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ORIGINAL ARTICLE

Association between gallbladder stones and chronic hepatitis C: Ultrasonographic survey in a hepatitis C and B hyperendemic township in Taiwan

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KEYWORDS
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Abstract Gallbladder (GB) stones have been associated with several metabolic factors and liver diseases. This community-based study aimed at investigating the prevalence rate of GB stones and its associated factors in a hepatitis B virus (HBV)/hepatitis C virus (HCV)-endemic township in southern Taiwan. A total of 1701 residents (689 males and 1012 females; mean age: 51.2 $\pm$ 16.0 years) were enrolled in this prospectively designed screening project. Serum biochemistry tests, including testing for levels of serum aspartate aminotransferase, alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), and antibody to HCV (anti-HCV) were conducted. In addition, a hepatobiliary ultrasonographic (US) examination was also conducted. Of the 1701 residents, 243 (14.3%) and 475 (27.9%) were found to be positive for HBsAg and anti-HCV, respectively. Results of the US examination revealed the prevalence rate of GB stone and fatty liver to be 6.8% and 55.6%, respectively. Using univariate analyses we found that significantly higher proportions of the participants with GB stone were male, over 50 years of age, positive for anti-HCV ($p = 0.001$, $p < 0.001$, and $p = 0.001$, respectively), with significantly higher mean age and ALT level ($p \leq 0.001$ and $p = 0.048$, respectively) than did those without GB stone. By applying multivariate analyses, male gender, positive anti-HCV, and older age (>50 year) were identified as independent factors associated with the formation of GB stones. Anti-HCV was associated with GB stones in males but not in females in both univariate and multivariate analyses. GB stones were found to have a prevalence rate of 6.8% in this HCV/HBV hyperendemic township and are associated with higher mean age. A correlation between chronic hepatitis C and GB stones is observed only among males.

Introduction

Ultrasonography (US) is a noninvasive tool for evaluating disorders of the internal organs. Because of its extensive application in the clinical diagnosis of abdominal diseases, diagnosis of gallbladder (GB) stones and polyps is common in US examinations [1,2]. The criteria for diagnosing GB stones are the presence of echogenic densities casting distal acoustic shadow or mobility upon postural change with or without distal acoustic shadow [3,4]. The risk of GB stones has been reported to increase in patients with chronic liver disease, particularly liver cirrhosis [5,6], while metabolic factors such as lipid profile, obesity, or abnormal glucose levels have also been reported to be associated with increases in the risk level [7–9].

Taiwan is a country endemic for hepatitis B virus (HBV). Results of recent reports suggest that the prevalence rate of hepatitis B surface antigen (HBsAg) is approximately 14–17% in adults [10–12]. The prevalence rate of antibody to hepatitis C virus (anti-HCV) is approximately 3–4%, with higher rates reported in southern Taiwan [10–12]. Several HCV hyperendemic townships have been discovered, with anti-HCV present in more than 20% of the adult population [13–15]. Tzukuan Township is one such area, with a previous study reporting an anti-HCV prevalence rate of 39.2% [16]. The impact of chronic hepatitis on GB stones and the relationship between metabolic factors and GB stones warrant further evaluation. This community-based study aimed at investigating the prevalence rate of GB stones and its associated factors in an HBV/HCV-endemic township in southern Taiwan based on a screening project.

Patients and methods

A prospective survey of liver diseases in the Tzukuan Township of Kaohsiung County on the southern coast of Taiwan was conducted. Adult residents were invited to participate in laboratory tests and abdominal US examination, with a 12-hour overnight fasting before the tests.

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting plasma glucose (FPG), triglycerides, and total cholesterol (TC) levels were measured on a multichannel auto-analyzer (Hitachi Inc., Tokyo, Japan). HBsAg and anti-HCV antibody were detected using a third-generation, commercially available enzyme-linked immunosorbent assay kit (AxSYM 3.0; Abbott Laboratories, Chicago, IL, USA). Experienced hepatologists from Kaohsiung Medical University Hospital, a medical center in Kaohsiung City, performed the US examination using a 3.5-MHz convex transducer (Toshiba SSA-250; Toshiba, Tokyo, Japan). To minimize interobserver differences, training for standardized diagnosis in US was conducted for doctors.

