Gallbladder Polyps With Metabolic Comorbidities Increase the Risk of Ischaemic Heart Disease in Korean Adults

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Abstract

Background: This study aimed to investigate the longitudinal effects of gallbladder (GB) polyps, as a surrogate metabolic indicator, on incident ischaemic heart disease (IHD). We also assessed the combined effects of GB polyps and comorbidities on the risk of developing IHD.

Methods: We enrolled 19,612 participants from the health risk assessment study and Korean Health Insurance Review and Assessment Service database. The control group without GB polyps consisted of 18,413 patients, and the GB polyp group comprised 1,119 patients. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for IHD according to the presence of GB polyps using multivariate Cox proportional hazards regression models.

Results: The prevalence of newly developed IHD was 2.4% during an average follow-up period of 50 months. Individuals with GB polyps had an increased risk of IHD compared with the control group after adjusting for potential confounding variables (HR = 1.425; 95% CI, 1.028–1.975). Furthermore, the coexistence of hypertension or dyslipidaemia resulted in an increased risk (HR = 2.14, 95% CI, 1.34–3.44 or HR = 2.09, 95% CI, 1.32–3.31, respectively) of new-onset IHD in the GB polyp group. However, this cumulative effect was observed only in patients with impaired fasting blood glucose (HR=1.86, 95% CI, 1.06–3.26), but not in those with type 2 diabetes mellitus.

Conclusion: The presence of GB polyps was positively associated with increased risk of developing IHD and was independent of cardiovascular risk factors. In addition, GB polyps in patients with impaired fasting blood glucose increased the risk of IHD as those in the presence of the comorbidities hypertension or dyslipidaemia.

Background

Ischaemic heart disease (IHD) is the leading cause of morbidity and mortality among middle-aged and older individuals [1]. The incidence of cardiovascular disease has increased in developed Asian countries because life style and eating habits have become more westernised [2, 3]. Therefore, it is crucial for physicians to assess the presence of IHD-related risk factors for early prevention of IHD [4].

Gallbladder (GB) polyps are defined based on the presence of polypoidal lesions in the GB mucosa, and ultrasonography (USG) is generally used in clinical settings to detect these polyps [5]. USG is a non-invasive tool with greater than 90% sensitivity and specificity for diagnosing GB polyps [6]. The prevalence of GB polyps in Korea is estimated at 2.2 %–8.5 %, which is higher than that for Western countries but lower than the prevalence in China [7–9]. Although, most GB polyps are cholesterol polyps and benign lesions, the presence of GB polyps is used for the early detection of malignancy and to determine the appropriate time to undergo GB resection surgery [10].

Previous studies suggested that the presence of GB polyps is closely associated with insulin resistance, obesity, and cardiovascular disease (CVD) [11, 12]. Hence, GB polyps and IHD may share common risk factors.
factors; however, few studies have explored the relationship between these two conditions [13].

We conducted a regional and community-based cohort study to investigate the association between GB polyps found by USG and the development of IHD. We included data from the health risk assessment study (HERAS) and Korea Health Insurance Review and Assessment Service (HIRA) database.

**Methods**

**Study participants**

This retrospective study was derived from the HERAS, which has been previously described in details on design and methodology [14]. In brief, the cohort consisted of 20,530 sequential subjects who visited the Health Promotion Center at the Yonsei University Gangnam Severance Hospital for health examinations between November 2006 and June 2010. We excluded 528 participants who had previously been diagnosed with IHD or ischaemic stroke. In addition, patients who met at least one of the following criteria were excluded: less than 20 years of age, missing data, or high-sensitivity C-reactive protein (hsCRP) levels ≥ 10 mg/L (n = 390).

