequently withdrawn in a stepwise fashion using distal markings on the catheter as reference. Pressures were recorded at each station for 1 to 2 minutes. The intraluminal duodenal pressure served as zero reference for plotting of the tracings and calculation of bile duct pressure and basal sphincter pressure.

On completion of the biliary manometry a diagnostic cholangiogram was obtained and the size of the sphincterotomy opening was assessed by balloon pull-through. At the end of the procedure a biopsy specimen was taken from the proximal common hepatic duct using Olympus duodenal biopsy forceps (FB-19N, 180 cm, 2.2 mm; and FB-45Q, 195 cm, 2.2 mm).

Laboratory procedures

All bile samples were inoculated onto a blood-agar plate, a CLED-plate, a chocolate-agar plate, and a blood-nalidixin plate. In addition, samples were inoculated onto a blood-agar plate and a blood-gentamicin plate under anaerobic conditions. All plates were incubated at 37° C and examined after 24 and 48 hours. Bacterial growth was reported semiquantitively as no growth, moderate growth, or heavy growth.

Bile salts, cholesterol, cholesterol nucleation, and phospholipids were determined using standard techniques.[14-17] β-Glucuronidase was determined with a fluorometric assay at pH = 5.2 (lysosomal activity) and pH = 7.0 (bacterial activity).[18, 19] Significant bacterial β-glucuronidase production was defined as a ratio bacterial activity: lysosomal activity greater than 0.30.[19] Phospholipase A_2 activity was determined using the phospholipase A_2 toolkit from Boeringher.

Biopsy specimens were routinely processed: formalin fixed, paraffin embedded, and stained with hematoxylin and eosin. All biopsy specimens were examined by the same pathologist (JO).

RESULTS

Manometry demonstrated absence of basal sphincter pressure and choledochoduodenal pressure gradi-

Table 1.
Manometric findings, bacterial characteristics, and histologic changes 15 to 17 years after endoscopic sphincterotomy

Patient no.	Indication	Sphincter function		Cholangiography	Bacterial culture‡	Biopsy	Definitive diagnosis
		Basal pressure	Phasic contractions				
1	Pain/cholestasis*	–	–	Normal	++§	Inflammation	Passed stone?
2	Pain/cholestasis*	–	–	Normal	++‖	Not done	Passed stone?
3	Pain/cholestasis†	–	–	Stones/sludge	++¶	Not done	Cholelithiasis
4	Cholestasis†	–	+	Normal	–	Inflammation	Cholestasis eci
5	Cholestasis*	–	+	Normal	–	Inconclusive	Cholestasis eci
6	Cholestasis*	–	–	Normal	–	Failed	Cholestasis eci
7	Nonspecific pain	–	–	Normal	–	Inflammation	Possibly IBS
8	Nonspecific pain	–	–	Normal	–	Failed	Possibly IBS

IBS, Irritable bowel syndrome; *eci*, e causa ignota (cause unknown).
*Cholestasis: alkaline phosphatase (AP) and gamma glutamyl transferase (GGT) <3 times upper limit.
†Cholestasis: AP and/or GGT >3 times upper limit.
‡Bacterial culture: ++ = heavy growth, + = moderate growth, – = no growth.
§*Escherichia coli, Klebsiella oxytoca.*
‖*E. coli.*
¶*E. coli, K. oxytoca, Clostridium perfringens, Enterococcus* species, *Streptococcus* species.

Table 2.
Results of bile analysis in 8 patients 15 to 17 years after endoscopic sphincterotomy

Patient no.	Tot lipid (mmol/L)	Phos lip (mmol/L)	Chol (mmol/L)	CSI	Crystals	Bile salts (mmol/L)	TC %	GC %	TCDC %	GCDC %	TDC %	GDC %	Phos lip A_2 (U/L)	β-gluc ratio
1	4.1	11.6	6.5	1.8	—	59.8	13.9	26.3	7.4	25.6	5.8	21.0	11	0.295
2	1.6	7.8	2.3	1.4	—	18.3	23.4	39.4	16.1	21.1	0.0	0.0	389	0.166
3	2.6	9.3	5.5	1.9	—	30.9	0.0	21.4	0.0	13.3	0.0	65.3	290	0.673
4	3.3	11.4	4.1	1.3	—	45.6	3.8	26.0	3.8	34.5	0.0	31.9	25	0.100
5	3.1	10.1	6.6	2.2	—	42.9	30.0	26.2	28.6	27.7	0.0	0.0	995	0.181
6	4.5	16.7	7.7	1.5	—	58.9	16.2	14.3	13.1	22.3	11.0	23.1	11	0.207
7	2.8	11.2	5.6	2.0	—	35.4	18.9	17.0	3.0	18.7	4.3	38.1	340	0.152
8	4.1	10.5	3.5	1.0	—	62.8	4.9	20.8	12.8	61.5	0.0	0.0	473	0.254