In the US findings, GB stone was diagnosed by movable hyperechoic contents in the GB lumen with or without acoustic shadows. The diagnosis of fatty liver (FL) was based on the brightness of the liver on US compared with the kidneys, deep attenuation in the right hepatic lobe, and vascular blurring of the hepatic vein trunk, while the severity of FL change was classified according to standardized US criteria with some modification: normal liver, normal echo texture, and absence of fatty change; mild FL, mild increase in fine echoes, and attenuation of the lower fourth of the screen in the parenchyma with slightly impaired visualization of the intrahepatic vessels and diaphragm;

moderate FL, marked increase in fine echoes and attenuation of the lower half of the screen in the parenchyma with poor visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver; severe FL, marked increase in fine echoes, and attenuation of the more than lower half of the screen in the parenchyma with non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver [17,18]. Body mass index (BMI) was calculated as weight per height squared (kg/m^2).

Statistical analysis

The frequency of GB was compared between groups using the Chi-square test with Yate correction or Fisher exact test. Group means were compared using Student *t* test, while stepwise logistic regression method was used as appropriate. A two-tailed $p < 0.05$ was considered to be statistically significant. The procedures were performed using the SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

A total of 1701 participants were enrolled, including 243 (14.3%) and 475 (27.9%) who were positive for HBsAg and anti-HCV, respectively, and 49 (2.9%) who were positive for both. Results of US examination revealed the prevalence rates of the GB stones and FL to be 6.8% (115) and 55.6% (156), respectively (Table 1).

Table 1 Basic characteristics of the study participants ($n = 1701$).

Factors	*N* (%)
Gender (male/female)	689/1012
Age (y)	51.2 ± 16.0
>50 y	917 (53.9)
Body mass index (kg/m^2)	24.1 ± 3.9
AST (U/L)	28.8 ± 21.6
ALT (U/L)	27.9 ± 26.8
Positive HBsAg	243 (14.3)
Positive anti-HCV	475 (27.9)
Fasting plasma sugar (mg/dL)	92.4 ± 29.7
Triglycerides (mg/dL)	115.1 ± 79.2
Cholesterol (mg/dL)	192.1 ± 37.2
Ultrasonographic diagnosis	
With gallstone	115 (6.8)
With gallbladder polyp	100 (5.9)
Fatty liver[a]	
No	756 (44.4)
Mild	579 (34.0)
Moderate	297 (17.5)
Severe	69 (4.1)

Data are presented as mean ± standard deviation or *n* (%).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GB = gallbladder; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.
[a] The severity of fatty liver was classified according to standardized ultrasonographic criteria mentioned in text.

The clinical factors between participants with and those without GB stones were compared (Table 2). Using univariate analyses we found that significantly higher proportions of residents with GB stones were males ($p = 0.001$), aged > 50 years ($p < 0.001$), and positive for anti-HCV ($p = 0.001$), with significantly higher mean age ($p < 0.001$) and ALT levels ($p = 0.048$) than those without GB stones. The presence of GB stones was not associated with HBsAg positivity, mean BMI, AST, FPG, triglycerides, and TC levels, as well as severity of FL. Using multivariate analyses, male gender, positivity for anti-HCV, and higher mean age were found to be independent factors associated with GB stones [odds ratios (OR) and 95% confidence intervals (CI) are shown in Table 3].

The relationship between anti-HCV and GB stones was further evaluated for male and female participants (Table 2). Among the male residents, those with GB stones had significantly higher frequency of positive anti-HCV ($p < 0.001$) and significantly higher mean age ($p < 0.001$) in univariate analyses. Among the female residents, those with GB stones had significantly higher proportion of age >50 years ($p < 0.001$) and higher mean age ($p = 0.003$), but were not positive for anti-HCV in univariate analyses.

Clinical factors among the 475 anti-HCV-positive participants with and without GB stones were compared (Table 4). Significantly higher proportions of participants with GB stones were males ($p = 0.001$). Using multivariate analyses, we found that positive anti-HCV was an independent factor associated with GB stones in males but not in females (OR and 95% CI shown in Table 3).

