ORIGINAL INVESTIGATION

Gallstone Disease and Related Risk Factors in Patients With Crohn Disease

Analysis of 330 Consecutive Cases

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Background: The reported prevalence of gallstone disease (GD), defined as current gallstones or previous cholecystectomy for gallstones, in patients with Crohn disease ranges from 13% to 34%. The aim of this study was to characterize the still undefined risk factors of this complication.

Methods: A total of 330 consecutive patients with Crohn disease (189 males and 141 females aged 17-82 years, mean±SD age, 41±14 years) underwent liver ultrasonography.

Results: A diagnosis of GD was made in 78 patients (24%), 54 with current gallstones and 24 who had undergone previous cholecystectomy. Its frequency was comparable in males and females (23% vs 25%), but was significantly associated with age ($P=.001$), being 13%, 36%, and 51% in patients aged 44 years and younger, 45 to 59 years, and 60 years and older, respectively ($P=.001$). Its prevalence significantly differed according to the site of the disease at diagnosis ($P=.02$) and was unrelated to disease duration. Gallstone disease was more frequent in patients who had undergone surgery (34% vs 14%; $P=.001$) and was significantly associated with the number ($P=.001$) and site of bowel resections ($P=.001$), increasing from 28% in the patients who had undergone 1 resection to 53% in those having had 2 or more resections ($P=.005$) and being significantly higher in patients with a resection involving the ileocecal region. Multivariate analysis showed that age; site of disease at diagnosis; and the presence, number, and site of bowel resections were significantly related to GD.

Conclusions: In patients with Crohn disease, the frequency of GD is significantly higher than that reported in the general population with comparable characteristics ($z=5.04$, $P<.001$). Age; site of disease at diagnosis; and the history, number, and site of bowel resections are independently associated with GD.

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THE REPORTED prevalence of gallstones in patients with Crohn disease ranges from 13% to 34% in different series, accounting for a total of about 700 patients.[1-10] However, some of these studies included selected patients (eg, all having surgery)[3,6,8] or patients with disease limited to the terminal ileum[4] and others enrolled only a few patients,[1,2,5,7] thus limiting the validity and precision of the estimate. Furthermore, only few and controversial data are available concerning the role of different risk factors for gallstones in these patients, some of which may be similar to those in the general population (eg, sex, age, body mass index, parity) and others may be disease specific, such as the site and duration of inflammatory bowel disease, and the history and/or extent of bowel resections.

The pathogenesis of gallstones in Crohn disease still remains to be elucidated. For many years, it was mainly attributed to bile acid malabsorption in the diseased or resected ileum leading to hepatic excretion of cholesterol-supersaturated bile,[1,4,11] but the fact that one study found that bile cholesterol saturation was significantly lower in patients with Crohn disease than in controls[12] indicates that other factors may play a role in gallstone formation.

The aims of this ultrasonographic study of a large series of consecutive patients with Crohn disease were to evaluate the prevalence of gallstone disease (GD), defined as actual gallstones or previous cholecystectomy for gallstones, and to assess the possible related risk factors.

RESULTS

Of the 330 patients examined (189 male and 141 female; mean±SD age, 41±14 years), GD was diagnosed in 78 patients (24%). Of the 54 patients with current gallstones (69%), 26 had a single one, 11 had more than one, and 17 had microlithiasis. Of the 24

PATIENTS AND METHODS

From January 1 to December 31, 1999, all consecutive inpatients and outpatients attending the referral center for Crohn disease at Milan (Italy) University's Postgraduate School of Gastroenterology gave their written informed consent to the study, which was approved by the Ethics Committee of IRCCS Ospedale Maggiore, Milan.

In the case of the 301 patients with certain Crohn disease followed up for a mean ± SD of 9 ± 7 years, their medical records were retrospectively analyzed to establish the time from Crohn disease diagnosis, disease location, and the history and characteristics of previous operations involving the small intestine and/or colonic segments; in the case of the 29 newly diagnosed patients, all the data from their medical records were recorded. The patients who had undergone previous cholecystectomy for gallstones were not enrolled if the surgery had been performed before the diagnosis of Crohn disease.

The sex, age, and body mass index (calculated as weight in kilograms divided by square of height in meters) of all the patients were recorded. For the purposes of this study, 3 age groups were arbitrarily defined: 44 years and younger, 45 to 59 years, and 60 years and older. The location of Crohn disease at the time of diagnosis was classified as ileal, ileocecal, ileal and colonic, or colonic (with or without rectal involvement).

After an overnight fast, all the patients underwent liver ultrasonography (US) using an ATL 5000 apparatus (Advanced Technology Laboratories, ATL Inc, Washington, DC) equipped with 3.5- and 7.5-MHz probes. All of the US examinations were performed by 2 of us (M.F. and A.C.) with specific, long-term training. Gallstone disease was defined as the presence of stones with echoes and an acoustic shadow within a visible gallbladder lumen[13] or the absence of the gallbladder due to its surgical removal after the diagnosis of Crohn disease.

