Age is one of the risk factors in developing gallstone disease in Taiwan

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Abstract

Objectives: to assess the prevalence and risk factors of gallstone disease (GSD) in Taiwan.
Design: descriptive and cross-sectional.
Methods: a prospective ultrasonographic study of GSD was conducted in 3647 Chinese subjects who received a paid hospital physical check-up. Their demographic characteristics and biochemical parameters were recorded and compared. Ultrasonographic diagnosis revealed 2946 (M/F: 1838/1108) with normal gallbladder, 286 (M/F: 196/90) with gallbladder stones, 100 (M/F: 56/44) with previous cholecystectomy for gallstones, 243 (M/F: 174/69) with gallbladder polyps, 17 (M/F: 10/7) with mixed gallbladder stones/polyps and 35 as 'miscellaneous'. We enrolled subjects showing either gallbladder stones or cholecystectomy for gallstones in the GSD group.
Results: excluding those subjects with mixed gallbladder stones/polyps, the overall prevalence of GSD in the studied group was 10.7%. The studied factors manifesting an increase in risk for the development of GSD were age \( (P < 0.05) \), high body mass index \( (P < 0.05) \), diabetes mellitus (adjusted odds ratio: 1.998; \( P < 0.05 \)) and glucose intolerance (adjusted odds ratio: 2.056; \( P < 0.05 \)) by multivariate analysis. Other demographic characteristics and biochemical parameters, such as body height, ABO blood type, cigarette smoking, alcohol consumption, blood pressure, lipid profiles, hepatitis B virus infection, liver function and multiparity did not show any correlation to GSD.
Conclusions: age, high body mass index, diabetes mellitus and glucose intolerance are the risk factors for developing GSD in Taiwan.

Keywords: ageing, diabetes, gallstone disease, risk factors, ultrasound

Introduction

In industrialized countries cholesterol gallstones are very common [1, 2]. The traditional risk factors for gallstone disease (GSD) are the four 'F's—'female, fat, forty and fertile'—but age, multiparity and cigarette smoking are now additional risk factors in Western countries, where cholesterol is the leading component of stones [3-10]. In Eastern countries pigment gallstones—the risk factors for which are age and being female—have traditionally been more common [11, 12]. However, with rapid westernization of diet and environment, cholesterol GSD is no longer rare in younger Oriental adults [13, 14].

Marked differences in race, food, culture and geographic characteristics still exist between Oriental and Occidental countries. The increased prosperity and improvement in living standards in Taiwanese society has occurred only in recent decades, so it is unclear whether the pattern of GSD risk factors has changed. The present prospective study assesses this question.

Materials and methods

During the period between January 1995 and July 1995, 3647 (M/F: 2304/1343) healthy subjects voluntarily admitted themselves to Veterans General Hospital, Taipei, for a paid physical check-up. Abdominal sonography and a 75 g oral glucose tolerance test were performed routinely. A real-time ultrasonography (Hewlett Packard 8500 GP, 3.5 MHz, HP, Palo Alto, CA, USA) was performed, with subjects fasting for 8 h before examination.

Ultrasonographically, gallbladder stones were diagnosed based on the presence of 'movable hyperechoic material with acoustic shadow' [15]. According to the

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ultrasonographic observations, the subjects were classified as having a normal gallbladder, gallbladder stones, previous cholecystectomy, gallbladder polyps, mixed gallbladder stones/polyps or as ‘miscellaneous’. Subjects showing either gallbladder stones or previous cholecystectomy for gallstones were enrolled in the studied GSD group [4, 7, 10], while subjects exhibiting normal gallbladder served as the control group.

The following demographic characteristics were recorded: age, gender, cigarette smoking, alcohol consumption, history of diabetes mellitus and parity.

After fasting blood measurements, subjects were classified as normal, glucose-intolerant or having diabetes in accordance with the World Health Organisation criteria [16]. In addition, those under dietary and hypoglycaemic treatment were regarded as having diabetes mellitus.

Body height and weight were measured in each individual. Body mass index (BMI; kg/m$^2$) was calculated as an index of overall obesity. Blood pressure was measured by two nurses and a physician and the average of the three recordings documented. The plasma concentrations of fasting cholesterol, triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein, albumin, aspartate transaminase (AST) and alanine transaminase (ALT) were examined by an autoanalyser based on a standard protocol. The ratio of cholesterol to HDL-C was calculated. Hepatitis B virus (HBV) carriers were identified from blood hepatitis B surface antigen state, determined with a radioimmunoassay kit (Austria II-125; Abbott, Chicago, IL, USA).

**Statistical analysis**

Results are expressed as the mean ± SD. Categorical differences were analysed using $\chi^2$ test. Student’s $t$ test was used to study the group difference for continuous variables. $\chi^2$ and Student’s $t$ tests were applied to evaluate univariate analysis. Multivariate analysis with logistic regression using an SPSS package (SPSS Inc., Chicago, IL, USA) was conducted to evaluate the putative potential risk factor associated with GSD. A $P$ value < 0.05 was considered to be significant.

