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Gallstone prevalence and risk factors in patients with ulcerative colitis in Korean population

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Abstract

This study aims to evaluate the prevalence, risk factors, and relative risk of gallstones and associated disease in patients with ulcerative colitis (UC). Medical records of 311 patients diagnosed with UC between January 2004 and February 2015 were reviewed retrospectively. To assess relative risk, 622 patients matched by age, sex, and body mass index were included as a control group. Gallstones were detected in 8% (25/311) of UC patients and in 3.9% (24/622) of the control group. Prevalence was significantly higher in the UC group (odds ratio [OR], 2.178; $P = .007$). Mean age of gallstone patients was 57.1 ± 17.8 years in the UC group, and mean disease duration of UC was 67.2 ± 38.8 months. The male-to-female ratio of gallstone patients in the UC group was 2.13:1. Mean interval from diagnosis of UC to detection of gallstones was 17.8 ± 30 months. Six UC patients with gallstones underwent cholecystectomy or endoscopic retrograde cholangiography for symptomatic disease and complications. In univariate analysis, diabetes, hypertension, age ≥65 years, and history of more than 3 admissions were significantly associated with gallstone in UC patients. In multivariate analysis, age ≥65 years (OR, 2.655; $P = .033$) and hospitalization ≥3 times (OR, 4.1; $P = .001$) were statistically significant risk factors for gallstones in UC patients. This study shows that UC patients have a significantly higher risk of gallstones compared to the general population (OR, 2.178; $P = .007$), especially those who are older, with a history of multiple admissions.

Abbreviations: AZA = azathioprine, BMI = body mass index, CD = Crohn disease, CT = computed tomography, GD = gallstone disease, IBD = inflammatory bowel disease, UC = ulcerative colitis.

Keywords: gallstone, risk factors, ulcerative colitis

1. Introduction

The relationship between inflammatory bowel disease (IBD) and gallstones has been recognized since the late 1960s.[1] The occurrence of gallstone in patients with Crohn disease (CD) has been investigated in several studies, with prevalence rates ranging from 13% to 34%.[1–8]

In the general population, major risk factors for gallstone development include female sex, increasing age, and obesity.[9] The prevalence may vary between series relying on the collection of patients. Variances in prevalence have been discovered between countries, and also between different medical centers in the same country.[10] Since several risk factors of gallstones in ulcerative colitis (UC) and CD patients may be comparable to those in the IBD-free population, the precise relative risk for IBD patients of developing gallstones compared by age, sex and a body mass index (BMI)-matched IBD-free control has not been evaluated in detail.[11] Few studies have been case controlled, and they were either not age- or sex-matched, or comprised only a small series of patients.[7,12]

The pathogenesis of gallstones in UC remains uncertain. Results concerning the risk of developing gallstone in UC patients are restricted and inconsistent.[11] The aims of this study were to evaluate the prevalence and relative risk of gallstones in a well-defined cohort of UC patients compared to the general population, matched by age, sex, and BMI and to assess various risk factors of gallstone development in UC patients.

2. Methods

A total of 331 UC patients who had been examined using either abdominal ultrasonography or abdominal computed tomography (CT) in Yeungnam University Hospital from 2004 to 2015 were enrolled in this study. The diagnosis of UC was based on standard clinical, radiographic, endoscopic, and pathological criteria.[13] Patients who already documented gallstone disease (GD) and have a history of cholecystectomy before UC diagnosis were excluded.

The medical records of the patients were reviewed retrospectively. Baseline characteristics including age, underlying disease, severity of disease, number of hospital admissions, treatment, total parenteral nutrition history, disease extent at diagnosis, major surgical intervention, and previously per-

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formed ultrasonography were evaluated. Disease severity and extent were categorized according to Mayo score and Montreal classification, respectively.[12] If there was no applicable Mayo score, the score of the day closest to that of ultrasonography was applied.

