

Impaired absorption of cholesterol and bile acids in patients with an ileoanal anastomosis

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Abstract

Background—No data exist on cholesterol absorption in patients with an ileoanal anastomosis (IAA).

Aims—To study cholesterol absorption and its effects on cholesterol and bile acid metabolism in patients with an IAA.

Patients and methods—Cholesterol absorption, and serum, biliary, and faecal lipids were studied in 24 patients with an IAA and 20 controls.

Results—Fractional cholesterol absorption was significantly lower in the patients (36% versus 47% in controls). Surprisingly, the calculated intestinal influx of endogenous cholesterol was reduced so that the absolute absorption of cholesterol was decreased; elimination of cholesterol as faecal neutral steroids remained normal. Thus, the slightly increased cholesterol synthesis was mainly due to increased faecal bile acid excretion, which, in turn, was associated with reduced absorption and biliary secretion of bile acids. Serum total and low density lipoprotein (LDL) cholesterol and LDL triglycerides were lower in the patients. Molar percentage and saturation index of biliary cholesterol were slightly higher in patients with an IAA. Proportions of secondary bile acids in bile and faeces were diminished, and faecal unidentified bile acids were higher in patients.

Conclusions—Cholesterol absorption is significantly impaired in patients with an IAA, and is closely related to changes in serum and biliary lipids observed in these patients.

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Keywords: cholesterol absorption; cholesterol synthesis; faecal bile acids; inflammatory bowel disease

Since the invention of the ileoanal pouch anastomosis in 1978 by Parks and Nicholls,¹ its use with various modifications in patients with ulcerative colitis has markedly increased. Earlier studies showed that proctocolectomy with conventional ileostomy does not affect bile acid metabolism,^{2,3} whereas the ileoanal anastomosis may disturb absorption of bile acids or vitamin B₁₂,⁴⁻⁶ both of which are absorbed in the ileum. Bile acid malabsorption has actually been suggested as being responsible for the lithogenic bile in these patients in some studies^{7,8} but not in all.⁹ Interestingly, steatorrhoea may also occur in some patients with ileoanal anastomosis.⁴ Thus, one can

infer that cholesterol absorption, dependent on micellar solubilisation with bile acids and fatty acids,^{10,11} may also be disturbed and markedly influence serum and biliary lipids in patients with an ileoanal anastomosis. However, to our best knowledge, no data are yet available on cholesterol absorption and synthesis in this condition. Therefore, in the present study we explored absorption, elimination, and synthesis of cholesterol, biliary lipids, faecal bile acids, and serum lipoproteins in 24 patients with ileoanal anastomosis and in 20 control subjects.

Methods

SUBJECTS

The series consisted of 24 patients with ulcerative colitis who had undergone an ileoanal anastomosis with a double limb J shaped pouch. In construction of the pouch, any resection of the terminal ileum was avoided, and it was 1-3 cm at most. Liver function tests (serum albumin, alanine aminotransferase, alkaline phosphatase) were normal in all patients, and none was using constipating drugs. Six had a history of pouchitis, but each had been without symptoms of pouchitis and off antibiotics for at least three months.

The control subjects comprised 20 men selected from a random 50 year old male population of Helsinki on the basis that their body mass index (BMI, kg/m²) range fell within that of the patients with ileoanal anastomosis (mean (2SD)). However, because mean body weight was slightly higher in the controls, where appropriate, the data are expressed per kg of body weight.

All subjects were informed of the nature and purpose of the studies, and the study protocol was approved by the Ethics Committee of the hospital.

