Bile Acid Secretion and Biliary Bile Acid Composition Altered by Cholecystectomy

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After cholecystectomy, bile secretion is continuous and 24-hour bile acid output exceeds that in health. Cholecystokinin-pancreozymin (CCK-PZ) influences neither bile acid secretion nor the bile acid composition of bile after the operation. It is proposed that the absence of the gallbladder causes more rapid enterohepatic recycling of bile acids and therefore increased bile acid secretion. The bile acid composition of bile following cholecystectomy is abnormal for the same reasons. A high proportion of secondary bile acids is present, including several found to be keto bile acids, and this is attributed to increased exposure of the bile acid pool to degradation by intestinal microorganisms.

The gallbladder stores bile and, following ingestion of meals, discharges bile into the intestine. In health, contraction of the gallbladder is initiated mainly by cholecystokinin-pancreozymin (CCK-PZ), which is released from the small intestinal mucosa by hydrolytic products of digestion. Discharge of bile acids is precisely timed and essential for the micellar solubilization prior to absorption of lipid (1). Following cholecystectomy, maldigestion and malabsorption of fat do not occur; as yet unidentified compensatory changes in bile secretion may result from the operation. Cholecystectomy should also influence the kinetics and metabolism of bile acids, since the procedure removes the reservoir in which almost all of the bile acid pool is normally sequestered (1) and necessitates an alternative storage area or more rapid enterohepatic cycling. Under the latter circumstance, alterations in bile acid synthesis by the liver (2) and greater exposure of the bile acid pool to degradation by enteric bacteria are to be anticipated.

This report quantifies changes in bile acid secretion after cholecystectomy and documents the alterations in the bile acid composition of bile which follow the operation. These results, complemented by recent findings of others and ourselves, help to characterize some of the new conditions of bile acid metabolism which are created by removal of the gallbladder.

MATERIAL AND METHODS

Forty-seven Caucasian individuals volunteered for these studies. Thirteen (12 female and 1 male, aged 47 to 69) had undergone cholecystectomy for cholelithiasis at least 1 year previously. A second group was comprised of 24 female patients with radiolucent gallstones and radiologically functioning gallbladders, from whom duodenal bile had been analyzed in our Unit to determine bile acid composition, as previously reported (3). In addition, 10 healthy males (aged 22 to 52) acted as a control group. Ethical considerations precluded studies involving radiation exposure of females in this age group. Further, we have found no differences in bile acid output between young males (4) and postmenopausal females (5).

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Table 1. Bile Acid Output in Response to CCK-PZ in Health and After Cholecystectomy

	Bile Acid Output (mmoles/hr, mean ± SE)				
	Health	Cholecystectomy			
IV CCK-PZ (CHR U/kg/min)	Total	Total	Cholic acid	Chenodeoxy-cholic acid	Secondary bile acids
0 (Basal)	0.92 ± 0.2	1.50 ± 0.2	0.34 ± 0.1	0.54 ± 0.1	0.63 ± 0.1
0.008	1.37 ± 0.3	1.61 ± 0.2	0.34 ± 0.1	0.58 ± 0.1	0.69 ± 0.1
0.031	1.89 ± 0.2	2.05 ± 0.4	0.52 ± 0.1	0.74 ± 0.2	0.79 ± 0.1
0.125	5.16 ± 2.0	1.91 ± 0.4	0.44 ± 0.1	0.67 ± 0.2	0.79 ± 0.1
0.250	2.09 ± 0.1	1.75 ± 0.5	0.38 ± 0.2	0.59 ± 0.2	0.77 ± 0.1

Bile Acid Secretion

In health and after cholecystectomy bile acid secretion was quantified as total bile acid output using a duodenal perfusion method already described (6). After subjects had fasted overnight, a two-lumen polyethylene tube was placed under fluoroscopic control so that the perfusion site was in the second part of the duodenum and the sampling port was located 20 cm distally at the ligament of Treitz. Gastric juice was continuously aspirated from an additional tube placed in the gastric antrum. Isotonic saline (37° C) containing a nonabsorbable marker (polyethylene glycol, PEG 5 g/liter) was infused at a constant rate (10 ml/min) into the duodenum. Following the establishment of steady state conditions, specimens from the duodenum were drained by siphonage, collected over ice and pooled at 20-minute intervals. Concentrations of total bile acids and PEG were determined by standard methods (3, 7). Total bile acid outputs were calculated from concentrations of these materials relative to PEG (6). Bile acid kinetics following cholecystectomy were the subject of a companion study (8).

