

Chronological changes in epidemiologic features of patients with gallstones over the last 20 years in a single large-volume Korean center

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Purpose: South Korea has a high prevalence of gallstones, the type of which could be influenced by changes in diet and socioeconomic status. Here we aimed to investigate the epidemiological characteristics and changing patterns of gallstones over the past 20 years in Korea.

Methods: A total of 5,808 patients who underwent cholecystectomy due to gallstones at Seoul National University Hospital between 1996 and 2015 were analyzed. Patients were divided into 4 subgroups: period 1 (1996–2000, n = 792), period 2 (2001–2005, n = 1,215), period 3 (2006–2010, n = 1,525), period 4 (2011–2015, n = 2,276). Gallstones were classified by type: pure cholesterol (PC), mixed cholesterol (MC), calcium bilirubinate (CB), black pigment (BP), and combination (COM).

Results: The female to male ratio was 1.16 with mean ages of 53.6 and 55.3 years old, respectively. The ratio of cholesterol stones to pigment stones was 0.96:1. The mean age and male to female ratio of the patients increased over time. The proportion of cholesterol vs pigment stone did not differ significantly. Proportions of PC and MC stone subtypes did not change notably, whereas proportion of BP stones increased (34.0% to 45.5%), and CB stones decreased (20.7% to 5.3%).

Conclusion: Gallstone types and occurrences were affected by environmental changes, and pigment stones remained common in Korea. Although no distinct increase in cholesterol stones was noted, the proportion of CB stones decreased. As the mean age at gallstone presentation increases, BP stones could become more prevalent.

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Key Words: Cholecystolithiasis, Cholelithiasis, Classification, Gallstones

INTRODUCTION

The incidence rate of gallstones varies among geographic areas and ethnicities worldwide. However, studies of the prevalence of gallstone disease in South Korea are lacking. Ultrasonographic surveys of the adult population reported that the prevalence of gallstones has changed from 0.72% to 2.7% [1,2].

Gallstone formation is influenced by constitutional and environmental factors [3]. Many previous investigators reported

that the occurrence of gallstones is highly related to advanced age, female sex, obesity, body mass index (BMI), pregnancy, rapid weight loss, drugs, diet, metabolic disorders, and genetic factors. Due to differences in socioeconomic status, gallstone prevalence and types vary among developed and developing countries or regions.

Therefore, the patterns of gallstone occurrence in Korea could be changed by the environment and socioeconomic status. This study aimed to explore the chronological changes in epidemiologic characteristics and analyze changing patterns of

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gallstone occurrence over the past 20 years.

METHODS

From 1996 to 2015, a total of 7,728 patients underwent cholecystectomy due to various etiological factors at Seoul National University Hospital (SNUH). Among them, cases of gallbladder polyps, sludge, intrahepatic duct stones, and common bile duct stones as well as those of patients with no records of gallstones were excluded. Finally, 5,808 patients were included in this study. Age, sex, region, and BMI were collected through medical records. Patients were divided into 4 subgroups: period 1 (1996–2000), period 2 (2001–2005), period 3 (2006–2010), and period 4 (2011–2015).

Gallstones were classified into pigment stones and cholesterol stones and subdivided into pure cholesterol (PC), mixed cholesterol (MC), calcium bilirubinate (CB), black pigment (BP), and combination (COM) stone subtypes based on external appearance (color, shape) and internal structure (cross-sectional shape) according to the Japanese Society of Gastroenterology classification system proposed in 1986 [4]. The patients' gallstone characteristics were analyzed according to period, while gallstone types were analyzed by sex and residential area.

Continuous data are expressed as mean ± standard deviation and were assessed using Pearson linear function test. Categorical variables were compared using the chi-square test and linear-by-linear test; correlations were considered significant at the P < 0.05 level. This study was approved by the

Institutional Review Board of SNUH (approval number: 1709-057-884).

RESULTS

Characteristics of all patients

The number of overall patients with gallstones has continuously increased over the past 20 years (period 1, 792; period 2, 1,215; period 3, 1,525; and period 4, 2,276; P = 0.018). The mean patient age was 54.4 years old (range, 8–94 years); 53.7% were female and 46.3% were male. The mean patient BMI was 24.4 kg/m². The patient characteristics are shown in Table 1.