**Results**

Following ultrasonography, gallbladders were classified as normal in 2946 subjects (M/F: 1838/1108), while 286 (M/F: 196/90) had gallbladder stones, 100 (M/F: 56/44) had cholecystectomy, 243 (M/F: 174/69) had gallbladder polyps and 17 (M/F: 10/7) had mixed gallbladder stones/polyps. Gallbladder status was ‘miscellaneous’ in 35 (M/F: 20/15). This included five with gallbladder wall thickening, 10 with gallbladder sludge and 20 in whom the study was unsatisfactory.

All subjects in the cholecystectomy group had undergone surgery purely for their gallstones. After exclusion of 17 subjects with mixed gallbladder stones/polyps and 20 subjects with unsatisfactory ultrasonography, the overall prevalence of GSD in our study was 10.7% (386/3610).

Tables 1 and 2 present the demographic characteristics of controls and subjects with GSD analysed using univariate analysis. From these comparisons, both diabetes mellitus (odds ratio (OR): 2.974) and glucose intolerance (OR: 2.815) emerge as risk factors for GSD. Age ($P<0.0001$), high BMI ($P=0.001$), higher systolic blood pressure ($P<0.0001$) and multiparity in females ($P<0.05$) characterized subjects with GSD. No correlation was found between GSD and the following demographic characteristics: gender, body height, diastolic blood pressure, blood grouping, cigarette smoking, alcohol consumption and being an HBV carrier.

Table 3 compares biochemical parameters in controls and subjects with GSD. Apart from lower blood HDL-C concentrations in GSD subjects ($P<0.01$), no other blood lipid profile manifested any difference between controls and GSD subjects. Lower serum albumin concentrations were found in GSD subjects.

Table 1. Comparisons of demographic characteristics in continuous variables in controls and subjects with gallstone disease

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Gallstone disease</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.2 ± 13.2</td>
<td>62.5 ± 10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>24.3 ± 3.4</td>
<td>25.0 ± 3.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.3 ± 16.6</td>
<td>128.5 ± 15.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.3 ± 9.6</td>
<td>79.0 ± 9.1</td>
<td>0.187</td>
</tr>
<tr>
<td>Parity$^a$ (childbirth)</td>
<td>3.1 ± 1.9</td>
<td>3.4 ± 1.8</td>
<td>0.031</td>
</tr>
</tbody>
</table>

$^a$In women.
Risk factors for gallstone disease

Table 2. Comparisons of demographic characteristics in categorical variables among controls and subjects with gallstone disease

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 2946)</th>
<th>Gallstone disease (n = 386)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1838 ± 62.3</td>
<td>252 ± 65.3</td>
<td>1.134 (0.908-1.416)</td>
</tr>
<tr>
<td>Blood group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>824 ± 28.0</td>
<td>112 ± 29.0</td>
<td>1.0</td>
</tr>
<tr>
<td>B</td>
<td>749 ± 25.4</td>
<td>104 ± 26.9</td>
<td>0.909 (0.699-1.181)</td>
</tr>
<tr>
<td>O</td>
<td>1174 ± 40.0</td>
<td>145 ± 37.6</td>
<td>0.924 (0.583-1.465)</td>
</tr>
<tr>
<td>AB</td>
<td>199 ± 6.8</td>
<td>25 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1115 ± 39.1</td>
<td>151 ± 39.1</td>
<td>1.005 (0.808-1.250)</td>
</tr>
<tr>
<td>Drinker</td>
<td>913 ± 31.0</td>
<td>112 ± 29.0</td>
<td>1.099 (0.870-1.387)</td>
</tr>
<tr>
<td>With diabetes</td>
<td>221 ± 7.5</td>
<td>64 ± 16.6</td>
<td>2.974 (2.183-4.051)</td>
</tr>
<tr>
<td>Glucose-intolerant</td>
<td>321 ± 10.9</td>
<td>88 ± 22.8</td>
<td>2.815 (2.146-3.693)</td>
</tr>
<tr>
<td>HBV carrier</td>
<td>346 ± 11.8</td>
<td>47 ± 12.2</td>
<td>1.040 (0.751-1.439)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus.

