Pathogenesis of gall stones in Crohn's disease: an alternative explanation

R Hutchinson, P N M Tyrrell, D Kumar, J A Dunn, J K W Li, R N Allan

Abstract

The increased prevalence of gall stones in Crohn's disease is thought to be related to depletion of the bile salt pool due either to terminal ileal disease or after ileal resection. This study was designed to examine whether this hypothesis is correct and explore alternative explanations. Two hundred and fifty one randomly selected patients (156 females, 95 males, mean age 45 years) were interviewed and screened by ultrasonography to determine the prevalence of gall stones in a large population of patients with Crohn's disease. Sixty nine (28%) patients had gall stones proved by ultrasonography (n=42), or had had cholecystectomy for gall stone disease (n=27). The risk factors for the development of gall stones including sex, age, site, and duration of disease, and previous intestinal resection were examined by multivariate analysis. Age and duration of disease were positive risk factors for gall stones and were covariables. The site of disease and of previous intestinal resection did not predispose to gall stones. Previous surgery was an independent risk factor for the development of gall stones, the risk increasing with number of laparotomies. It is suggested that mechanisms other than ileal dysfunction may predispose to gall stones. Postoperative gall bladder hypomotility with biliary sludge formation may be precursors of gall stone formation in patients with Crohn's disease.

(Gut 1994; 35: 94-97)

Several studies have shown an increased prevalence of gall stones in patients with inflammatory bowel disease. Surveys using cholecystography have shown gall stones in 30-34% of patients with Crohn's disease.^{1,2} The high prevalence of gall stones has been established in an ultrasonographic study,³ where 34% of terminal ileal Crohn's disease patients had gall stones compared with 8% among healthy, age and sex matched controls. The prevalence of gall stones is lower in patients with colonic Crohn's disease⁴ and is 24.5% in patients after ileostomy or ileal resection for inflammatory bowel disease.⁵

The pathogenesis of gall stones in these patients is usually attributed to the disturbance in the enterohepatic circulation of bile salts because of disease or removal of terminal ileum.⁶ The accepted mechanism is that intestinal disease or resection leads to a decrease in the total bile acid pool, leading to supersaturated gall bladder bile, which predisposes to gall stone formation. It is now clear, however, that lithogenic bile alone will not lead to cholelithiasis, and

that other factors are necessary for gall stone formation including nucleation factors and gall bladder stasis.^{7,8}

Clinically we noted a high incidence of gall stones in patients with Crohn's disease but there was no obvious correlation with terminal ileal disease, which suggested that gall stones were not necessarily attributable to the disturbance in the enterohepatic circulation of bile salts. We therefore surveyed a large number of patients with Crohn's disease to determine the prevalence of gall stones and the risk factors for their development.

Patients and methods

Two hundred and fifty one consecutive patients with Crohn's disease attending the inflammatory bowel disease clinic were studied and clinical details of their Crohn's disease and any biliary disease was recorded. The details of Crohn's disease, which were recorded and verified from the case notes, included duration, site of disease (small bowel, large bowel or both), and site and extent of any previous resection. Site of macroscopic Crohn's disease was determined by radiological methods, supplemented with information from surgical exploration and histological examination when available. The case notes, operation notes, and histology reports of all patients previously treated by cholecystectomy were reviewed and the diagnosis of gall stones established. Patients were questioned about symptoms characteristic of cholelithiasis, and on this basis, those treated by cholecystectomy were divided into symptomatic and non-symptomatic groups.

Those patients with an intact gall bladder had abdominal ultrasound scanning on the same day as their clinic attendance.

ANALYSIS OF DATA

The overall prevalence of gall stones in patients with Crohn's disease was determined and related to sex, age, duration of disease, site of disease, and number and site of previous intestinal resections. The BMDP statistical software package was used for data analysis.⁹ The Mann-Whitney U test, the χ^2 test, and the χ^2 test for linear trend were used for statistical comparisons. A multivariate stepwise discriminant analysis was performed to identify independent factors associated with gall stones. The values from the final model are presented. The analysis was repeated removing the most influential variable to determine any correlations inherent in the data.

The General Hospital,
Steelhouse Lane,
Birmingham
R Hutchinson
P N M Tyrrell
D Kumar
J A Dunn
J K W Li
R N Allan

Correspondence to:
Mr R Hutchinson, Research
Registrar, Department of
Surgery, Queen Elizabeth
Medical Centre, Edgbaston,
Birmingham B15 2TH.

Accepted for publication
10 May 1993

Figure 1: Summary of patients.

Results

There were 156 (62%) women (mean age 45 years, range 17–75), and 95 (38%) men (mean age 45 years, range 14–82). The mean duration of Crohn's disease was 17 years (range 1–54). The site of macroscopic Crohn's disease was ileum in 121 (48%), colon in 76 (30%), and both ileal and colonic disease in 54 (22%).