PROCEDURES

All patients were hospitalised and placed on a standardised solid food diet of 300 mg of cholesterol and 100 g of fat per day. Daily energy content was adjusted to maintain constant body weight. For determination of cholesterol absorption,¹² faecal fat, and faecal steroids, each patient received a capsule containing ¹⁴C-cholesterol (0.15 µCi/day) and ³H-β-sitosterol (0.80 µCi/day) three times a day with the main meals for seven days. At the end of this period, a three day stool collection was performed. Then, after overnight fasting, a blood sample was taken and the patients received intravenously a bolus (1 IDU of body

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weight up to 100 IDU) of cholecystokinin (Cholecystokinin, Ferring Pharmaceuticals, Malmö, Sweden) to make the gall bladder contract, in order to allow aspiration of a duodenal bile sample through a gastroscope. The bile samples were placed in a water bath at 70°C for five minutes to destroy lipase activity and then stored at -20°C until analysed. The total intestinal transit time was measured by determination of time between ingestion of carmine red (1 g in 200 ml of water) and first appearance of the dye in the faeces. Small bowel transit time was measured with the lactulose hydrogen breath test, carried out by administration of 20 g of lactulose, and thereafter by collection of breath samples at 10–15 minute intervals up to 120 minutes. Appearance of peak concentration of breath hydrogen (a rise 50% above the baseline value) was regarded as small bowel transit time.¹³ Absorption of vitamin B₁₂ with intrinsic factor was measured according to Bayly *et al.*¹⁴

The control subjects were studied at our outpatient clinic. All subjects were asked to continue their customary home diet and to keep a dietary record for seven days, with mean daily intake of cholesterol and fat being computed from these records.^{15, 16} Daily analysis of the control data disclosed that intake of cholesterol and fat (4.9 (0.4) mg/kg/day and 1.3 (0.1) g/kg/day, respectively) very closely corresponded to intake in the patients (4.6 (0.2) mg/kg/day and 1.5 (0.1) g/kg/day, respectively). During the seven day period, cholesterol absorption, faecal steroids, faecal fat, blood, and bile sampling were carried out as described above.

MEASUREMENTS

Serum total cholesterol and triglycerides, and their content of very low density lipoprotein

(VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) were quantified according to the Lipid Research Clinic's manual.¹⁷ Biliary and faecal sterols of cholesterol origin were determined by gas liquid chromatography^{18, 19} on a 50 m SE-30 capillary column,¹⁹ and biliary phospholipids were determined as described by Bartlett.²⁰ Faecal fat was determined according to van de Kamer *et al.*²¹ and chromic oxide by the method of Bolin *et al.*²² Faecal radioactivities were determined with a liquid scintillation counter with 0.5% 2,5-diphenyloxazole in toluene (Wallac Rackbeta Scintillation; Model 1215). Because equal recoveries for ³H-β-sitosterol and chromic oxide in faecal samples disclosed no marked degradation of the sterol nucleus, faecal data were calculated in relation to chromic oxide (Cr₂O₃).

CALCULATIONS

The percentage absorption of cholesterol was calculated from the ¹⁴C:³H ratios in the capsules administered and in the faecal samples collected.¹² The intestinal cholesterol influx, consisting of dietary, biliary, and mucosal cholesterol, was determined by an indirect method²³ assuming that exogenous and endogenous cholesterol were similarly absorbed.²⁴ The average intestinal influx of cholesterol was calculated from the absorption percentage of cholesterol and faecal neutral steroids, and biliary cholesterol secretion was calculated by subtraction of cholesterol intake from intestinal cholesterol influx. The biliary secretion rates for cholesterol and bile acids obtained with this indirect calculation have been similar to those measured by the intestinal perfusion technique.²⁴ Biliary bile acid

TABLE 1 Clinical data and absorption, elimination, and synthesis of cholesterol in 24 patients with an ileoanal anastomosis and 20 control subjects