**Data collection**

Each participant completed a questionnaire that described lifestyle and medical history. Smoking status was classified as never-smoker, ex-smoker, or current smoker. A regular alcohol drinker was defined as a person who consumed more than 140 g of alcohol per week. Regular exercise was defined as moderate physical activity three or more times per week. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light indoor clothing without footwear. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the sitting position after 10 min of rest using a standard mercury sphygmomanometer (Baumanometer, W.A. Baum Co Inc., Copiague, NY, USA). Mean arterial pressure was calculated from SBP and DBP. Dyslipidaemia was defined as total cholesterol ≥ 240 mg/dL, triglycerides ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women, or the use of lipid-lowering medication. Diabetes was defined as a fasting plasma glucose (FPG) greater or equal to 126 mg/dL, a self-reported history of diabetes, or current use of diabetes medication. Among individuals without diabetes, impaired fasting glucose was defined as FPG levels between 100 mg/dL and 126 mg/dL.

**Study outcomes**

The primary outcome, previously described, was IHD, which consisted of angina pectoris (ICD-10 code I20) or acute myocardial infarction (ICD-10 code I21) that occurred after enrolment into the study [14]. To define baseline and post-survey outcomes, we linked a personal 13-digit identification number that was assigned to each participant by the Korean HIRA between November 1, 2006 and December 31, 2010.

**Statistical analysis**
We compared the baseline characteristics according to the presence of GB polyps using Student’s t-tests for continuous variables and chi-squared tests for categorical variables. Kaplan–Meier curves with log-rank tests were used to estimate the cumulative incidence of IHD for each group. Using the Cox proportional hazards regression model, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for new-onset IHD after adjusting for potential confounding variables. Furthermore, we evaluated whether the presence of GB polyps affected the incidence of IHD when combined with metabolic comorbidities. All analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was set at $P < 0.05$. The data are presented as numbers ± standard deviation or percentage.

**Results**

A total of 19,612 participants (10,267 men and 9,345 women) were included in the final analysis (Fig. 1). Table 1 presents the baseline characteristics of the HERAS-HIRA cohorts according to the presence of GP polyps. The control group without GB polyps consisted of 18,413 patients, and the GB polyp group comprised 1,119 patients. There were no differences in BMI, total cholesterol, FPG, TG, or hsCRP between the two groups. The prevalence of comorbidities, including hypertension, type 2 diabetes mellitus (T2DM), and dyslipidaemia, was not significantly different between the two groups.
### Table 1
Clinical and biochemical characteristics of the study population

|                          | Total (n = 19,612) | Controls (n = 18,413) | Gallbladder polyp (n = 1,119) | P-value |
|--------------------------|--------------------|-----------------------|-------------------------------|---------|
| Age, years               | 45.7 ± 10.9        | 45.7 ± 10.8           | 46.8 ± 10.7                   | < 0.001 |
| Male sex, %              | 52.4               | 51.9                  | 59.0                          | < 0.001 |
| Body mass index, kg/m²   | 23.4 ± 3.1         | 23.4 ± 3.1            | 23.4 ± 3.0                    | 0.939   |
| Systolic blood pressure, mmHg | 122.4 ± 15.7   | 122.4 ± 15.7          | 122.6 ± 15.5                  | 0.674   |
| Diastolic blood pressure, mmHg | 76.3 ± 10.2    | 76.3 ± 10.2           | 76.5 ± 10.0                   | 0.668   |
| Mean arterial pressure, mmHg | 91.7 ± 11.6       | 91.7 ± 11.7           | 91.8 ± 11.4                   | 0.661   |
| Fasting plasma glucose, mg/dl | 94.4 ± 18.9    | 94.3 ± 19.0           | 95.1 ± 18.4                   | 0.145   |
| Total cholesterol, mg/dl | 189.3 ± 34.1       | 189.3 ± 34.1          | 190.3 ± 34.2                  | 0.325   |
| Triglyceride, mg/dl      | 126.3 ± 90.9       | 126.4 ± 89.8          | 125.2 ± 106.7                 | 0.715   |
| HDL-cholesterol, mg/dl   | 53.2 ± 12.7        | 53.2 ± 12.8           | 52.0 ± 12.1                   | < 0.001 |
| Aspartate aminotransferase, IU/L | 21.9 ± 12.1  | 21.9 ± 12.3           | 21.0 ± 8.6                    | < 0.001 |
| Alanine aminotransferase, IU/L | 23.3 ± 21.8  | 23.4 ± 22.1           | 22.2 ± 15.7                   | 0.015   |
| γ-glutamyltransferase, IU/L | 32.3 ± 40.8  | 32.3 ± 41.3           | 32.2 ± 31.8                   | 0.894   |
| C-reactive protein, mg/L | 1.1 ± 1.4          | 1.1 ± 1.4             | 1.0 ± 1.2                     | 0.104   |
| Current smoker, %        | 24.6               | 24.6                  | 25.0                          | 0.009   |
| Alcohol drinking, %      | 43.6               | 43.8                  | 40.5                          | 0.031   |
| Regular exercise, %      | 31.7               | 31.6                  | 33.2                          | 0.270   |
| Hypertension, %          | 23.2               | 23.2                  | 24.0                          | 0.495   |
| Type 2 diabetes, %       | 5.3                | 5.3                   | 5.1                           | 0.773   |
| Dyslipidemia, %          | 38.7               | 38.8                  | 38.2                          | 0.693   |
| Impaired fasting glucose, % | 16.9            | 16.7                  | 19.9                          | 0.004   |