Discussion

In the present study, the prevalence rates of HBV and HCV infection were 19.2% and 33.5%, respectively, confirming that Tzukuan Township is an HBV- and HCV-endemic community. In this community-based study using US, the prevalence rates of gallstones and FL were 6.8% and 55.6%, respectively. To date, this is the first community-based report on the association between clinical factors, including chronic viral hepatitis, and GB stones in an HBV/HCV hyperendemic area. The results demonstrated that gender, positivity for anti-HCV, and higher mean age were independent factors associated with GB stones. Furthermore, the link between chronic hepatitis C and GB stones was observed only among males.

Chronic hepatic inflammation has been recognized as one of the causes of GB stone formation [1]. Increased prevalence of GB stones has been reported in patients with chronic HCV infection [5,19]. Acalovschi et al. in their hospital-based study reported that HCV infection was a risk factor for GB stones when comparing CHC patients and controls without liver diseases [9]. With the present community-based report in an HBV/HCV hyperendemic area, an association between GB stones and chronic HCV infection, but not HBV infection, was shown.

The mechanisms of HCV infection on GB stone formation remain undetermined. Uchida et al. have previously reported that HCV core antigen can be demonstrated by immunoperoxidase staining in proliferated bile duct epithelia [20], while Loriot et al. have shown that HCV RNA

Table 2 Comparison of clinical characteristics between individuals with and those without GB stone.

	GB stone		*p*	GB stone		*p*	GB stone		*p*
	Positive ($n = 115$)	Negative ($n = 1586$)		Positive ($n = 64$)	Negative ($n = 625$)		Positive ($n = 51$)	Negative ($n = 961$)	
	All, $n = 1701$			Male, $n = 689$			Female, $n = 1012$		
Male	64 (55.7)	625 (39.4)	0.001	—	—		—	—	
Age (years)	58.8 ± 13.8	50.7 ± 16.0	<0.001	60.8 ± 14.4	51.1 ± 17.1	<0.001	56.1 ± 12.7	50.4 ± 15.3	0.003
>50 years	86 (74.8)	831 (52.4)	<0.001	49 (76.6)	326 (52.2)	0.005	37 (72.5)	505 (52.6)	<0.001
Body mass index (kg/m^2)	24.6 ± 3.7	24.1 ± 4.0	0.235	24.5 ± 3.6	24.6 ± 3.8	0.807	24.6 ± 4.0	23.7 ± 4.0	0.144
AST (U/L)	32.0 ± 18.7	28.6 ± 21.8	0.103	33.4 ± 19.2	31.2 ± 25.7	0.488	30.4 ± 18.1	26.9 ± 18.5	0.183
ALT (U/L)	32.8 ± 29.8	27.6 ± 26.5	0.048	35.4 ± 30.3	32.6 ± 30.4	0.523	29.5 ± 29.1	24.3 ± 23.4	0.126
HBsAg	12 (10.4)	231 (14.6)	0.222	5 (7.8)	96 (15.4)	0.136	7 (13.7)	135 (14.0)	0.948
Anti-HCV	48 (41.7)	427 (26.9)	0.001	29 (45.3)	149 (23.8)	<0.001	19 (37.3)	278 (28.9)	0.203
Fasting plasma sugar	95.1 ± 31.2	92.2 ± 29.6	0.339	94.9 ± 25.4	94.3 ± 35.6	0.913	95.5 ± 38.0	90.9 ± 24.9	0.250
Triglycerides (mg/dL)	112.3 ± 57.0	115.4 ± 80.7	0.707	118.5 ± 62.3	129.8 ± 92.7	0.358	103.9 ± 48.3	106.3 ± 70.7	0.802
Cholesterol (mg/dL)	188.9 ± 36.2	192.4 ± 37.3	0.353	185.3 ± 35.8	187.3 ± 35.6	0.672	193.8 ± 36.5	195.6 ± 38.0	0.766
Ultrasonographic finding									
Gallbladder polyp	8 (7)	92 (5.8)	0.611	8 (12.5)	49 (7.8)	0.229	0 (0)	43 (4.5)	0.123
Fatty liver[a]									
No	46 (40)	710 (44.8)	0.278	25 (39.1)	262 (41.9)	0.393	21 (41.2)	448 (46.6)	0.685
Mild	38 (33)	541 (34.1)		20 (31.3)	215 (34.4)		18 (35.3)	326 (33.9)	
Moderate	28 (24.3)	269 (17)		17 (26.6)	1149 (18.2)		11 (21.6)	155 (16.1)	
Severe	3 (2.6)	66 (4.2)		2 (3.1)	34 (5.4)		1 (2.0)	32 (3.3)	

Data are presented as mean ± standard deviation or *n* (%).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GB = gallbladder; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

[a] The severity of fatty liver was classified according to standardized ultrasonographic criteria mentioned in text.