For comparing prevalence, 662 patients from the general population who had undergone ultrasonography or abdominal CT scan for health-screening tests at the health promotion center in our hospital from 2010 to 2015 were selected as a control group. Age, sex, and BMI were matched with the UC group. The diagnosis of gallstone was made by ultrasonography or CT scan. We analyzed the risk factors of gallstone in patients with UC. Continuous variables were reported as means ± SD and analyzed using independent *t* tests. Results are expressed as count and percentages (categorical data), and analyzed using Pearson chi-square test or Fisher exact test, as appropriate. A *P* value <.05 was considered statistically significant. A multivariate analysis was performed using logistic regression, assuming GD as a dependent variable. Goodness of fit was checked using the Hosmer–Lemeshow test and residual analysis. Prevalence and odds ratio (OR) were calculated with a 95% confidence interval (CI). Analysis was performed using SPSS version 18.0 (IBM Inc., Chicago, IL). This study was approved by Institutional Review Board of Yeungnam University Hospital (2016-09-001).

3. Results

3.1. Clinical characteristics and prevalence of gallstones

Three-hundred thirty-one UC patients were included in the analysis. Mean age and disease duration were 47.6 ± 17.92 years and 65.5 ± 42.40 months, respectively. Patients included 176 (56.6%) men and 135 (43.4%) women. Mean BMI was 21.9 ± 2.844 kg/m^2. Extent of disease were proctitis in 186 patients (59.8%), left colitis in 43 (13.8%), and extensive colitis in 82 (26.4%). Previous colorectal surgery history was noted in 10 patients (3.2%). Two-hundred fifty-eight patients had a UC severity index ≥3 (82.9%). The number of patients treated with a steroid or azathioprine (AZA) was 146 (46.9%) and 60 (19.3%), respectively (Table 1). Gallstones were diagnosed in 25 UC patients (8%) and 24 in the control group (3.9%, *P* = .007). The estimated risk of gallstones for UC patients was 2.178 (95% CI, 1.222–3.881) after adjustment for age, sex, and BMI.

3.2. Clinical features and gallstone risk factors in patients with UC

In the patients group, mean duration from UC diagnosis to detection of gallstones was 17.8 ± 30 months. Among 25 UC patients with gallstones, 6 patients (24%) underwent cholecystectomy or ERCP (endoscopic retrograde cholangiography) for symptomatic disease or complications.

Mean age of the UC patients with and without gallstones was 57.1 ± 17.84 and 46.9 ± 17.53, respectively. There was no significant difference in mean age between the 2 groups (*P* = .06), but there was significant difference between patients ≥65 and <65 years old (*P* = .033; OR, 2.655; 95% CI, 1.110–6.349). Mean BMI was not significantly different between the 2 groups (*P* = .251). When comparing patients ≥23 kg/m^2 with patients <23 kg/m^2, there was no significant difference in gallstone development (*P* = .058; OR, 2.263; 95% CI, 0.982–5.213). In UC patients, the male-to-female ratio was 1:0.77. Female sex did not increase the risk of gallstone development (*P* = .294; OR, 0.589; 95% CI, 0.246–1.409). The risk factors in the general population were not correlated with those in UC patients.

Male sex showed a high tendency in development of gallstones without statistical significance. In the UC group, there were 10 patients who underwent colorectal surgery. Uncontrolled UC symptoms such as severe diarrhea and massive bleeding (3), colorectal malignancy (5), colon perforation (1), and perirectal abscess (1) were the reasons for colorectal surgery. Previous colorectal surgery history indicated a high tendency of developing gallstones, but did not reach statistical significance.

Hypertension (*P* = .047; OR, 2.799; 95% CI, 1.035–7.569), diabetes mellitus (*P* = .039; OR, 3.325; 95% CI, 1.129–9.793), age ≥65 years (*P* = .033; OR, 2.655; 95% CI, 1.110–6.349), and more than 3 hospitalizations (*P* = .002; OR, 4.099; 95% CI, 1.751–9.595) strongly increased the risk of developing GD in univariate analysis. Among these, age ≥65 years (*P* = .033; OR, 2.655; 95% CI, 1.110–6.349), and hospitalization ≥3 times (*P* = .01; OR, 4.099; 95% CI, 1.751–9.595) reached statistical significance by multivariate analysis (Table 2).