The proportion of cholesterol stones slightly increased (period 1, 45.3%; period 2, 49.2%; period 3, 50.6%; and period 4, 49.2%), while that of pigment stones decreased (period 1, 54.7%; period 2, 50.8%; period 3, 49.4%; and period 4, 50.8%); there was no statistically significant difference between the 2 types (P = 0.115). The proportions of the 5 gallstone subtypes gradually altered over time (P < 0.001) (Table 1). Overall, the proportion of cholesterol stone subtype did not increase significantly; on the other hand, BP stones showed an increasing tendency (P = 0.076), while CB stones decreased significantly (P = 0.006) (Fig. 1).

Change in patient age over time

The mean age of pigment stone patients was older than that of the cholesterol stone patients (56.5 vs. 52.1, respectively, P < 0.001). Throughout the groups, patient age showed a gradually

Table 1. Changes of gallstone types and patients' characteristics according to periods

Variable	Total (n = 5,808)	Periods				P-value
		1996–2000 (n = 792)	2001–2005 (n = 1,215)	2006–2010 (n = 1,525)	2011–2015 (n = 2,276)	
Age (yr)	54.4 ± 14.1	53.2 ± 13.1	53.9 ± 13.9	54.9 ± 14.3	54.6 ± 14.4	0.014
Sex						
Male	2,692 (46.3)	346 (43.7)	564 (46.4)	683 (44.8)	1,099 (48.3)	0.035
Female	3,116 (53.7)	446 (56.3)	651 (53.6)	842 (55.2)	1,177 (51.7)	
Body mass index (kg/m ²)	24.4 ± 3.4	24.0 ± 3.3	24.2 ± 3.2	24.5 ± 3.4	24.5 ± 3.6	0.719
Region						
Urban	5,055 (87.0)	673 (85.0)	1,054 (86.7)	1,325 (86.9)	2,003 (88.0)	0.033
Rural	753 (13.0)	119 (15.0)	161 (13.3)	200 (13.1)	273 (12.0)	
Group						
Pigment	2,959 (50.9)	433 (54.7)	617 (50.8)	753 (49.4)	1,156 (50.8)	0.115
Cholesterol	2,849 (49.1)	359 (45.3)	598 (49.2)	772 (50.6)	1,120 (49.2)	
Subgroup						
BP	2,304 (39.7)	269 (34.0)	408 (33.6)	591 (38.8)	1,036 (45.5)	<0.001
CB	655 (11.3)	164 (20.7)	209 (17.2)	162 (10.6)	120 (5.3)	
MC	1,920 (33.0)	246 (31.0)	416 (34.2)	499 (32.7)	759 (33.3)	
PC	774 (13.3)	106 (13.4)	161 (13.3)	230 (15.1)	277 (12.2)	
COM	155 (2.7)	7 (0.9)	21 (1.7)	43 (2.8)	84 (3.7)	

Values are presented as mean ± standard deviation or number (%).

BP, black pigment; CB, calcium bilirubinate; MC, mixed cholesterol; PC, pure cholesterol; COM, combination.

increasing trend over time. The mean age of patients with the cholesterol stone type did not change significantly ($P = 0.493$); however, that of patients with the pigment stone significantly increased ($P = 0.002$) (Fig. 2A).

By gallstone subtype, the patients with the CB stone were the oldest, while those with the PC stone type were the youngest ($P < 0.001$). The mean age of patients with BP stones significantly increased from 52.6 in period 1 to 56.9 in period 4 ($P < 0.001$) (Fig. 2B).

Change of gallstone types by sex and region

The proportion of cholesterol stones was significantly higher in females than in males ($P < 0.001$). The proportions of cholesterol versus pigment stones did not change significantly in the females over time ($P = 0.560$); on the other hand, the

proportion of cholesterol stones gradually increased in the males (from 37.3% in period 1 to 46.4% in period 4) ($P = 0.002$).

By subtype, the proportion of CB stones gradually decreased in both males and females ($P = 0.002$ and $P = 0.041$, respectively), while the proportion of BP stones gradually increased in males ($P = 0.010$) (Fig. 3A, B).

The proportion of patients with cholesterol stones was significantly higher in urban areas compared to rural areas ($P < 0.001$). Nevertheless, there was no significant change in the relative frequency of pigment stones versus cholesterol stones in the urban or rural groups over time ($P = 0.203$ and $P = 0.773$, respectively).