Data are expressed as the mean ± SD or percentage. P-values were calculated using t-test or the chi-squared test.

Table 2 shows the incidence of and difference in IHD between the control and GB polyp groups. A total of 473 individuals (2.4 %, 473/19,612) developed IHD during the follow-up and the patients with GB polyps
had a higher risk of developing IHD. Furthermore, the GB polyp group showed a higher cumulative incidence of IHD over a 50-month period after the baseline survey (log-rank test, \( P = 0.002 \)) (Fig. 2).

| Table 2 | Overall incidence of ischemic heart disease according to the presence of gallbladder polyp |
|----------|---------------------------------------------------------------|
|          | Controls                                      | Gallbladder polyp |
| New cases of ischemic heart disease, n | 430                                      | 43                  |
| Mean follow-up, years                  | 2.4 ± 1.1                                  | 2.2 ± 1.2           |
| Pearson-years of follow-up             | 43539                                     | 2613                |
| Incidence rate/1000 person -years      | 9.9                                       | 16.5                |

Table 3 presents the HRs of IHD categorised by age, sex, alcohol intake, blood tests including lipid profiles, and baseline comorbidities. The increase in IHD risk was dependent upon greater age, male sex, increased BMI, total cholesterol, or alanine aminotransferase, and GB polyps. Table 4 shows Cox proportional hazard regression analyses for the risk of IHD in patients with GB polyps in the presence of different comorbidities. The coexistence of GB polyps and hypertension or dyslipidaemia resulted in greater risk of IHD compared with GB polyps alone. However, this cumulative effect was observed only in patients with impaired FPG, not in participants with diabetes (Table 4; Fig. 3).
### Table 3
Multivariate Cox proportional-hazards regression models for incident ischemic heart disease