Tot lipid, Total biliary lipid concentration; *Phos lip*, phospholipid concentration; *Chol*, cholesterol concentration; *CSI*, cholesterol saturation index; *TC*, taurocholate; *GC*, glycocholate; *TCDC*, taurochenodeoxycholate; *GCDC*, glycochenodeoxycholate; *TDC*, taurodeoxycholate; *GDC*, glycodeoxycholate; *phos lip A_2*, phospholipase A_2; *β-glucuronidase ratio*, ratio bacterial activity: lysosomal activity. (A ratio > 0.30 was considered positive for bacterial β-glucuronidase production.[19])

ent in all patients. Residual sphincter contractions were observed in two patients (Table 1).

The ERCP showed brown pigment stones and sludge in one patient. In the other seven patients no abnormalities, including bile duct dilatation, were observed at cholangiography. The definitive diagnosis in these patients is given in Table 1. The five patients with cholestatic liver function tests (all mild) were followed-up for up to 2 years after the ERCP. No cause of the persisting cholestatic liver function tests could be determined. A liver biopsy was not performed in these patients.

No patient had evidence of sphincter stenosis; a 10 mm stone extraction balloon could easily be passed through the sphincterotomy opening in all patients. Positive cultures were obtained in three patients, including the patient with stones. Almost all samples showed a relatively high content of biliary lipids and all samples were considerably supersaturated with cholesterol (Table 2). Cholesterol crystals were not observed. A considerable variation was observed in the distribution of bile salt species. Some samples contained very high amounts of hydrophobic bile salts (glycochenodeoxycholate and glycodeoxycholate). Surprisingly, some samples lacked the presence of secondary bile salts (Table 2). Five of the eight samples contained very high levels of phospholipase A_2 activity; however, significant bacterial β-glucuronidase was found in only one patient. The latter patient also had positive cultures and bile duct stones.

After two of the first three patients in whom biopsy was performed had suffered from mild complications (hematobilia in one, post-ERCP fever in the other), we tried to obtain bile duct biopsy specimens by means of sideways biopsy forceps (FB-45Q Olympus duodenal biopsy forceps). This failed, however, in the next two patients, whereas in a third patient insufficient tissue for meaningful assessment was obtained. In the last two patients, therefore, no attempts were made to obtain a bile duct biopsy specimen. Hence, in only three

patients were sufficiently large biopsies obtained for meaningful assessment. Results of the light microscopy of these three biopsy specimens was similar and showed nonspecific changes like chronic inflammation with fibrosis and reactive epithelium (Fig. 1).

DISCUSSION

This study investigated the function of the biliary sphincter, bacterial colonization, bile composition, and histology of the biliary system 15 to 17 years after endoscopic sphincterotomy for bile duct stones. To our knowledge no studies have been published evaluating the long-term effects of endoscopic sphincterotomy on the biliary system. Although unique, our study has some important limitations. First, no data are available prior to the endoscopic sphincterotomy. The effect of the underlying stone disease and prior cholecystectomy can, therefore, not be separated from secondary changes after endoscopic sphincterotomy. Second, because only a limited number of patients (all with symptoms to some extent) were examined, this study may suffer from selection bias. It cannot be excluded that results may be different in patients who are completely asymptomatic. Nevertheless, some important conclusions can be drawn from the present data.

Biliary manometry

Several series have been published describing manometric follow-up after endoscopic sphincterotomy.[3, 20, 21] However, the maximum length of follow-up in these studies is rather limited: Geenen et al.[3] reported on 22 patients who underwent manometry 12 and 24 months after endoscopic sphincterotomy.[3] In their patients the basal sphincter pressure and choledochoduodenal pressure gradient were found to be abolished at 12 and 24 months. However, in the eight patients evaluated at 24 months, the amplitude of phasic sphincter contractions was significantly higher than after 12 months and not significantly different from presphincterotomy values. This might suggest a return of the sphincter's phasic contractile function and a tendency to regeneration of the biliary sphincter function.[3] In the present study we did not detect any evidence of residual *basal* sphincter function after endoscopic sphincterotomy. There were, however, residual *phasic* contractions seen in two of our eight patients, 15 to 17 years after endoscopic sphincterotomy. The significance of this finding is not clear, but we believe that it is probably due to incomplete sphincterotomy. We are, however, not able to exclude regeneration of sphincter function as we have no manometric data earlier in the follow-up period. Nevertheless, in six of our eight patients there was no manometric evidence of any sphincter function, suggesting that endoscopic sphincterotomy results in a permanent abolition of sphincter function in the majority of patients.