In 5 healthy individuals and in 5 patients after cholecystectomy, total bile acid output was quantified by this method following the intravenous administration of CCK-PZ (kindly supplied by Professor E. Jorpes, Karolinska Institutet, Stockholm, Sweden, batch #27112). The material was diluted in normal saline and given continuously by vein using a Harvard pump. Doses were changed every hour, following a control period, and were given in the following sequence: 0.008, 0.031, 0.125, and 0.250 CHR units/kg/ min as detailed elsewhere (9).

Analytic Methods

Bile acids in duodenal aspirates, obtained either during perfusion studies or after intravenous CCK-PZ had been given in the fasting state, were analyzed by methods which are standard in our laboratory (3, 10, 11). Quantitative measurements were made by gas liquid chromatography; thin layer chromatography was used for qualitative determinations. Bile acids were identified using both methods by relating their mobility to that of standards (kindly supplied by Dr. Alan F. Hofmann). The relative amounts of each bile acid were calculated as a percentage of the total.

RESULTS

Bile Acid Secretion

After cholecystectomy, basal total bile acid output, determined during the first hour of perfusion with normal saline, was significantly greater ($P < 0.05$) than in health (Table 1). When CCK-PZ was given, gallbladder contraction occurred in healthy subjects at doses of 0.125 CHR units/kg/min and was accompanied by an increased bile acid output ($P < 0.01$ over basal levels. Following cholecystectomy, CCK-PZ had no effect upon total bile acid output or upon the outputs of the component bile acids at any dose. Extrapolation to 24 hours of total bile acid output after cholecystectomy yielded a value of 648 ± 108 μmoles/ kg/24 hr. This output is significantly higher ($P < 0.01$) than that found by us in health (307 ± 20 μmoles/kg/24 hr) when using a similar perfusion method in conjunction with three meals during a 24-hour study (4). Since the size of the total bile acid pool after cholecystectomy is similar to that in health (8, 12), our data suggest that the pool re-

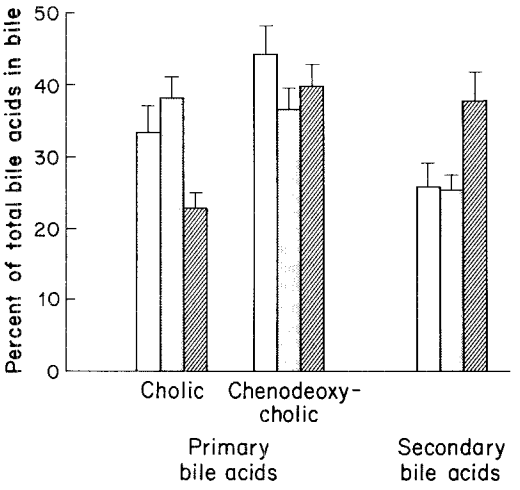

Fig 1. Biliary bile acid composition: health (**white bars**), gallstones (**stippled bars**), and cholecystectomy (**line bars**).

cycles twice as frequently (8-16 times/24 hr) following cholecystectomy than was found (4) in our healthy volunteers (4-8 times/24 hr). If the pool size remains small after surgery, even more frequent recycling would occur.

Bile Acid Composition of Bile

Biliary bile acid composition in health and in patients with cholelithiasis was similar (Figure 1). The two primary bile acids, cholic and chenodeoxycholic acid, and two secondary bile acids, deoxycholic and lithocholic acid, were constantly present and the ratio between primary and secondary bile acids was 4.16 ± 1.0. Scant amounts of other secondary bile acids appeared in a few chromatograms but accounted for less than 1% of the total.