4. Discussion

GD is one of the most common gastrointestinal diseases and represents a major burden on healthcare systems. Most patients

Table 1

Demographic and clinical characteristics of UC patients and the control group.

	UC group (n = 311)	Control group (n = 622)	*P*
Age, mean ± SD	47.7 ± 17.75	48.6 ± 14.15	.369
Sex			
Male	176 (56.6%)	373 (60%)	.323
Female	135 (43.4%)	249 (40%)	.323
BMI, kg/m^2	21.9 ± 2.844	22.1 ± 2.732	.286
Disease duration, mo	65.5 ± 42.40		
Extent of disease			
Proctitis	186/311 (59.8%)		
Lt. colitis	43/311 (13.8%)		
Extensive colitis	82/311 (26.4%)		
UC severity index (≥3)	258/311 (82.9%)		
Previous colorectal	10/311 (3.2%)		
Surgery history			

BMI = body mass index, UC = ulcerative colitis.

Table 2

Gallstone risk factors in patients with UC.

Parameter	UC with Gallstone (n = 25)	UC without Gallstone (n = 286)	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Age ≥65	9 (36%)	50 (17.5%)	2.655	1.110–6.349	.033	2.655	1.084–6.505	.033
Sex (female)	8 (35.0%)	127 (44.4%)	0.589	0.246–1.409	.294			
Hypertension	6 (24%)	29 (10.1%)	2.799	1.035–7.569	.047	1.787	0.597–5.352	.244
Diabetes	5 (20%)	20 (7%)	3.325	1.129–9.793	.039	1.383	0.394–4.849	.477
BMI ≥ 23	15 (60%)	114 (399%)	2.263	0.982–5.213	.058			
Previous colonSurgery history	1 (4%)	9 (3.1%)	1.282	0.156–10.553	.573			
Disease duration, y					.596			
<5	3 (12%)	47 (16.4%)						
5–10	10 (40%)	112 (39.2%)						
≥10	12 (48%)	127 (44.4%)						
Extent of disease					.110			
Proctitis	19 (76%)	167 (58.4%)						
Left colitis	2 (8%)	41 (14.3%)						
Extensive colitis	4 (16%)	78 (27.3%)						
UC severityIndex (≥3)	17 (68%)	241 (84.3%)	0.397	0.162–0.975	.051			
≥3 times of hospitalization	11 (44%)	46 (16.1%)	4.099	1.751–9.595	.002	4.100	1.732–9.701	.001
Steroid Treatment	8 (32%)	138 (48.3%)	0.505	0.211–1.207	.118			
AZA treatment	1 (4%)	59 (20.6%)	0.160	0.021–1.209	.060			
TPN history	9 (36%)	132 (46.2%)	0.656	0.281–4.534	.382			

AZA = azathioprine, BMI = body mass index, TPN = total parenteral nutrition, UC = ulcerative colitis.

with gallstones remain asymptomatic, and generally they do not need further treatment. In Western nations, the gallstone prevalence among Caucasian is 10% to 15%, and is lower in Asians and Africans.[14,15] The prevalence of gallstones in Asia varies from 3% to 10%, and it ranges from 2% to 5% in Korea.[14] In this study, the prevalence of gallstones in the control group was 3.9% and was similar to previous Korean data. The prevalence of gallstones in patients with UC in this study was significantly higher than that in age-, sex-, and BMI-matched general populations (8% vs 3.9%; $P = .007$; OR, 2.178; 95% CI, 1.22–3.88). We observed prevalence of gallstones 2 times greater in patients with UC than in the matched general population. In spite of known information of a causal association between IBD and gallstones, the accurate relative risk of this extra-intestinal manifestation of IBD patients has not been well evaluated. This could be owing to the deficiency of well controlled cohort studies. The included patients in previous studies could not represent the entire IBD population.[11,16,17] To find out the actual relative risk of gallstones in IBD, the inclusion of patients irrespective of disease severity, in addition to the collection of a well matched control group with similar age, sex, and environmental area is important to diminish the effect of those environmental, and genetic factors that influence to gallstone formation.[18,19] Many studies have investigated the prevalence and risks for gallstones associated with IBD. The prevalence of gallstone in patients with CD ranges from 13% to 34%. It is higher compared with those of general population.[3,20,21]

