

• BRIEF REPORTS •

Composition of common bile duct stones in Chinese patients during and after endoscopic sphincterotomy

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CONCLUSION: Bilirubinate stone is the predominant composition of initial or recurrent CBD stone in Chinese patients. The composition of CBD stones may be different from initial stones after ES.

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Key words: Endoscopic sphincterotomy; Common bile duct stone; Bilirubinate stone; Cholesterol stone

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Abstract

AIM: Endoscopic sphincterotomy (ES) is a well-established therapeutic modality for the removal of common bile duct (CBD) stones. After ES there are still around 10% of patients that experience recurrent CBD stones. The aim of this study is to investigate the composition of CBD stones before and after ES and its clinical significance in Chinese patients.

METHODS: From January 1996 to December 2003, 735 patients with CBD stones received ES at Kaohsiung Veterans General Hospital and stone specimens from 266 patients were sent for analysis. Seventy-five patients had recurrent CBD stones and stone specimens from 44 patients were sent for analysis. The composition of the stones was analyzed by infrared (IR) spectrometry and they were classified as cholesterol or bilirubinate stones according to the predominant composition. Clinical data were analyzed.

RESULTS: In the initial 266 stone samples, 217 (82%) were bilirubinate stones, 42 (16%) were cholesterol stones, 3 were calcium carbonate stones, 4 were mixed cholesterol and bilirubinate stones. Patients with bilirubinate stones were significantly older than patients with cholesterol stones (66 ± 13 years vs 56 ± 17 years, $P = 0.001$). In the 44 recurrent stone samples, 38 (86%) were bilirubinate stones, 3 (7%) were cholesterol stones, and 3 were mixed cholesterol and bilirubinate stones. In 27 patients, both initial and recurrent stone specimens can be obtained, 23 patients had bilirubinate stones initially and 2 became cholesterol stones in the recurrent attack. In the four patients with initial cholesterol stones, three patients had bilirubinate stones and one patient had a cholesterol stone in the recurrent attack.

INTRODUCTION

The prevalence of gallstone diseases varied from 10% to 30% in the normal population and increased with age^[1-3]. Most gallstones are asymptomatic, but symptomatic gallstones may occur due to either cystic duct obstruction or common bile duct (CBD) stone formation. Endoscopic sphincterotomy (ES) is a well-established therapeutic modality for the removal of CBD stones. In follow-up studies after ES, 3-21% of patients developed recurrent CBD stones^[4-6] and most of them can be treated successfully by endoscopy^[4,7].

The main composition of gallstones is cholesterol and bile pigments^[8]. The major composition of GB stones obtained from Western patients is cholesterol (consisting of more than 50% cholesterol)^[8]. However, in the Asian patients, most gallstones are pigmented stones^[9]. Pigmented stones can be classified as black stones, associated with hemolysis or brown stones, associated with infection or bile stasis^[10-13]. Stones in the CBD are often brown, pigmented stones^[14-16]. After ablation of sphincter, bactobilia may happen and the pathogenesis of CBD stone formation may be different from the patients with intact sphincters^[17,18]. There have been few studies reporting the composition of recurrent CBD stones in patients after ES.

The aim of this study is to determine the composition of initial and recurrent CBD stones by infrared (IR) spectrometry and investigate the relationship of clinical characteristics and the change of the composition of recurrent stones after ES.

MATERIALS AND METHODS

Since January 1996 to December 2003, total 735 patients

with CBD stones received successful ES with clearance of CBD stones in Kaohsiung Veterans General Hospital and 266 stone specimens were collected and sent for stone analysis. During clinical follow-up, 75 patients had recurrent stones and 44 stone specimens were collected for stone analysis. Clinical data such as age, sex, diameter of CBD, size, number and color of stones, presence of juxtapapillary diverticulum (JPD), gallbladder (GB) status, and GB stones were recorded. GB stone was detected by sonogram or computed tomography of abdomen. Diameter of CBD and size and number of stones were measured during endoscopic retrograde cholangiopancreatography.

The stone sample was retrieved by Dormia basket (FG-22Q-1, Olympus) or snarenet (Roth snarenet, U.S.E.) from the bile duct. The stone specimen was pulverized into a homogenous powder, mixed with KBr and ground into fine particles. The mixed powder was pressed with a hydraulic pressure of 400 psi for 1 min to form a disc. Sample disc was analyzed with IR spectrometer. The stones were classified as cholesterol or bilirubinate stone according to the predominant composition. The characteristic band features and key band locations were in accordance with those reported in the literature^[9,19]. Bilirubinate stones had characteristic IR absorption bands at 970, 1 186, 1 250, 1 568, 1 627, and 1 650/cm with a key band at 1 250/cm; cholesterol stones had characteristic IR absorption bands at 728, 836, 952, 1 050, 1 375, 1 470, and 2 950/cm with key bands at 1 050 and 1 470/cm.