The proportion of CB stones gradually decreased in the urban and rural groups ($P = 0.020$ and $P = 0.110$, respectively), while that of BP stones gradually increased in both groups but significantly so in only the rural group ($P = 0.022$) (Fig. 3C, D).

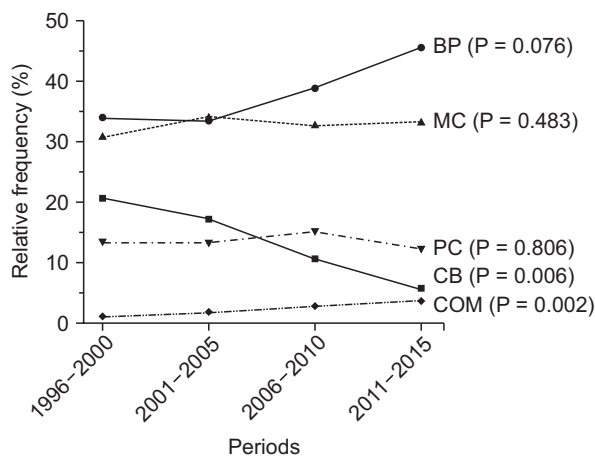
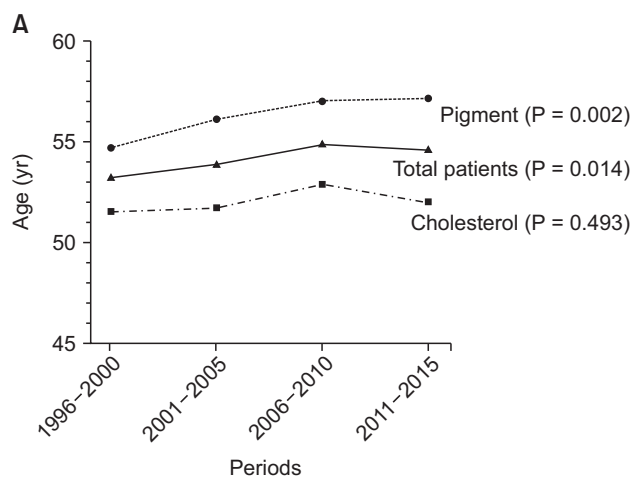


Fig. 1. Chronological changes of the proportions by types of gallstone. BP, black pigment; MC, mixed cholesterol; PC, pure cholesterol; CB, calcium bilirubinate; COM, combination.



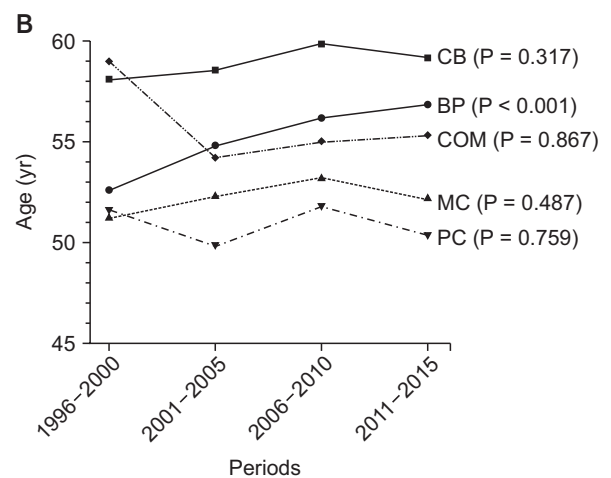
Change in BMI over time

The mean BMI of patients with the cholesterol stone type was higher than that of patients with the pigment stone type ($P < 0.001$), while the mean BMI of patients with the 5 subtypes was high to low in the order of PC, MC, COM, CB, and BP stones ($P < 0.001$). The mean BMI of the total patient cohort gradually increased over time ($P = 0.048$); in particular, that of patients with the MC or CB stone subtypes increased significantly ($P = 0.048$ and $P = 0.004$, respectively).

DISCUSSION

The incidence of gallstones varies among residential areas and ethnicities. In the National Health and Nutrition Examination Survey III study (NHANES III), the overall prevalence of gallstones was 7.9% in men and 16.6% in women [5]. Based on current research results, the lowest prevalence of gallstones

Fig. 2. Chronological changes of the mean ages (A) by pigment versus cholesterol types and (B) by 5 subtypes of gallstones. CB, calcium bilirubinate; BP, black pigment; COM, combination; MC, mixed cholesterol; PC, pure cholesterol.