Table 3. Comparisons of biochemical parameters in controls and subjects with gallstone disease

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 2946)</th>
<th>Gallstone disease (n = 386)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.94 ± 0.96</td>
<td>4.93 ± 0.93</td>
<td>0.777</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.66 ± 1.39</td>
<td>1.76 ± 1.42</td>
<td>0.193</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.18 ± 0.35</td>
<td>1.13 ± 0.33</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.04 ± 0.83</td>
<td>3.06 ± 0.81</td>
<td>0.673</td>
</tr>
<tr>
<td>Cholesterol/HDL-C</td>
<td>4.6 ± 2.4</td>
<td>4.70 ± 1.50</td>
<td>0.385</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43 ± 30.0</td>
<td>42.4 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>25.8 ± 29.8</td>
<td>25.1 ± 19.5</td>
<td>0.685</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>24.4 ± 28.5</td>
<td>24.3 ± 16.3</td>
<td>0.927</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; cholesterol/HDL-C, ratio of cholesterol to high-density lipoprotein; ALT, aspartate transaminase; AST, alanine transaminase.

Discussion

GSD is not rare in the Chinese population of Taiwan. Because we enrolled subjects with previous cholecystectomy, the prevalence (10.7%) of GSD in our series was much higher than those in Italian (5.6%) [5] and Japanese (3.6%, 6%) populations [17, 18]. Is the increased prevalence of GSD due to rapid 'westernization' in Taiwan society [14]? Age is a factor in the development of GSD and our survey confirmed this [4, 5, 7, 19]. Diehl et al. [20] indicated that the percentage of pigment stones increased in older people. Hence, age remains one of the major factors leading to GSD, irrespective of locality or standard of living. The long-term exposure to many other risk factors in elders may...
account for their increased chance of developing GSD. The longer duration of diabetes mellitus in subjects with GSD supports this suggestion. Higher systolic blood pressure, lower blood HDL-C and albumin concentrations were associated with GSD in univariate analysis. However, multivariate analysis excluded these risk factors since older people already tend to manifest these demographic characteristics.

Cholesterol gallstones are very common in Western women [1, 4]. On the other hand, pigment gallstone remains the major component of gallstones in Taiwan [14]. Contrary to an earlier report showing female sex to be a risk factor [12], our study did not reveal any gender differences in the development of GSD. Since that study was based on 85 post mortem examinations of subjects with GSD, the differences in the source of subjects might account for this discrepancy. We did not analyse stone composition in our study but believe that pigment gallstone is still the principal component of GSD in Taiwan. The risk factors for the disease in Taiwanese subjects are quite different from those shown in Occidentals, suggesting that the recent increases in living standards and prosperity in Taiwan have not yet led to cholesterol becoming the major gallstone component.

Obesity has long been associated with cholesterol gallstones [3, 4, 7]. The supersaturated bile in the gallbladders of obese subjects may account for this phenomenon [21]. Since we observed a significant correlation between high BMI and GSD using multivariate analysis, it is uncertain whether obesity is a factor leading to pigment gallstones. Fertility is one of the major factors in cholesterol gallstone formation in women [4]. Incomplete gallbladder emptying occurs in late pregnancy [22]. Although multiparity was once found to be significant in female GSD patients using univariate analysis, this characteristic disappeared following correction with multivariate analysis. Hence, multiparity may not be a risk factor in Taiwan where pigment gallstones are probably the commonest type.

HBV infection is endemic in Taiwan [23]. Chronic liver disease and liver cirrhosis are risk factors for pigment gallstones [24, 25], particularly in the Chinese population [23]. The hepatitis B virus carrier rate in our patients with GSD was 12.2%. This value was no different from the HBV prevalence in the general population (11.8%). Therefore, we do not believe that HBV infection is a risk factor in this population.

Diabetic subjects are susceptible to gallstones, the prevalence being 2-3 times greater than in non-diabetic controls [26]. We have confirmed that diabetes is a risk factor in the development of GSD: even glucose intolerance shows an increased risk. These observations were different from those obtained in Japanese studies [15, 16]. Hyperglycaemia inhibits bile secretion from the liver and disturbs gallbladder contraction [27]. Supersaturated bile in the gallbladder induces cholelithiasis in diabetes [28]. The impairment of gallbladder emptying and the subsequent bile stasis lead to gallstone formation in Western diabetic patients, especially those with autonomic neuropathy [29-31]. Moreover, obesity or a longer history of diabetes shows a positive correlation with the development of GSD [32, 33]. Impaired gallbladder motility increases the chance of developing GSD in subjects with either diabetes or glucose intolerance, in spite of the undetermined stone composition.

In conclusion, GSD is common in Taiwan where there has been improvements in living standards. The risk factors in the development of GSD here are age, high BMI, diabetes mellitus and glucose intolerance.

Acknowledgements

We wish to thank Hung-Sheng Chen and Wen-Chuang Lin for their expert statistical assistance.

Key points

- Of 3647 Chinese people aged 21-72 who requested investigations in Taiwan, 10.7% had ultrasonic features of gallstone disease.
- Using multivariate analysis, increasing age was shown to be an important risk factor in the development of gallstones.
- Other risk factors were high body mass index, diabetes mellitus and glucose intolerance.

References

Risk factors for gallstone disease


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