This protocol was approved by the Department of Medical Research and Education of Kaohsiung Veterans General Hospital. The values are expressed as mean±SD. Categorical variables were analyzed with χ^2 -test or Fisher's exact test and continuous variables were analyzed by Student's *t*-test. A *P* value <0.05 was regarded as significant.

RESULTS

Among the 735 patients with CBD stones and receiving successful ES, there were no significant differences in age, sex, presence of JPD, or cholecystectomy between the patients whose stones were collected for analysis or not (Table 1). In the group of patients with stone collection, their CBD diameter and stone size were larger.

Table 1 Patients' characteristics between stone collected and uncollected groups

	Collected (n = 266)	Uncollected (n = 469)	<i>P</i>
Age (yr)	64±14	65±14	0.454
Sex (M/F)	156/110	297/172	0.210
JPD ¹ (%)	105 (39) ²	158 (34)	0.116
Cholecystectomy (%)	65 (24) ²	108 (23)	0.665
CBD size (cm)	1.7±0.6	1.5±0.6	<0.001
CBD stone size (cm)	1.2±0.6	0.6±0.7	<0.001

¹JPD: Juxtapapillary diverticulum; CBD: common bile duct. ²Number of cases; the number inside the parenthesis shows the percentage.

In the 266 stone samples, 217 (82%) were bilirubinate stones, 42 (16%) were cholesterol stones, 3 were calcium carbonate stones, 4 were mixed cholesterol and bilirubinate

stones. Patients with bilirubinate stones were significantly older than patients with cholesterol stones (66±13 years *vs* 56±17 years, *P* = 0.001). There were no significant differences in sex, CBD diameter, size or number of CBD stones, presence of JPD, GB status, or presence of gallstones between patients with bilirubinate or cholesterol stones (Table 2).

Table 2 Patients' characteristics and initial stone compositions

	Bilirubinate (n = 217)	Cholesterol (n = 42)	<i>P</i>
Age (yr)	66±13	56±17	0.001
Sex (M/F)	130/87	22/20	0.365
CBD diameter (cm)	1.7±0.5	1.6±0.6	0.119
Stone size (cm)	1.2±0.6	1.2±0.7	0.410
Stone number (S/M)	111/106	16/26	0.121
JPD			0.084
Present	93 (43) ¹	12 (29)	
Absent	124 (57) ¹	30 (71)	
GB status			0.323
Cholecystectomy	57 (26) ¹	8 (19)	
Intact GB	160 (74)	34 (81)	
With stone	111 (51)	20 (48)	

Seven patients were excluded (three were calcium carbonate stones, four were mixed cholesterol and bilirubinate stones). CBD: Common bile duct; S/M: single/multiple; JPD: juxtapapillary diverticulum; GB: gallbladder. ¹Number of cases; the number inside the parenthesis shows the percentage.

A total 75 patients had recurrent CBD stones and received another endoscopic treatment. Stone specimens were collected from 44 patients for stone analysis. In the 44 recurrent stone samples, 38 (86%) were bilirubinate stones, 3 (7%) were cholesterol stones, and 3 were mixed cholesterol and bilirubinate stones. Among the three patients with recurrent cholesterol stones, two patients had intact GBs with stones and one had received a cholecystectomy 6 mo prior to recurrence. There were no significant differences in age, sex, CBD diameter, size or number of CBD stones, GB status, or presence of gallstones between patients with recurrent bilirubinate or cholesterol stones (Table 3).

Table 3 Patients' characteristics and compositions of recurrent CBD stones

	Bilirubinate (n = 38)	Cholesterol (n = 3)	<i>P</i>
Age (yr)	66±10	65±6	0.836
Sex (M/F)	21/17	3/0	0.254
CBD diameter (cm)	1.9±0.6	1.4±0.2	0.159
Stone number (S/M)	16/22	1/2	1.000
Stone size (cm)	1.4±0.8	0.8±0.4	0.096
JPD			0.543
Present	13 (34) ¹	2 (67)	
Absent	25 (66)	1 (33)	
GB status			1.000
Cholecystectomy	18 (47) ¹	1 (33)	
Intact GB	20 (53)	2 (67)	
With stone	15 (39)	2 (67)	

Three patients with mixed cholesterol and bilirubinate stones were excluded. CBD: Common bile duct; S/M: single/multiple; JPD: juxtapapillary diverticulum; GB: gallbladder. ¹Number of cases; the number inside the parenthesis shows the percentage.

In 27 patients, both initial and recurrent stone specimens can be obtained and sent for analysis, 23 patients had bilirubinate stones at initial treatment, 21 of them still had bilirubinate stones and 2 patients had cholesterol stones after recurrence. Both the patients with recurrent cholesterol stones also had GB stones. Four patients had cholesterol stones in the initial attack, three of them had bilirubinate stones, one patient still had cholesterol stones with recurrence and this patient had received cholecystectomy 6 mo prior to recurrence (Table 4).