Case no	Age (y)	Sex (F/M)	Body weight (kg)	BMI (kg/m ²)	Postoperative period (months)	Intestinal transit time (h)	Absorption of vitamin B ₁₂ (% of dose/24 h)	Faecal fat (g/day)	Cholesterol absorption (%)	Faecal steroids (mg/day)		
										Bile acids	Neutral steroids	Cholesterol synthesis (mg/day)
1	27	F	55	19.0	6	6.3	16.9	1.9	48.6	342	352	394
2	35	F	55	19.5	13	2.8	16.5	3.0	21.8	356	601	657
3	36	F	61	24.4	14	4.2	17.5	2.7	36.3	375	346	421
4	48	F	86	34.9	4	4.0	22.4	2.0	30.8	471	538	709
5	30	F	69	26.3	5	2.8	17.9	6.5	51.6	1525	561	1786
6	42	F	66	26.4	25	1.8	16.5	6.9	44.7	1357	778	1835
7	37	F	64	22.4	5	3.7	11.7	2.8	34.2	473	581	754
8	38	M	71	21.4	6	7.3	25.5	2.9	40.7	422	420	542
9	38	F	50	19.1	41	7.6	20.7	3.0	47.5	463	381	544
10	40	M	106	28.5	59	8.7	13.2	3.4	21.7	415	804	919
11	29	F	54	20.3	4	4.2	15.2	3.0	33.5	381	846	927
12	46	F	56	20.1	6	6.7	29.3	3.3	30.7	273	463	436
13	26	M	69	23.9	6	3.4	20.1	2.9	48.5	1048	400	1178
14	41	F	84	32.8	9	2.7	29.7	2.5	41.6	378	472	550
15	43	M	64	20.9	10	8.4	10.5	8.7	20.1	807	565	1072
16	40	F	66	23.9	4	4.8	27.8	2.3	29.2	932	355	987
17	29	F	63	21.3	6	5.5	23.0	2.2	38.2	429	520	649
18	56	M	70	25.1	12	4.0	18.7	5.1	29.1	1030	739	1469
Mean (SEM) for cases 1–18	38 (2)***	13/5	67.2 (3.2)*	23.9 (1.1)	13.1 (3.5)	4.9 (0.5)	19.6 (1.4)	3.6 (0.4)	36.0 (2.3)**	575 (87)	537 (38)	878 (104)
19	40	M	54	19.1	31	7.4	ND	5.5	43.3	436	674	810
20	50	M	80	27.0	51	24.8	23.8	3.9	24.7	778	563	1041
21	38	M	55	19.0	34	7.3	24.1	2.6	36.7	625	469	794
22	54	M	101	31.9	24	5.3	19.7	2.7	42.1	815	374	889
23	37	M	66	19.7	8	6.2	18.9	3.7	33.9	1039	620	1359
24	24	M	67	19.8	36	4.5	ND	4.9	35.0	1274	593	1567
Mean for cases 19–24	41 (4)*	0/6	70.5 (7.2)	22.8 (2.2)	30.7 (5.8)†	9.2 (3.1)	21.6 (1.4)	3.9 (0.5)	36.0 (2.7)**	828 (121)**	548 (45)	1077 (130)
Controls (n=20)	50 (1)	0/20	75.5 (1.8)	24.3 (0.5)	ND	ND	> 12	4.6 (0.5)	47.0 (1.6)‡	437 (34)	749 (71)	827 (110)

Patients 1–18 had no history of pouchitis; patients 19–24 had a history of pouchitis.

*p < 0.05, **p < 0.01, ***p < 0.001, †p < 0.01 from non-pouchitis group; ‡n = 15; ND, not done.

secretion was calculated by multiplying bile acids (mg/100 mg of cholesterol) by biliary cholesterol secretion (mg/day). The lithogenic index of bile was calculated according to the equations of Thomas and Hoffman.²⁵ Absorption of dietary, biliary, and total cholesterol was calculated by multiplying respective intestinal influxes of cholesterol by fractional absorption of cholesterol. Cholesterol synthesis was calculated as the difference between the sum of faecal neutral steroids plus faecal bile acids, and cholesterol intake.