| Variables                        | HRs (95% CIs)         | P-value |
|----------------------------------|-----------------------|---------|
| Age, years                       | 1.057 (1.047–1.067)   | < 0.001 |
| Male sex, yes or no              | 1.502 (1.122–2.010)   | 0.006   |
| Body mass index, kg/m2           | 1.046 (1.011–1.083)   | 0.010   |
| Current smoking, yes or no       | 1.278 (0.937–1.741)   | 0.121   |
| Alcohol drinking, yes or no      | 0.766 (0.618–0.949)   | 0.014   |
| Regular exercise, yes or no      | 1.163 (0.955–1.415)   | 0.132   |
| Mean arterial pressure, mmHg     | 0.996 (0.987–1.005)   | 0.354   |
| Fasting plasma glucose, mg/dl    | 1.004 (0.999–1.008)   | 0.103   |
| Total cholesterol, mg/dl         | 1.003 (1.001–1.006)   | 0.018   |
| Alanine aminotransferase, IU     | 1.004 (1.002–1.006)   | < 0.001 |
| C-reactive protein, mg/L         | 1.004 (0.939–1.074)   | 0.904   |
| Hypertension medication, yes or no| 1.714 (1.350–2.175)   | < 0.001 |
| Diabetes medication, yes or no   | 1.064 (0.715–1.583)   | 0.758   |
| Dyslipidemia medication, yes or no| 1.930 (1.412–2.638)   | < 0.001 |
| Gallbladder polyp, yes or no     | 1.425 (1.028–1.975)   | 0.033   |
Table 4
Age and sex-adjusted hazard ratios and 95% confidence intervals for ischemic heart disease according to gallbladder polyp in the context of metabolic diseases

|                        | All subjects | Controls                  | Gallbladder polyp |
|------------------------|--------------|---------------------------|-------------------|
|                        |              | HRs (95% CIs)\(^a\)      | P-value           | HRs (95% CIs)\(^a\) | P-value |
| Hypertension           |              |                           |                   |                   |
| No                     | 1.00 (reference) | 1.44 (0.94–2.19)           | 0.090             |
| Yes                    | 1.49 (1.22–1.83)   | < 0.001                   | 2.14 (1.34–3.44)  | 0.001             |
| Type 2 diabetes        |              |                           |                   |                   |
| No                     | 1.00 (reference) | 1.49 (1.07–2.07)           | 0.018             |
| Yes                    | 1.46 (1.09–1.94)   | 0.013                     | 1.59 (0.59–4.26)  | 0.358             |
| Dyslipidemia           |              |                           |                   |                   |
| No                     | 1.00 (reference) | 1.51 (0.98–2.33)           | 0.059             |
| Yes                    | 1.55 (1.28–1.87)   | < 0.001                   | 2.09 (1.32–3.31)  | 0.001             |
| Nondiabetic subjects   |              |                           |                   |                   |
| Controls               | HRs (95% CIs)\(^a\) | P-value                   |                   |
| Impaired fasting glucose|              |                           |                   |                   |
| No                     | 1.00 (reference) | 1.49 (0.99–2.23)           | 0.053             |
| Yes                    | 1.34 (1.06–1.68)   | 0.014                     | 1.86 (1.06–3.26)  | 0.029             |

**Discussion**

We found that the presence of GB polyps alone was associated with a 42.5 % increase in the risk of developing IHD compared with a non-polyp control group. To our knowledge, only one other report has described a relationship between GB polyps and CVD [12]. However, in this latter study, the authors did not fully assess IHD-related risk factors to sufficiently show a causal relationship between GB polyps and IHD. In our study, we evaluated multiple risk factors that influence the development of IHD, including blood glucose levels, lipid profiles, blood pressure, liver function, alcohol intake, smoking status, and self-reported diseases, such as T2DM and hypertension. By including these factors, we discovered that when patients with GB polyps and impaired FPG presented with hypertension or dyslipidaemia, these comorbidities increased the risk of IHD by approximately 2-fold.

It is generally believed that GB disease is positively correlated with metabolic syndrome, obesity, and T2DM because these conditions share common risk factors, such as sedentary life styles, dyslipidaemia, and fat rich diets [11, 15]. Our results imply that GB polyps are closely related to the development of IHD,
although this association may be an epiphenomenon and not a causal effect. However, our findings suggest that GB polyps may be a risk factor for IHD that is independent of traditional risk factors.