The following variables were considered in the statistical analysis: sex, age class (≤44, 45-59, and ≥60 years), body mass index, location of Crohn disease at diagnosis (as classified above), disease duration (≤5, 5-10, and >10 years), number of bowel resections (1 or ≥2), and site of bowel resections (divided on the same basis as the disease location classification), nephrolithiasis (present or absent), and liver steatosis (present or absent). The differences between patients with or without GD were evaluated using the χ^2 test with continuity correction in the 2×2 contingency table; the χ^2 test for trend was carried out in the case of more than 2 classes.

A multivariate analysis was performed using logistic regression analysis (with GD as the dependent variable) and a backward procedure. Factors with more than 2 classes of variables were considered using dummy variables, thus allowing a comparison between the classes with a higher prevalence of GD and the lowest frequency reference class. The goodness of fit was checked by means of the Hosmer-Lemeshow test and the analysis of residuals.[14] Prevalence and odds ratios were calculated with their 95% confidence intervals. The prevalence of GD in our series was compared with that in the general population by means of a z test. $P<.05$ was considered statistically significant.

patients having previously undergone cholecystectomy (31%), 3 had had emergency laparotomy for acute cholecystitis and 5 for recurrent biliary colic, and the remaining 16 had been operated on during the course of laparotomy for intestinal and/or colonic resections. In the last group of 16 patients, the presence of cholelithiasis had already been demonstrated by US before laparotomy and 10 of these patients had experienced biliary colic(s) within 3 to 10 months before the surgical procedure, which was performed for symptoms related to the intestinal involvement.

The results of the univariate analysis are given in **Table 1**, which shows the variables that were significantly associated with GD. The prevalence of GD was similar in male and female patients (23% vs 25%) and showed a significant age-related linear increase, being 13%, 36%, and 51% in the patients 44 years and younger, 45 to 59 years, and 60 years and older, respectively ($P=.001$). It was also significantly associated with the location of Crohn disease at diagnosis ($P=.02$), but not with disease duration ($P=.36$), body mass index (22.3 ± 2.07 in the patients with GD and 22.3 ± 2.04 in those without; $P=.89$), or the presence of liver steatosis (20% in patients with GD and 12% in those without; $P=.10$). None of the patients with GD, but 8% of those without GD, showed the concomitant presence of nephrolithiasis. Gallstone disease was more frequent in patients who had undergone surgery (34% vs 14%; $P=.001$) and increased linearly with the number of resections, being significantly higher in the patients who had undergone 2 or more resections (53% vs 28%; $P=.005$).

As shown in **Table 2**, multivariate analysis showed that age class, the site of Crohn disease at diagnosis, and a history of previous bowel resections were independently associated with GD in our first model. In a second multivariate model (which included the number of bowel resections), the odds ratios for age and site of bowel disease at diagnosis remained substantially unchanged. Finally, when the site of bowel resections was considered, only age and the site of resection were independently associated with GD. The goodness of fit of the first 2 multivariate models was very similar ($P=.84$ and $P=.83$); the third showed a lower value ($P=.62$).

Considering pairs of variables, the highest odds ratio (38.0; 95% confidence interval, 11.8-122.5) was found in patients 60 years and older who had undergone multiple bowel resections compared with those 44 years and younger who had not had resections. When 3 variables were considered together, the highest odds ratio (117.0; 95% confidence interval, 27.1-504.7) was found in patients 60 years and older with ileocecal involvement who had undergone multiple bowel resections compared with those 44 years and younger with ileal involvement who had not had resections.

COMMENT

The prevalence of GD in the present large series of patients with Crohn disease was significantly higher than that observed in a nationwide epidemiological study of

Table 1. Prevalence of Gallstone Disease (GD) in 330 Consecutive Patients With Crohn Disease According to Different Variables*

Variable	Total No. of Patients	No. (%) of Patients With GD	*P* Value
Age class, y			.001
≤44	203	27 (13)	
45-59	90	32 (36)	
≥60	37	19 (51)	
Site of Crohn disease at diagnosis			.02
Ileal	156	28 (18)	
Ileocecal	46	18 (39)	
Ileal and colonic	91	21 (23)	
Colonic	37	11 (30)	
Bowel resections			.001
Absent	173	25 (14)	
Present	157	53 (34)	
No. of bowel resections			.001
0	173	25 (14)	
1	119	33 (28)	
≥2	38	20 (53)	
Site of bowel resections			.001
No resection	173	25 (14)	
Ileal	47	15 (32)	
Ileocecal	40	19 (48)	
Ileal and colonic	54	13 (24)	
Colonic	16	6 (38)	

*Sex, disease duration, nephrolithiasis, and hepatic steatosis were nonsignificant variables.