Statistical analysis was carried out with Student's *t* test, and correlations were calculated with a VAX-8600 using BMDP software.²⁶

Results

CLINICAL DATA

The time since surgery was significantly shorter in the patients with no pouchitis history than in those with previous pouchitis (13.1 versus 30.7 months, table 1). Total gut transit time, as measured by carmine red, was similar between the two patient groups. Absorption of vitamin B₁₂ was normal in all patients except one patient in the non-pouchitis group. Faecal fat was increased (>7.0 g/day) in one patient in the non-pouchitis group, but the mean values of faecal fat in both patient groups and in the control group were similar.

TABLE 2 Serum lipids and lipoproteins in patients with an ileal pouch and control subjects

Parameter	Controls (n=20)	Patients without pouchitis history (n=18)	Patients with pouchitis history (n=6)
Serum cholesterol			
VLDL	0.45 (0.10)	0.29 (0.04)	0.29 (0.05)
LDL	4.40 (0.18)	2.06 (0.16)***	2.09 (0.12)***
HDL	1.37 (0.07)	1.50 (0.09)	1.17 (0.15)
Total	6.30 (0.18)	4.31 (0.23)***	3.85 (0.21)***
Serum triglycerides			
VLDL	0.69 (0.15)	0.56 (0.08)	0.54 (0.10)
LDL	0.50 (0.04)	0.20 (0.02)***	0.21 (0.02)***
HDL	0.19 (0.01)	0.18 (0.01)	0.15 (0.01)*
Total	1.58 (0.22)	1.08 (0.09)*	1.03 (0.14)*

Results expressed in mmol/l (mean (SEM)).

p* < 0.05, **p* < 0.001 versus control values.

TABLE 3 Cholesterol and bile acid metabolism in control subjects and patients with an ileoanal anastomosis

Parameter	Controls (n=15)	Patients without pouchitis history (n=18)	Patients with pouchitis history (n=6)
Cholesterol (mg/kg/day)			
Absorption (%)	47.0 (1.6)	36.0 (2.3)**	36.0 (2.7)**
Faecal elimination as neutral steroids			
Dietary	2.6 (0.2)	2.9 (0.1)	2.8 (0.2)
Endogenous	6.9 (1.0)	5.3 (0.6)	5.5 (1.0)
Total	9.8 (0.8)	8.2 (0.6)	8.3 (1.2)
Intestinal influx			
Dietary	4.8 (0.4)	4.6 (0.2)	4.5 (0.4)
Endogenous	13.0 (1.8)	8.2 (0.8)*	8.7 (1.8)
Total	17.9 (1.7)	12.8 (0.9)*	13.2 (2.2)
Absorption			
Dietary	2.3 (0.3)	1.7 (0.1)	1.6 (0.2)
Endogenous	6.1 (0.9)	3.1 (0.4)**	3.2 (0.9)*
Total	8.5 (0.9)	4.6 (0.5)***	4.8 (1.0)*
Synthesis	10.3 (1.2)	12.2 (1.4)	15.9 (2.2)*
Bile acids (mg/kg/day)			
Faecal elimination	5.7 (0.4)	9.6 (1.3)**	12.0 (1.8)**
Biliary output	121.4 (16.3)	58.0 (8.4)**	81.5 (29.8)
Reabsorption (%)	94.1 (0.9)	81.6 (2.7)***	77.4 (4.8)**

Results expressed as mean (SEM).

p* < 0.05, *p* < 0.01, ****p* < 0.001 versus control values.

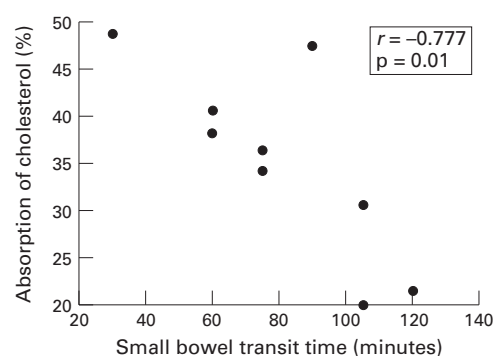


Figure 1: Correlation between absorption percentage of cholesterol and small intestinal transit time (measured with hydrogen breath test) in ileal pouch patients.