PREVALENCE OF GALL STONES (Fig 1)

Two female patients and one male patient had had cholecystectomy before the diagnosis of their Crohn's disease and are excluded from the analysis. Sixty nine (28%) of the remaining 248 patients either had gall stones on ultrasonographic screening (n=42) or had previously had cholecystectomy for gall stone disease (n=27). Cholecystectomy had been undertaken for symptomatic cholelithiasis in 15 and 'incidentally' for gall stones detected at laparotomy for Crohn's disease in 12. Only three of 42 cases detected by ultrasound reported recurrent attacks of biliary colic. Although the overall prevalence of gall stones in this series was 28%, only 7% had symptomatic stones.

Figure 2: Prevalence of gall stones in different age groups.

Results table

Factor	Groups	Gall stones		Degrees of freedom	χ^2 value	P Value
		Yes	No			
Sex	Females	42	112			
	Males	27	67	1	0.06	0.08
Age (y)	<20	1	8			
	21–30	10	44			
	31–40	10	43			
	41–50	18	32			
	51–60	8	22			
	>61	22	30	1	10.0*	0.002
Duration of disease (y)	0–5	9	38			
	6–10	9	31			
	11–15	11	40			
	16–20	10	32			
	21–25	6	13			
	26–30	5	7			
	>31	19	18	1	12.65*	0.0004
Site of disease	Ileal	32	87			
	Colonic	17	58			
	Both	20	34	2	3.33	0.19
Previous laparotomy	Yes	62	131			
	No	7	48	1	8.02	0.005
Number of previous laparotomies	0	7	48			
	1	19	59			
	2	10	25			
	3	9	18			
	4	11	12			
	>5	13	17	1	14.06*	0.0002
Site of resection	Ileal	24	57			
	Colonic	15	26			
	Both	23	48	2	0.61	0.74

* χ^2 test for linear trend.

UNIVARIATE ANALYSIS OF RISK FACTORS (Table)

Sex

Sex did not influence the probability of gall stones as 42 (27%) of 154 women with Crohn's disease had gall stones at some time, compared with 27 (29%) of 94 men ($\chi^2=0.06$, $df=1$, $p=0.8$, not significant).

There was some evidence that sex may be a risk factor for symptomatic gall stones. Of 42 women with gall stones, 14 (33%) were symptomatic, whereas only four (15%) of 27 men with gall stones had symptoms ($\chi^2=2.92$, $df=1$, $p=0.09$).

Age

The median age at which gall stones were detected was 47 years (range 20–82). The median age of the 179 patients without gall stones was 39 years (range 14–75). The prevalence of gall stones increased with age and was 42% in patients over 60 years of age (Fig 2). The association of gall stones with age was statistically significant ($\chi^2_{(trend)}=10.0$, $df=1$, $p=0.002$).

Duration of disease

The median duration of Crohn's disease among patients with gall stones was 19 years (range 1–54) at the time of diagnosis of the gall stones. The median duration of Crohn's disease in patients without gall stones was 13 years (range 1–50).

Figure 3 shows the prevalence of gall stones related to the duration of Crohn's disease. The prevalence of gall stones increases with duration of disease and rises to 51% in patients with Crohn's disease for more than 30 years. The association of gall stones with duration of Crohn's disease was statistically significant ($\chi^2_{(trend)}=12.65$, $df=1$, $p=0.0004$).

Figure 3: Prevalence of gall stones and duration of Crohn's disease.

Site of macroscopic disease

Of 69 patients with gall stones, 32 (46%) had predominantly ileal disease, 17 (25%) colonic disease, and 20 (29%) both ileal and colonic disease. The site of macroscopic disease was similar to that in patients without gall stones (Fig 4) and there was no association of gall stones with site of disease ($\chi^2=3.33$, $df=2$, $p=0.19$, not significant).

Previous laparotomy for Crohn's disease

One hundred and ninety three (78%) of 248 patients had had at least one laparotomy for complications of their Crohn's disease, and 62 (32%) were found to have gall stones. Fifty five (22%) of the 248 patients had not had any abdominal surgery. Only seven (13%) of the conservatively treated patients had gall stones. Ninety per cent of the patients with gall stones had at least one laparotomy compared with 73% of the patients without gall stones. There was a significant difference in the prevalence of gall stones between those patients who had had laparotomy and the group treated conservatively ($\chi^2=8.02$, $df=1$, $p=0.005$).

Furthermore, the risk of gall stones was strongly associated with the number of previous laparotomies ($\chi^2_{(trend)}=14.06$, $df=1$, $p=0.0002$) (see Fig 5).

Figure 4: Site of disease and risk of gall stones.

Site of intestinal resection

Twenty four (39%) of 62 patients with gall stones and previous surgery had had ileal resection, 15 (24%) colonic resection, and 23 (37%) both ileal and colonic resections. Of the 131 patients who had had previous surgery but who did not have gall stones, 57 (44%) had had ileal resection, 26 (20%) colonic resection, and 48 (37%) both ileal and colonic resections. The site of resection was similar in the groups with and without gall stones, and therefore, there was no association of gall stones with site of intestinal resection ($\chi^2=0.61$, $df=2$, $p=0.74$, not significant).