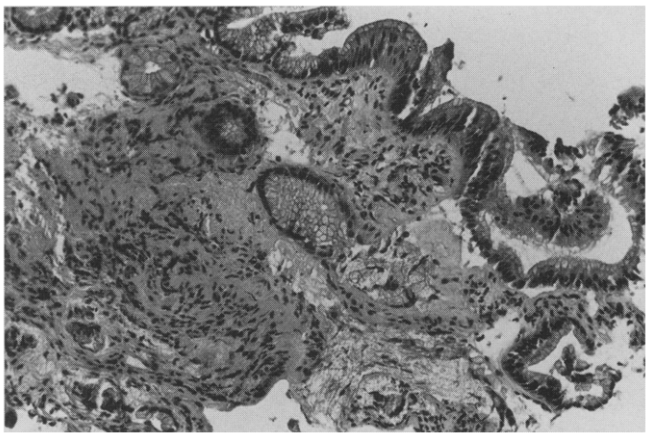

Figure 1. Light microscopy photograph of a bile duct biopsy obtained 15 years after endoscopic sphincterotomy for bile duct stones, showing chronic inflammation with fibrosis and reactive epithelium.

Bacterial cultures

After endoscopic sphincterotomy for bile duct stones, bactobilia has been reported in 60% to 88% of patients.[4, 5, 22, 23] In the present study three of the eight patients (38%) had positive cultures. False-negative culture results due to inadequate culture techniques cannot be excluded but are an unlikely explanation for the relatively low rate of bactobilia inasmuch as no bacterial β-glucuronidase was found in patients with negative culture results. We believe that the small number of patients in this series makes a chance phenomenon a more likely explanation. This is illustrated by the wide 95% confidence interval for rate of bactobilia: CI [9%, 76%].

In the three patients in whom sufficient material was obtained for histologic examination, chronic inflammation and reactive changes of the bile duct epithelium were observed. Remarkably, inflammation was also demonstrated in two patients without evidence of bacterial colonization (Table 1). This suggests either an intermittent presence of bacteria in the bile duct or a nonbacterial cause of inflammation, e.g., reflux of gastroduodenal contents or biochemical changes in bile composition.

Bile composition

Bile analysis revealed that all but one patient had concentrated bile, which is remarkable taking into consideration that after endoscopic sphincterotomy the biliary tree communicates freely with the duodenum. Although all samples were considerably supersaturated with cholesterol, no cholesterol crystals were observed. Apparently transit time is too short to allow for cholesterol crystallization. Despite the con-

stancy of total biliary lipid and the degree of cholesterol saturation, there was a large variation in the distribution of bile salt species. Bile of three patients contained very high amounts of deoxycholate and some samples contained in addition a considerable amount of the primary dihydroxy bile salt chenodeoxycholate. These dihydroxy bile salts are very cytotoxic and it cannot be excluded that some of the inflammatory changes are due to the cytotoxic effects of hydrophobic bile salts. Furthermore, in five of our eight patients a high phospholipase A_2 activity was found. The activity was about two orders a magnitude higher than normally present in gallbladder bile[24] and may lead to a considerable production of the toxic compound lysolecithin.

Histologic changes

There are only a few studies reporting histologic changes of the biliary tree after endoscopic sphincterotomy. Greenfield et al.[7] performed aspiration liver biopsy in five patients after endoscopic sphincterotomy and found portal tract fibrosis and inflammation in four and three patients, respectively. Eleftheriadis et al.[8] investigated common bile duct mucosa in nine patients 1 to 12 years after choledochoduodenostomy and found hyperplasia, pseudopyloric gland metaplasia, and intestinal metaplasia. Recently, Kurumado et al.[10] described the same histologic changes of the choledochal epithelium after choledochoduodenostomy in rats.[10] They also observed squamous pseudostratification of the epithelium with atypia and speculated that long-lasting exposure to digestive enzymes and bacteria might eventually lead to carcinogenesis of the biliary epithelium. Although in the present series no specific (e.g., neoplastic) changes were observed, the microscopic findings point to chronic irritation of the epithelium, which is a well known risk factor for neoplastic change. No clinical follow-up studies have shown that malignant degeneration of the biliary system actually occurs after endoscopic sphincterotomy; however, sufficiently large follow-up studies for meaningful assessment of risk factors are not available.

In conclusion, after endoscopic sphincterotomy for bile duct stones, the function of the biliary sphincter is permanently lost. This is associated with bacterial colonization, presence of cytotoxic components in the bile, and chronic inflammation of the biliary system. The clinical consequences of these local pathophysiologic changes after endoscopic sphincterotomy need further documentation. Stone removal without sphincter ablation (e.g., by laparoscopic bile duct exploration[25, 26] or endoscopic balloon dilation[27, 28]) holds the advantage of preservation of the physiologic status of the biliary system[29] and may, therefore, become the preferred procedure, especially in younger patients.

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