Parente et al[11] reported that patients with CD were twice as likely to develop gallstones than well matched controls. Another study based on ultrasonography also showed that the prevalence of gallstones in CD patients was 13.5%. That is nearly twice as high as that (7%–8%) for age-matched control group in the same area.[13] The physiological reason about the higher prevalence of gallstones in patients with CD involves the decreased absorption of bile acids in patients with widespread involvement of the terminal ileum, or following resection of ileum.[7,22]

In contrast to CD, the prevalence of gallstones in patients with UC remains controversial issue. Two recent sonographic surveys showed that patients with UC are less affected by gallstones compared to the general population.[13,23] Findings consistent with the present study have also been reported. A case–control study showed an increased risk of gallstones in both patients with CD (OR, 3.6) and patients with UC (OR, 2.5). The risk was highest in patients with CD involving the distal ileum (OR, 4.5), and in patients with total UC extending to the cecum (OR, 3.3).[7] In another study by Ha et al[23], the prevalence was significantly higher than that of the general population (13.8% vs 3.1%). The prevalence of gallstone was almost 4 times higher in patients with UC than in the control group. The reason for conflicting results about the prevalence in previous studies could be associated with relatively small number of patients. In each study, the different proportion of disease extent and severity of enrolled UC patients can be the cause of conflicting results.

The risk factors for the development of gallstones include high BMI, diabetes mellitus, estrogen and pregnancy, hemolytic diseases, and cirrhosis. Other suggested risk factors include rapid weight loss on low-calorie diets or following bariatric surgery, and low physical activity.[17,24–31] In the present study, hypertension, diabetes mellitus, age ≥65 years, and more than 3 hospitalizations were significant risk factors. Age ≥65 years and hospitalization ≥3 times reached statistical significance in multivariate analysis. Hospitalization ≥3 times indicates multiple UC flare-ups because almost causes of hospitalization in UC patients are flare-up. Therefore, we presume that multiple UC flare-ups are intimately related with developing gallstones. UC-related factors such as disease extent at diagnosis, activity of disease, steroid or AZA use, and colon surgery history were not statistically significant for development of gallstones. Other studies demonstrated BMI and extent of disease as risk factors for gallstones in patients with UC,[7] but there was no statistical significance in our study. The results could be due to the proportion of disease extent in our study. Because proctitis was present in almost 60% of patients in the present study, proctitis

was most frequent disease extent in both groups. Overall BMI of enrolled patients was low (21.9±2.844). It could be associated with decreased food intake due to chronic disease course and accompanying symptoms, including abdominal pain, diarrhea, and hematochezia. It was the reason that high BMI could not reach statistical significance in this study.

The present study has intrinsic limitation due to its retrospective nature and single-center design. Our single-center data may not represent character of UC patients in Korea. We could not evaluate the comorbidities of controls, which could be a risk factor for gallstones. The inclusion of patients with diabetes and hypertension also could be a confounding factor. However, there has been no clear association of these comorbidities with the development of gallstone yet. Although we consider these factors, the flare-up of UC was an independent factors. We also could not determine the exact time between the diagnosis of UC and development of gallstones, as well as details such as number, size, and nature of gallstones. In addition, there is time difference between patients and control group and it could be affect the diagnosis and detection due to technical aspect. Despite these limitations, relatively large numbers of patients and controls were included in the analysis compared with previous studies, and we found the significant risk factors by multivariate analysis. Previous studies mentioned several risk factors in univariate analysis, but none of these factors reached statistical significance in multivariate analysis.[11,23] In this study, however, significant risk factors were found in multivariate analysis.

In conclusion, patients with UC had a higher prevalence of gallstones compared to age- and sex-matched general populations. Old age, multiple hospitalizations, hypertension, and diabetes mellitus indicated increased risk for gallstones. Patients with multiple UC flare-ups or old age should be screened for gallstones, and control of UC activity could be an option for prevention of gallstones. We cautiously suggest that screening for gallstone in UC patients with risk factors is needed, and gallstone complication could be also included in the causes of abdominal pain in UC patients with these risk factors.

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