SERUM LIPIDS AND LIPOPROTEINS

Serum levels of total and LDL cholesterol were significantly lower in both patient groups, whereas those of VLDL and HDL cholesterol were similar to those of controls (table 2). Serum levels of total and LDL triglycerides were also noticeably reduced in the patients, as was that of HDL triglycerides in the pouchitis group.

CHOLESTEROL AND BILE ACID METABOLISM

The percentage absorption of cholesterol was significantly lower in both patient groups compared with control values (36% versus 47%) (table 1). The elimination of cholesterol as faecal neutral steroids, however, was not higher in patients, owing to the unexpected finding that the intestinal influx of endogenous cholesterol (biliary cholesterol secretion) and thus also the total intestinal influx of cholesterol were significantly lower (28% and 36% lower, respectively) in the patients than in the controls. Thus, whereas absolute absorption of dietary cholesterol only tended to be reduced, the intestinal absorption of endogenous cholesterol and that of total cholesterol were significantly lower in patients than in controls. Synthesis of cholesterol was only slightly higher in the patients, and was mainly due to their increased faecal bile acid excretion (table 3). Furthermore, calculations disclosed that the increased faecal bile acid loss in the patients was mainly attributable to their significantly lower reabsorption of bile acids, which probably resulted in reduced biliary bile acid output, particularly in the non-pouchitis group. The percentage absorption of cholesterol was not significantly associated with total intestinal transit time (measured by mouth to faeces carmine transit), but showed a negative correlation (fig 1; $r = -0.777$; $p < 0.01$) with the small intestinal transit time (measured by the breath hydrogen test).

BILIARY LIPIDS AND BILE ACIDS

The molar percentage of cholesterol in the bile was higher in the non-pouchitis group than in the controls, but otherwise neither their molar percentages of biliary lipids nor their lithogenic index differed (table 4). On the other hand, the percentage distribution of different biliary bile

TABLE 4 Biliary lipids, lithogenic index, and bile acid composition and secretion in control subjects and patients with an ileoanal anastomosis

Parameter	Controls (n=15)	Patients without pouchitis history (n=16)	Patients with pouchitis history (n=6)
Biliary lipids (molar %)			
Cholesterol	8.3 (0.7)	11.3 (1.0)**	9.2 (1.1)
Bile acids	70.7 (1.2)	69.8 (2.2)	70.0 (2.2)
Phospholipids	21.0 (0.9)	18.9 (1.4)	20.5 (1.0)
Lithogenic index	0.83 (0.07)	1.16 (0.09)	0.92 (0.10)
Biliary bile acids (% distribution)			
Cholic acid	47.1 (2.5)	56.5 (1.9)**	60.7 (3.3)**
Deoxycholic acid	11.9 (1.8)	0.9 (0.6)***	0.03 (0.01)***
Chenodeoxycholic acid	37.3 (1.6)	40.9 (1.4)	38.6 (3.2)
Lithocholic acid	1.7 (0.4)	0.22 (0.03)***	0.12 (0.03)***
Ursodeoxycholic acid	1.9 (0.5)	1.4 (0.4)	0.5 (0.3)*

Results expressed as mean (SEM).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control values.

TABLE 5 Faecal bile acid composition in control subjects and patients with an ileoanal anastomosis