Table 4 Change of stone compositions between initial and recurrent stone

Recurrent	Initial	
	Bilirubinate (n = 23)	Cholesterol (n = 4)
Bilirubinate (n = 24)	21	3
Cholesterol (n = 3)	2	1

Among the initial 266 stone samples, colors of stones were recorded. In the 217 patients with bilirubinate stones, 55 were yellowish, 93 were blackish, 64 were brownish and 5 were greenish. In the 42 patients with cholesterol stones, 15 were yellowish, 12 were blackish, 15 were brownish. In patients with mixed bilirubinate and cholesterol stones, two were yellowish and two were blackish. In patients with calcium carbonate stones, two were yellowish and one was blackish (Table 5).

Table 5 Compositions and color of stones

	Bilirubinate stone (n = 217)	Cholesterol stone (n = 42)	Mixed bilirubinate and cholesterol stone (n = 4)	Calcium carbonate stone (n = 3)
Yellow	55	15	2	2
Black	93	12	2	1
Brown	64	15	0	0
Green	5	0	0	0

DISCUSSION

We found that 82% of our patients had bilirubinate stones in the first attack, so the mechanism of CBD stone formation is different from the Western countries, but it is similar to some Asian studies^[9,20,21]. After ablation of sphincter of Oddi by ES, bactobilia may happen from direct extension of duodenal organisms into the CBD and β -glucuronidase released by the bacteria can promote the formation of bilirubinate stones^[17,18,22-24]. This explains why bilirubinate stone is the predominant composition of recurrent CBD stones (86%) after ES. Unlike the cholesterol stones, bilirubinate stones are often soft and easily broken^[16], so complete clearance of bilirubinate stones even after ES may be inadequate; some radiologically undetectable small fragments of bilirubinate stones may be left in the CBD; in addition to impaired biliary emptying, it may lead to bilirubinate stone formation at a later time.

Among the initial 42 patients with cholesterol stones, 8

patients received cholecystectomy at least 3 mo (median: 60 mo, range: 3-120 mo) before ES and 14 patients had intact GB but no GB stones. Besides spontaneous pass-out of stones, *de novo* formation of cholesterol stones from CBD may also be possible in these patients^[14,16].

In previous reports, JPD may facilitate primary CBD stone, but not GB stones formation^[16,25]. In our study, patients with initial bilirubinate stones had higher incidence of JPD than patients with initial cholesterol stones (43% *vs* 29%), but the difference did not reach statistical significance ($P = 0.084$).

In the 23 patients with initial bilirubinate stones, 21 had bilirubinate stones at recurrence, 2 had cholesterol stones when recurrence and these 2 patients also had GB stones at the time of recurrence, so stone pass-out from the GB may possibly explain the cholesterol composition of their CBD stones. In the four patients with initial cholesterol stones, three patients had bilirubinate stones and one had cholesterol stones at recurrence. The patient, who had recurrent cholesterol stones, had received cholecystectomy 6 mo before. It is difficult to determine whether the cholesterol stone is formed in the bile duct or GB. Our results indicated that different mechanism of CBD stone formation might occur in the same patient after ablation of sphincter leading to the formation of a different composition of stones.

In this study, we found that patients with bilirubinate stones are older than patients with cholesterol stones. Similar data have been found in Western patients with cholesterol *vs* pigment GB stones^[26]. It is well known that the duodenum is usually sterile in young healthy patients, but immunological and motor function of the alimentary tract may deteriorate gradually with age^[27]. The bacterial colonization of the CBD is an age-dependent phenomenon^[23] and this may explain the higher incidence of bilirubinate stones in older patients.

Cholesterol stones were usually yellowish or brownish^[15,28], but 12 out of 42 (29%) cholesterol stones in our patients were black in color, whereas 93 out of 217 (43%) bilirubinate stones were black in color. The nature of CBD stones cannot be completely determined by gross appearance alone^[28,29] and the IR spectroscopy is an important tool to determine the exact composition of stones.

For most patients, endoscopic retrieval of stones for analysis is more difficult than surgical procedure. In our study, only 266 out of 735 patients had received the analysis of stones. It could be speculated that different stone composition may influence the collection of stone for analysis during extraction procedure. Cholesterol stones are often smoother and harder while bilirubinate stones, on the other hand, are softer and tend to be broken down into small fragments when retrieved by basket or even a snarenet. This infers that the real percentage of bilirubinate stones in our patients may be actually higher. However, our analysis does not show significant difference in age, sex, presence of JPD, or cholecystectomy between patients whose stones were collected for analysis or not. Even though the CBD diameter and stone size are larger in the patients with stone analysis, there is no difference in CBD size or stone size between bilirubinate or cholesterol stones. We believe that little selection bias has taken place in our patients, despite only about 36% of patients' stones were collected for analysis.

In conclusion, bilirubinate stones are the predominant composition of initial and recurrent CBD stone after ES in Chinese patients. Patients with bilirubinate stones are older than those with cholesterol stones. The composition of stones may change after ES.

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