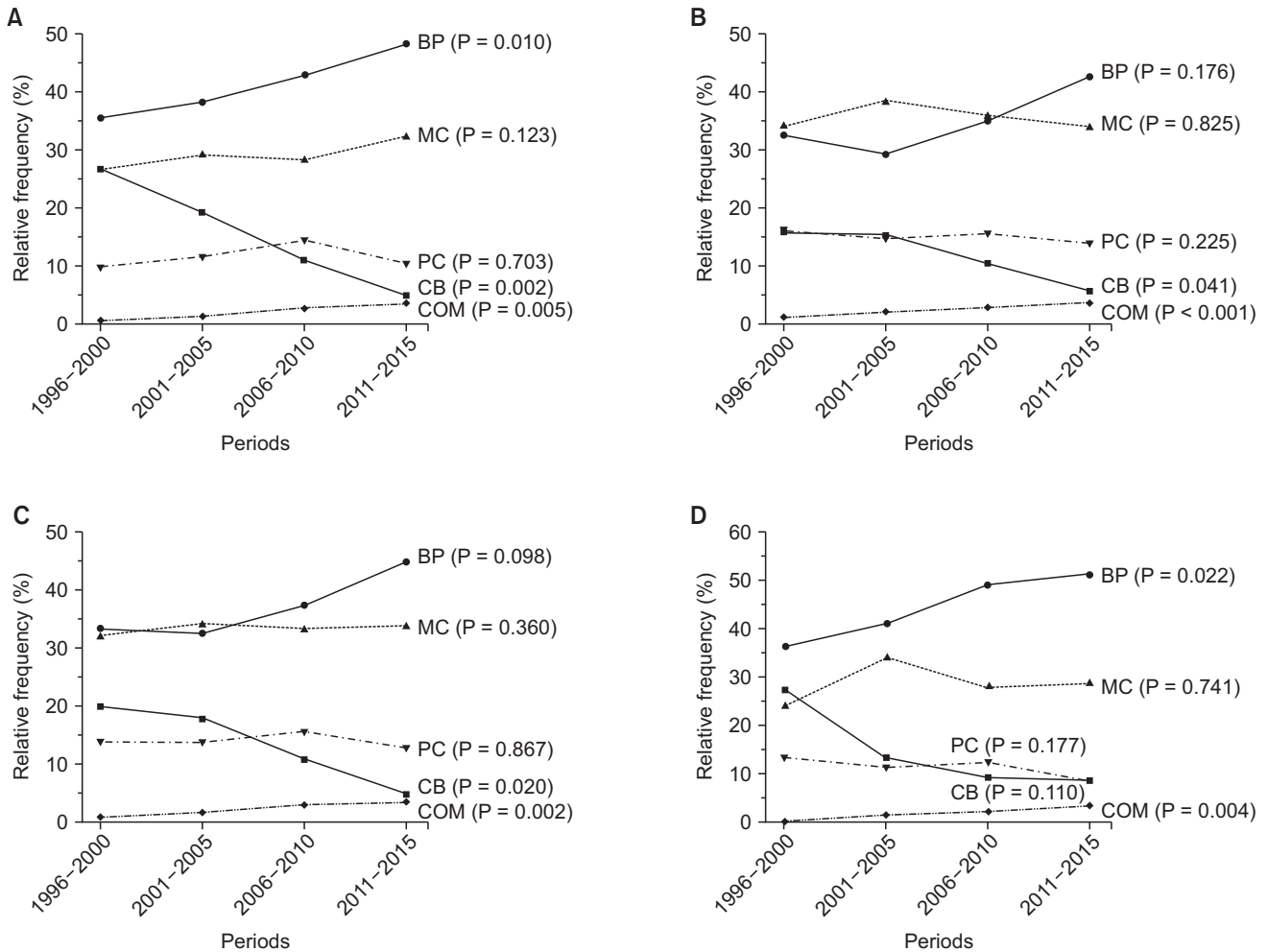


Fig. 3. Chronological changes of the proportions by types of gallstones in males (A), females (B), urban (C), and rural (D) area. BP, black pigment; MC, mixed cholesterol; PC, pure cholesterol; CB, calcium bilirubinate; COM, combination.

is seen in Africa [6], while the highest is seen in North and South America [7]. In Asian countries, recent research showed that prevalence of gallstone disease was lower in developed countries such as Japan [8], higher in developing countries such as India [9], and highest in the Uighur population of China [10]. Only a few recent studies have reported the prevalence of gallstone disease in Korea. The prevalence of gallstones changed from 0.72% to 2.7% based on ultrasonography surveys of an adult population of more than 40,000 patients (from 1987 to 2004) [1,2].