Parameter	Controls (n=19)	Patients without pouchitis history (n=18)	Patients with pouchitis history (n=6)
Cholic acid origin	2.55 (0.21)	3.88 (0.81)	4.53 (1.08)
Cholic acid	0.20 (0.05)	3.45 (0.80)***	4.27 (1.04)***
Deoxycholic acid	1.95 (0.16)	0.34 (0.11)***	0.15 (0.06)***
Epi-deoxycholic acid	0.39 (0.06)	0.09 (0.02)***	0.12 (0.03)***
Chenodeoxycholic acid origin	1.79 (0.17)	2.74 (0.44)	3.05 (0.58)
Chenodeoxycholic acid	0.17 (0.04)	2.15 (0.43)***	2.51 (0.58)***
Lithocholic acid	0.96 (0.11)	0.14 (0.04)***	0.16 (0.03)***
Isolithocholic acid	0.55 (0.10)	0.15 (0.03)***	0.33 (0.06)†
Ursodeoxycholic acid	0.11 (0.04)	0.32 (0.06)**	0.09 (0.04)†
Unidentified bile acids	1.34 (0.12)	2.74 (0.26)***	4.26 (0.71)***†

Results expressed in mg/kg/day (mean (SEM)).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control values; † $p < 0.05$ versus patients without pouchitis.

acids was noticeably changed in the patients, showing their markedly lower levels of secondary bile acids—especially of deoxycholic acid and lithocholic acid, but less so of ursodeoxycholic acid.

COMPOSITION OF FAECAL BILE ACIDS

Faecal bile acid composition was significantly changed in the patients in comparison with that of the control group (table 5). Faecal cholic acid and chenodeoxycholic acid excretion was significantly higher, because in the

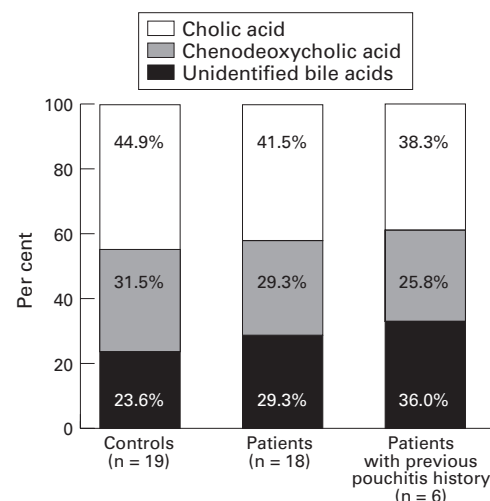


Figure 2: Percentage distribution of faecal bile acids identified to be of cholic acid or chenodeoxycholic acid origin and faecal unidentified bile acids in controls and patients with an ileal pouch.

two patient groups their conversion to identifiable secondary bile acids was significantly lower. In patients compared with controls percentages of unidentified faecal bile acids were significantly higher, whereas those of bile acids identified to be of cholic acid or chenodeoxycholic origin were reduced (fig 2). However, the mean ratio of faecal bile acids identified to be of cholic acid origin to those of chenodeoxycholic acid origin was similar (1.4 for all three groups).

Discussion

The main findings in the present study were, in the patients with an ileal pouch compared with the controls, reduced serum total and LDL cholesterol, and LDL triglyceride levels, markedly lower absorption of cholesterol, and slightly higher bile acid synthesis and cholesterol saturation of the bile.

SERUM LIPIDS AND LIPOPROTEINS

Data on serum lipoprotein levels in ileal pouch patients are practically non-existent. Thus, the low serum levels of total and LDL cholesterol, and LDL triglycerides are novel observations in patients with an ileoanal anastomosis. The lipid levels were not correlated with the fractional or absolute absorption of cholesterol nor with the faecal elimination of cholesterol as bile acids or neutral steroids. In bile acid malabsorption, the lowering of LDL cholesterol is due to the increased expression of hepatic LDL apoB receptors, yet cholesterol synthesis is increased.²⁷⁻²⁹ Interruption of the enterohepatic circulation of bile acids is also associated with increased secretion of triglyceride rich VLDL particles from the liver^{30,31} and a tendency to elevated serum levels of total and VLDL triglycerides.³² In our patients the serum VLDL levels were not significantly reduced, but their triglyceride:cholesterol ratios were higher. It is thus tempting to speculate that simultaneous cholesterol malabsorption and an insufficient increase in cholesterol synthesis may have reduced hepatic cholesterol content in the patients so that biliary cholesterol secretion fell, and less cholesterol remained for VLDL production, resulting in cholesterol poor VLDL formation and lowered serum VLDL and especially LDL levels. This suggestion is also supported by the positive correlation between the serum LDL cholesterol level and cholesterol synthesis ($r=0.425$; $p<0.05$) in the patients, although rapid catabolism of VLDL particles by the activated hepatic B/E receptors cannot be excluded. In cholesterol malabsorption—at least in hamsters—decreased VLDL secretion and increased hepatic uptake of the VLDL remnants result in LDL lowering by a decreased conversion of VLDL to LDL, without actual activation of the hepatic LDL receptors.³³ In neomycin or sitostanol induced cholesterol malabsorption, a fall in serum LDL cholesterol is associated with a reduction in LDL production, whereas the catabolism of LDL is unaffected.^{4,34,35}