Table 2. Gallstone Disease in 330 Consecutive Patients With Crohn Disease: Results of Multiple Logistic Regression*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Age class, y		<.001
45-59 vs ≤44	3.14 (1.68-5.85)	
≥60 vs ≤44	6.77 (3.04-15.00)	
Site of Crohn disease at diagnosis		.01
Ileocecal vs ileal	2.93 (1.32-6.51)	
Ileal and colonic vs ileal	1.28 (0.64-2.55)	
Colonic vs ileal	2.16 (0.89-5.23)	
Bowel resection		.007
Present vs absent	2.24 (1.24-4.04)	
No. of bowel resections		<.001
1 vs 0	1.63 (0.85-3.09)	
2 vs 0	5.41 (2.34-12.50)	
Site of bowel resection		.002
Ileal vs none	2.15 (0.97-4.74)	
Ileocecal vs none	4.83 (2.18-10.70)	
Ileal and colonic vs none	1.35 (0.61-3.02)	
Colonic vs none	3.18 (0.99-10.10)	

*Model 1 included age class, site of Crohn disease at diagnosis, and bowel resection; model 2, age class, site of Crohn disease at diagnosis, and number of bowel resections; and model 3, age class and site of bowel resection. See "Patients and Methods" section for explanation.

the general population[15] involving 29 684 subjects with comparable demographic characteristics ($z=5.04$, $P<.001$) in whom the overall prevalence of GD was 13.8% (9.5% in males and 18.9% in females).

Regardless of patient sex, the frequency of GD significantly increased with age, and was significantly higher than that reported in comparable age groups from the general population (17%, 28%, and 61% vs 11%, 20%, and 30% in females; 10%, 43%, and 46% vs 4%, 11%, and 17% in males). It is interesting to note that this difference was mainly due to the 3- and 2-fold higher frequency in male patients 44 years and younger and female patients 60 years and older. This finding is even more striking considering the female-male ratio of GD; in the 3 age groups, it decreased from 2.56 to 1.93 and 1.72 in the reference population and from 1.70 to 0.64 and 1.33 in patients with inflammatory bowel disease, which thus represents a per se relevant risk factor for gallstones and significantly reduces the sex-related difference in the frequency of GD.

Another interesting finding of the present study is the lack of a relationship between the prevalence of GD and body mass index, a factor that has previously been assessed only in the small series of Lorusso et al,[7] with comparable results.

Unlike results reported by Hutchinson et al[9] and Lapidus et al,[10] the present findings indicate that the location of Crohn disease is independently associated with gallstones. The relevance of an ileocecal or colonic location in our series is in agreement with the data from Kangas et al[8] relating to 52 patients with Crohn disease who had already undergone surgery. On the contrary, in another Italian study,[7] the highest risk for GD was observed in patients with small bowel involvement limited to the terminal ileum, but this study involved only 45 patients with Crohn disease, 10 of whom had colonic involvement alone.

Other studies have previously shown that disease duration is an important risk factor for GD in patients with Crohn disease.[7,9] In the study by Hutchinson et al[9] of 251 patients, the prevalence of GD significantly increased with disease duration, approaching 50% after a duration of more than 30 years. Our data failed to confirm this association but the median disease duration in our study was 8 years compared with 19 years in the British series.

In agreement with the findings of others,[9,10] our data indicate that previous surgery and the number of resections are significantly associated with GD in patients with Crohn disease; we have also shown that a resection involving the ileocecal region is more frequently associated with gallstones. This could be explained in various ways: the interruption of the enterohepatic circulation of bile salts and the consequent hepatic excretion of bile with an increased proportion of cholesterol,[16] the absence of mechanisms preventing bacterial overgrowth as a result of the modification of the ileal microclimate,[17,18] and/or the reduction in small intestine transit time.[19] The first mechanism has been accepted for a long time, but recent animal and human data indicate that the excretion of supersaturated bile in patients with a diseased or resected terminal ileum is only transient,[16,20] and a recent study found a significantly lower cholesterol saturation in patients with Crohn disease than in healthy subjects.[21] Furthermore, as reported in patients undergoing major abdominal or cardiac surgery,[22] it may also be due

to a prolonged fasting state and/or the use of total parenteral nutrition,[23] both of which can induce the biliary sludge that represents a prerequisite for gallstone formation.[24,25] A further contributory role in GD formation could be played by reduced gallbladder motility; we did not specifically investigate this aspect, but there is evidence of impaired fatty-meal–induced gallbladder motility in patients with ileal and ileocolonic disease.[26,27] Another possibility is a decreased release and/or hypersecretion of hormones stimulating (eg, cholecystokinin) or inhibiting (eg, somatostatin) gallbladder contractility, as we have recently reported in patients with celiac disease.[28]

We also observed that patients with colonic involvement or resection had an increased risk for GD. In this context, various data indicate that the enrichment of bile with deoxycholic acid (the typical colonic bile acid) leads to increased cholesterol levels that favor gallstone formation.[29,30]

Overall, in the present large series of patients with Crohn disease, the prevalence of GD is significantly higher than that observed in a general population with comparable demographic characteristics. Age, the site of disease at diagnosis, and the number and site of previous resections were all independently associated with GD, the pathogenesis of which is multifactorial.

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