We reported information regarding the epidemiology of gallstone disease based on the data obtained at our institute every 5 years since 1982 [11-16]. To further understand the recent epidemiological characteristics of gallstones in Korea, we have consistently analyzed the mentioned content over a period of 20 years at SNUH.

The total number of gallstone patients nearly tripled over the past 20 years. Nonetheless, such a result does not completely account for the increasing prevalence of gallstones;

rather, it only indicates that increasing numbers of patients are undergoing cholecystectomy in Korea. The increase in the number of patients may be associated with the spread of laparoscopic or robotic cholecystectomy and improvements in quality of life of the population, which directly leads to an increase in hospitalizations and health care screenings. As the Korean society ages, the increased proportion of elderly individuals will continue contributing to the increase in gallstone patients.

Compared to a previous study [16], the mean patient age increased in our study (to 54.6 years). Cholesterol stones and pigment stones were more common in younger and elderly patients, respectively. Why pigment stones are more common in older individuals remains unclear, but the same phenomenon has been documented elsewhere [17]. Likewise, the age distribution from high to low was patients with CB, BP, COM, MC, and PC stone subtypes. The mean age of the BP stone subtype patients significantly increased, which may be related to total number of such patients that steadily increased

over the study period as the Korean society continues to age. Regarding the mechanism of formation of BP stones, factors that play a role include an altered pH, increase in ionized calcium, and increase in unconjugated bilirubin. Because there is no evidence of infection playing a role, it is possible that abnormal glucuronidase activity within the gallbladder mucosa may be important. Hemolysis is also known to be an etiological factor [18].

The prevalence of cholesterol stones was higher in females, and the risk of gallstone disease is greater in women at all ages and in the majority of studies [19]. The basis for this sex-based difference has been attributed to sex hormones [20], pregnancy, and biliary sludge as a potential precursor to stone formation [21]. Interestingly, the proportion of cholesterol stone significantly increased in males; this outcome requires further examination to reveal the cause, although there are corollaries of differences in androgen/estrogen ratios and reduced gallbladder contractility contribute to cholesterol stone formation in men. In subtypes, the BP/CB stone ratio was increased, and BP stone formation is related to hemolytic anemia, liver cirrhosis, Crohn disease, cystic fibrosis, and other chronic diseases [22]. Formation of the CB stone, also known as a brown pigment stone, is related to bacterial infection and bile reflux [22]. Thus, we can conclude that the aging tendency of the population and improvements in sanitary conditions contribute to the change in prevalence of BP/CB stones.

Cholesterol stones are more prevalent in urban areas, possibly due to differences in economic status and diet patterns. However, in economic surveys, Engel's coefficients showed a downward trend over the past 20 years (32.1 in 1995 to 27.2 in

2015). However, the meat consumption growth rate decreased from 2.1% to 0.6% and the proportion of cereal consumption increased in Korea [23]. These factors were highly related to an inconspicuous increase in cholesterol stones. The cholesterol stones slightly increased only in younger individuals in urban areas. No matter how the participants' data were grouped, the proportion of BP stones increased and that of CB stones decreased, which shows that the changes are due to population aging. Mean BMI showed a high to low trend in the order of PC, MC, COM, CB, and BP stone types, and the prevalence of cholesterol stones was significantly higher than that of pigment stones. An increasing BMI was observed in all gallstone subtypes over time; however, it cannot explain the change in gallstone prevalence.

The limitation of this study is its single-center population, which prevents the generalization of our findings to other areas in Korea. In addition, the gallstones were classified using a visual inspection method by cross-sectional appearance, which may limit its accuracy.

In conclusion, although gallstone types and occurrences were affected by environmental changes, pigment stones remain common in Korea. Although an increasing incidence of cholesterol stones was not distinct, that of CB stones decreased. As age at gallstone onset increases, BP stones could become more mainstream.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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