CHOLESTEROL ABSORPTION

Cholesterol absorption, which occurs in the upper part of the small intestine¹¹ and requires micellar solubilisation with bile acids,¹⁰ was subnormal in our patients. The lower biliary bile acid output possibly reduced micellar solubilisation of cholesterol, resulting in impaired cholesterol absorption, even though the latter was not significantly correlated with the biliary secretion or the synthesis of bile acids. In patients with an ileal resection or bypass, bile acid malabsorption is markedly more severe, with no cholesterol malabsorption.²⁸ The positive correlation between faecal bile acids and fat ($r=0.563$; $p<0.01$) might be due to poor micellar formation, but the fact that there was no association of fractional cholesterol absorption with faecal bile acids or fat might be due to absorption of cholesterol only in the upper part of the small intestine, whereas that of fatty acids and unconjugated bile acids takes place more distally. Bacterial deconjugation of bile acids and subsequently disturbed micellar formation and cholesterol absorption cannot be excluded. In fact, in up to two thirds of patients with an ileoanal anastomosis, upper intestine bacterial overgrowth, deconjugation of intestinal bile acids, and increased postprandial serum levels of unconjugated bile acids do occur.^{13 36-38} In addition, the number of anaerobic bacteria, responsible mainly for the deconjugation of bile acids, is positively related to the small intestinal transit time of these patients.³⁹ Thus, our finding that rapid small intestinal transit is associated with well preserved cholesterol absorption indicates low bacterial growth in the proximal small intestine, whereas the opposite is true for those with prolonged transit, as shown by their breath tests. Normally, absorption of cholesterol shows an actual positive correlation with small intestinal transit time.⁴⁰

CHOLESTEROL ABSORPTION, SYNTHESIS, AND BILIARY LIPIDS

Low cholesterol absorption is normally associated with high synthesis and increased biliary and faecal output of cholesterol.⁴¹ In our series of patients with an anastomosis low absorption efficiency was not related to biliary cholesterol secretion ($r=0.247$), to faecal neutral steroids ($r=-0.160$), or to cholesterol synthesis ($r=0.123$), suggesting that the synthesis of cholesterol was not enhanced in relation to their impaired cholesterol absorption. In fact, unexpected positive correlations of absorbed cholesterol with cholesterol synthesis ($r=0.521$; $p<0.01$), with biliary cholesterol secretion ($r=0.854$; $p<0.001$), or with faecal neutral steroids ($r=0.574$; $p<0.01$) suggest that factors impairing cholesterol absorption limited the compensatory increase of cholesterol synthesis. Furthermore, dietary cholesterol was positively correlated with biliary output of cholesterol ($r=0.405$; $p<0.05$) and of bile acids ($r=0.473$; $p<0.05$), even though the correlation with cholesterol synthesis remained insignificant. Increased saturation of bile with cholesterol has previously been observed in patients with ileoanal anastomoses and is suggested to be due