Table 3 Multivariate logistic regression analysis of factors significantly associated with GB stones and GB polyps.

Variable	Independent factor	Comparison	Odds ratio (95% CI)	*p*
GB stone presence ($n = 1701$)				
Gender		Female = 0, Male = 1	1.972 (1.341–2.898)	0.001
Anti-HCV		Negative = 0, Positive = 1	1.539 (1.023–2.317)	0.039
Age		≤50 years = 0, >50 years = 1	2.360 (1.499–3.714)	<0.001
GB stone presence (male, $n = 689$)				
Anti-HCV		Negative = 0, Positive = 1	2.021 (1.146–3.508)	0.012
Age		≤50 years = 0, >50 years = 1	2.421 (1.293–4.535)	0.006
GB stone presence (female, $n = 1012$)				
Age		≤50 years = 0, >50 years = 1	2.230 (1.194–4.439)	0.013

CI = confidence interval; GB = gallbladder; HCV = hepatitis C virus.

can be detected in GB cell culture [21]. Recently, the association between HCV and cholangiocarcinoma has been suggested, based on the results US examinations [22,23]. Thus, HCV may alter GB function, which may contribute to the development of GB stones. Furthermore, HCV infection has an impact on metabolic derangements resulting from its interaction with lipid and glucose metabolisms [24–27]. It is possible that HCV infection alters bile composition, which facilitates and contributes to the formation of GB stones [28]. Nonetheless, the actual pathophysiology of HCV infection causing GB stones requires further investigation.

Table 4 Comparison of clinical characteristics between anti-HCV-positive individuals with GB stone and individuals without GB stone.

	GB stone		*p*
	Positive ($n = 48$)	Negative ($n = 427$)	
Male gender	29 (60.4)	149 (34.9)	0.001
Age (year)	62.3 ± 12.2	60.0 ± 12.5	0.237
>50 years	40 (83.3)	339 (79.4)	0.519
Body mass index (kg/m^2)	24.0 ± 3.9	24.6 ± 3.7	0.299
AST (U/L)	43.0 ± 23.7	39.0 ± 28.2	0.356
ALT (U/L)	47.4 ± 41.18	39.1 ± 35.0	0.139
HBsAg	3 (6.3)	46 (10.8)	0.455
Fasting plasma sugar	101.7 ± 42.7	96.3 ± 34.6	0.348
Triglycerides (mg/dL)	105.5 ± 62.7	107.9 ± 69.2	0.827
Cholesterol (mg/dL)	181.1 ± 36.7	186.1 ± 38.3	0.418
Ultrasonographic finding			
Fatty liver[a]			
No	24 (50)	193 (45.2)	0.937
Mild	16 (33.5)	155 (36.3)	
Moderate	7 (14.6)	68 (15.9)	
Severe	1 (2.1)	11 (2.6)	

Data are presented as mean ± standard deviation or *n* (%).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GB = gallbladder; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.
[a] The severity of fatty liver was classified according to standardized ultrasonographic criteria mentioned in text.

In the present study, old age was an independent factor associated with GB stones, which was similar to reports by Chang et al. [19], who showed that the prevalence of gallstones positively correlated with increasing age in anti-HCV-positive, HBsAg-positive, and both anti-HCV and HBsAg-negative patients groups. Furthermore, the association between HCV infection and GB stones existed in males but not in females, which is the first such report. The reasons for the different gender effects of HCV infection on GB stone formation remain unclear. While female gender has been associated with higher prevalence of GB stones in previous studies [9,19], in this study, there was a lower prevalence of gallstones among females in a hepatitis-endemic community. Whether the minimal impact of HCV infection on female gender can be attributed to a lower risk of GB stones in females also warrants further evaluation.

In conclusion, the present community-based study reveals that the prevalence rates of positive anti-HCV, positive HBsAg, and presence of GB stones and FL were 27.9%, 14.3%, 6.8%, and 55.6%, respectively in an HCV/HBV hyperendemic township. The presence of GB stones was associated with older age and chronic HCV, but not with HBV, infection in males.

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