MULTIVARIATE ANALYSIS OF RISK FACTORS

The multivariate stepwise discriminant analysis confirmed the results of the univariate analysis and identified age, duration of disease, and number of previous laparotomies as the significant factors associated with gall stones. Age and duration of disease were not, however, independent factors for gall stones but were so highly correlated (correlation coefficient $r=0.7$, $p<0.001$) that only one of these factors entered the final discriminant model. Duration of disease was more significantly associated with gall stones. Therefore, the discriminant model identified duration of disease (F to remove=12.65, $df=1,246$, $p<0.005$) and number of laparotomies (F to remove=4.98, $df=2,245$, $p=0.01$) as the only independent risk factors. Repeating the analysis excluding duration of disease, the model identified age (F to remove=10.51, $df=1,246$, $p<0.005$) and number of laparotomies (F to remove=8.45, $df=2,245$, $p<0.005$) as the two independent factors. Therefore, number of previous operations was a risk factor for gall stones independent of age and duration of Crohn's disease.

Discussion

Twenty eight per cent of our patients with Crohn's disease had gall stones confirming the increased prevalence of gall stone disease.¹⁻³ The 'true' prevalence of gall stones in Crohn's disease is uncertain because our sample of clinic attenders is not representative of the whole population with Crohn's disease. Nevertheless, it is the largest survey of its kind and includes patients with all types of disease. Other studies have assessed small numbers of patients or confined the analysis to certain subgroups of patients with Crohn's disease. For example, Cohen *et al* studied only 41 patients.² The ultrasonographic survey by Whorwell *et al* included 38 patients over 30 years of age with terminal ileal Crohn's disease.³ In the study by Hill *et al*, only 33 of 108 patients with ileostomies had Crohn's disease.⁵

We found the risk of gall stones was associated with increasing age as occurs in the general population.¹⁰ The prevalence of gall stones was 26% in women less than 50 years old and 30% in women more than 50 years old. It was 24% in men less than 50 years old and 39% in men more than 50 years old. These figures are much higher than corresponding figures for the healthy general population. The prevalence of gall stones among healthy white women less than 50 years

Figure 5: Prevalence of gall stones and number of previous laparotomies.

old is 5–15% and about 25% above this age. The equivalent figures for gall stone prevalence in men are 4–10% and 10–15% respectively.^{10 11} Gall stones were associated with increasing duration of Crohn's disease but this factor was associated with age.

In contrast with studies of gall stone prevalence in the general population, sex was not a risk factor for gall stones in Crohn's disease. Surveys of the general population suggest that the female: male ratio is highest in the younger age groups, falling to a ratio of 2:1 above 50 years of age.^{10 11}

Our study has shown no relation between gall stones and the site of macroscopic disease or resection. It is possible that there were differences between the groups in the extent of microscopic ileal disease and degree of ileal dysfunction as we did not assess ileal function, and the site of disease was determined with conventional radiological techniques. The increased prevalence of gall stones has been attributed to either ileal disease or ileal resection.^{1–3} Depletion of the bile salt pool has been proposed as the likely mechanism leading to lithogenic bile.^{1 12 13} This theory is attractive but not universally accepted as some authors have found normal or even low cholesterol saturation of bile after ileal resection.^{14 15}

Previous laparotomy was a significant, independent risk factor for the development of gall stones, and the risk increases with the number of operations. Patients with Crohn's disease treated without surgery had a 13% prevalence of gall stones, which is similar to that reported in the general population.¹⁰ Whether severity of disease is also a risk factor for the development of gall stones cannot be determined from our data as most patients who require surgery have either severe disease or a complication of Crohn's disease.

Gall stones have been reported after cardiac surgery,¹⁶ bariatric surgery,¹⁷ and gastrectomy.¹⁸ One study found a 28% cumulative prevalence of gall stones within three years of major abdominal surgery.¹⁹ Gall bladder sludge occurred in nearly half the patients within one month of gastrectomy and 18% eventually develop gall stones.²⁰ As well as occurring commonly after abdominal surgery, biliary sludge occurs commonly after prolonged fasting,²¹ during total parenteral

nutrition,^{22 23} and among patients in intensive care units.²⁴ Biliary sludge formation is associated with 'bowel rest' and gall bladder stasis, and is a precursor of gall stones.^{7 20–23 25}

Patients with Crohn's disease requiring surgery are often subject to prolonged fasting or total parenteral nutrition and this may explain the high prevalence of gall stones after surgery in this study. We have not studied gall bladder motility and sludge formation after surgery in patients with Crohn's disease, and such studies are needed to examine the importance of these factors in the pathogenesis of gall stones. Our findings, however, that the number of previous operations was a significant, independent risk factor for the development of gall stones, and that site of disease or of resection were not risk factors, lead us to suggest that surgery itself, or factors associated with the operation predispose to gall stones. Mechanisms other than ileal dysfunction may be important in the pathogenesis of gall stones in Crohn's disease.

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