to enhanced faecal bile acid loss.^{7 8} In the present study, the cholesterol saturation and the lithogenic index of the bile tended to be higher and the molar percentage of cholesterol (or lithogenic index) was related to the biliary secretion ($r=-0.669$; $p<0.01$), but not the synthesis of bile acids. Thus, the lower the biliary bile acid output, the higher the cholesterol saturation of the bile. In addition, the correlations of the biliary bile acid output with total cholesterol absorption ($r=0.477$; $p<0.05$), with biliary cholesterol secretion ($r=0.561$; $p<0.05$), and with faecal neutral steroids ($r=0.551$; $p<0.05$) suggest that in the ileal pouch patients, low biliary bile acid output and thus high bile cholesterol saturation are closely related to their impaired absorption of cholesterol and related less to bile acid malabsorption. The marked reduction in the proportion of secondary bile acids, those normally formed by colonic bacteria, resulted in higher proportions of primary bile acids, especially of cholic acid, findings which have also been reported by others.⁸

FAECAL BILE ACIDS

Normally, most conjugated bile acids are reabsorbed in the terminal ileum,⁴² and some unconjugated forms from the small intestine and colon.^{43 44} Minor bile acid malabsorption in patients with an ileal pouch has been related to ileal dysfunction, caused in a majority of these patients by reduced ileal surface and histological inflammation of the pouch mucosa.^{6 45 46} Slightly but significantly higher faecal bile acid excretion was attributable to reduced absorption from 94% in the controls to about 80% in our patients. The proportion of faecal bile acids of cholesterol synthesis in the patients (78%), was higher than in the controls (55%), tending to be even higher (74%) in the patients with an ileal resection.²⁹ The finding that faecal bile acid values were not correlated with the absorption values for vitamin B₁₂, which is an indicator of ileal function, is in agreement with studies in patients after proctocolectomy and ileostomy² and suggests a more proximal distribution of the absorption area for vitamin B₁₂ than for bile acids.²⁹ A quicker small intestinal transit time for the patients with an ileal pouch^{6 47} might also increase their faecal bile acid output.

FAECAL BILE ACID COMPOSITION

In the colon, bacterial enzymes convert bile acids to secondary forms. In addition to the predominant bile acids—deoxycholic acid and lithocholic acid—faeces of healthy subjects also contain several poorly defined bile acid derivatives.^{47 48} In agreement with other studies,^{4 6} the major secondary faecal bile acids, deoxycholic acid and lithocholic acid, were significantly reduced in our patients. In fact, the proportion of cholic acid ranged from 3.5% of total control bile acids to 36% for the patients with an anastomosis, with respective figures for chenodeoxycholic acid of 3% and 22%. Identifiable faecal bile acids of cholic acid and chenodeoxycholic acid origin were similar between patient groups, suggesting that the change in synthesis of the two primary bile acids was similar among patients.

In conclusion, the present data show that in the patients with an ileal pouch, disturbed metabolism of cholesterol is characterised by slight bile acid malabsorption, markedly lower fractional absorption of cholesterol, apparent loss of feedback regulation between absorption and synthesis of cholesterol, and lowered serum total and LDL cholesterol and LDL triglycerides. These findings differ markedly from the metabolic observations in patients with colectomy and ileal stoma without ileal resection, and suggest that the ileal pouch may be a primary factor responsible for the differences. In patients with an ileal pouch, ileal dysfunction apparently causes slight bile acid malabsorption. This alone, however, was hardly reason enough for their less efficient cholesterol absorption, which more probably was related to intestinal bacterial overgrowth. The latter as a toxic factor, or cytokines released from low grade inflammation of the pouch mucosa,⁴⁹ and the absence of colonic production of hepatic nutrients⁵⁰⁻⁵¹ could actually be factors in the only modest compensatory rise in hepatic cholesterol synthesis in relation to cholesterol and bile acid malabsorption. This would also explain the unusual positive correlation of cholesterol synthesis with dietary cholesterol and serum LDL cholesterol levels.

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