After cholecystectomy, the ratio between primary and secondary bile acids was decreased to 2.38 ± 0.63. The relative reduction in primary bile acids in bile was mainly due to a significantly lower ($P < 0.05$) proportion of cholic acid, since the proportion of chenodeoxycholic acid remained similar to that in health. The corresponding increase in the proportion of secondary bile acids after cholecystectomy ($P < 0.02$) reflected a variety of changes. The most significant was the appearance of a greater proportion of secondary bile acids other than deoxycholic and lithocholic acid. These unusual secondary bile acids were found in 11 of 13 patients and accounted for 2.5 to 25% (mean 9.31 ± 2.35%) of all bile acids present. Upon analysis, these unusual bile acids were identified as keto bile acids. A small and inconstant proportion of the bile acids present could not be characterized.

The proportion of deoxycholic acid following cholecystectomy (25.81 ± 5.2%) was not significantly different from that in health (20.70 ± 3.2%), but a wider scatter of values was present. In 5 patients, deoxycholic acid constituted more than one-third of total bile acids, whereas in 4 others the proportion of deoxycholic acid was less than 5%. Patients with the lowest proportions of deoxycholic acid in bile generally had the greatest proportion of unusual secondary bile acids. Similar percentages of lithocholic acid were present in health (3.2 ± 0.6%) and after cholecystectomy (3.6 ± 0.6%).

DISCUSSION

Cholecystectomy caused striking changes in bile acid secretion and in the bile acid composition of bile. Fortunately, these sequelae may preserve the efficiency of fat digestion despite loss of the gallbladder and reduce the lithogenic characteristics of bile present previously in association with cholesterol gallstones.

The fact that the extrapolated 24-hour total bile acid output after cholecystectomy exceeded that measured in health by a similar technic involving the added stimulus of three meals may explain preservation of fat digestion after cholecystectomy. The high total bile acid output after cholecystectomy is attributable to accelerated recycling of bile acids rather than to an abnormally expanded bile acid pool, since the pool size is normal in such patients (8, 12).

Bile acids can no longer be sequestered in the gallbladder and our calculations suggest that the pool consequently recycles at least twice as often as in health. Administration of CCK-PZ affected neither bile acid output nor the bile acid composition of bile after cholecystectomy. Continuous secretion and greater output of bile following the operation apparently ensures availability of sufficient bile acid in the small intestine despite loss of hormonal regulation of bile secretion. In addition, the increased secretion rate of bile acids following cholecystectomy may improve the composition of bile in patients who previously had cholesterol cholelithiasis, since the lithogenicity (ratio of cholesterol to bile acids and lecithin) of bile is least at high rates of bile secretion and greatest when bile is sequestered in the gallbladder (5, 13).

Absence of the gallbladder and more frequent recirculation of bile acids also logically explain the increased proportion of secondary bile acids present in bile after cholecystectomy, since the bile acid pool is more constantly exposed to degradation by microorganisms in the intestinal tract. The opposite situation has recently been described in nontropical sprue, when inadequate secretion of CCK-PZ from the diseased mucosa of the small intestine impairs evacuation of the gallbladder following a meal (14). Prolonged sequestration of bile in the gallbladder causes infrequent recycling of the bile acid pool (15) and results in an unusually small proportion of secondary bile acids in bile (14).

The ileum, from which bile acids are mainly absorbed, and the colon contain bacteria capable of oxidizing the hydroxyl groups of bile acids to keto derivatives such as those identified by us (16). In addition, the greater ratio of deoxycholic to other bile acids in the bile of several patients with cholecystectomy indicates that bacterial transformation of primary to secondary bile acids by 7α-dehydroxylation is also often increased.

Several keto bile acids are believed to be formed normally in the intestine, and their metabolism has been partially investigated; at least one is converted to other bile acids in the liver rather than being secreted from it (17). The appearance of considerable amounts of keto bile acids in the bile following cholecystectomy implies that the rapidity of their production and recycling in this condition exceeds the capacity of the liver to remove them.

The effect of keto bile acids on bile acid kinetics is unknown. If these compounds fail to inhibit hepatic synthesis of primary bile acids, enlargement of the total bile acid pool would occur. Expansion of the bile acid pool by the oral administration of bile acid abolishes the lithogenic potential of bile and causes dissolution of gallstones (18). Thus, if cholecystectomy increases the bile acid pool size towards normal in patients who previously had cholesterol cholelithiasis, the operation may account for the diminished lithogenic characteristics of bile which are reported to follow (19, 20).

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