In the present study, patients who presented with GB polyps and the comorbidity hypertension or dyslipidaemia developed an increased risk of IHD that was greater than patients with GB polyps alone. This interaction was observed in patients with impaired FPG, but not in those with T2DM. Epidemiological studies have reported that the development of IHD is enhanced when CVD risk factors are combined with obesity and metabolic syndrome, but not T2DM, in the general population \([16–19]\). This finding may be explained in part by the medications used (e.g. metformin) and life style modifications that may occur after a diagnosis of T2DM. Metformin has been shown to protect the heart from fibrosis and remodelling after myocardial infarction and decrease inflammation and oxidative stress \([20]\). As a result, patients with T2DM taking metformin may have a weakened risk of developing IHD \([21]\).

Recent epidemiological and experimental studies have reported possible mechanisms by which GB polyps influence the development of IHD. GB polyps are tumour or tumour-like protrusions arising from the GB mucosa and are divided into true polyps and pseudopolyps \([22]\). True polyps are classified as adenomas or adenocarcinomas, and pseudopolyps, which represent over 90% of GB polyps, consist mainly of cholesterol and inflammatory polyps \([23, 24]\). As the names suggest, the growth and development of the majority of GB polyps are closely related with cholesterol metabolism and inflammation \([24]\). Acetyl-CoA acetyltransferase 2 (ACAT2) is a key enzyme in the biogenesis of lipid bodies, which may facilitate the pinocytosis of cholesterol and papillary hyperplasia in the GB mucosa \([25]\). Additionally, this enzyme decreases GB contractility leading to cholesterol deposition in the GB wall \([26]\). ACAT2 is also responsible for incorporation of cholesteryl ester in apoprotein B-containing lipoproteins that leads to increased very low-density lipoprotein (VLDL) secretion and coronary artery atherosclerosis \([27]\). It has been reported that inflammation is closely related to ACAT2 activity and downregulating ACAT2 is associated with lowering cholesterol and preventing atherosclerosis \([28]\). Collectively, the interactive linkage between ACAT activity, inflammation, and dyslipidaemia may lead to the development of both GB polyps and IHD \([29]\).

Previous cross-sectional studies have consistently found that patients with metabolic syndrome have a high prevalence of GB polyps, suggesting that insulin resistance may be a potential cause \([15, 30]\). An epidemiological study reported that hyperinsulinemia increased the incidence of GB polyp in Korean men \([31]\). Therefore, we propose that screening patients with GB polyps for metabolic disturbances will be important for early detection and prevention of IHD.

The present study had several strengths. First, potential IHD-related confounding factors were assessed by blood tests along with traditional risk factors. Second, the identification of GB polyps occurred during the process of screening the general population rather than relying on the diagnosis by doctors based on symptoms of GB disease. Therefore, we minimised the mis-classification of asymptomatic patients into the control group in our study and decreased cohort bias. Third, this study was carried out using data
from a large scale, prospective cohort study to ascertain IHD risk factors and included analyses of multiple physiological tests.

Nevertheless, this study also has some limitations. Cholesterol polyps and adenomas may indicate underlying pathogenesis [32]. For the majority of patients with GB polyps, there was no information regarding a pathological condition because the data were obtained from asymptomatic patients who underwent health check-ups. Additionally, this study was a retrospective cohort study and USG was performed only at baseline. Therefore, we were unable to discover new-onset GB polyps during the follow-up period, which may have led to a selection bias and underestimation of the association between GB polyps and IHD incidence. Despite these limitations, this is the first study to assess a role for conventional IHD risk factors in the association between GB polyps and development of IHD.

Conclusions

In conclusion, the presence of GB polyps is associated with development of IHD. Additionally, GB polyps in patients with impaired FPG increase the risk of IHD in the presence of the comorbidities hypertension or dyslipidaemia. Further studies with more frequent evaluations, longer follow-up periods, and pathological analysis of GB polyps will provide more detailed information regarding the interactions between GB disease and IHD.

Abbreviations

IHD: ischemic heart disease; GB: gallbladder; USG (ultrasonography); CVD: cardiovascular disease; HERAS: health risk assessment study; HIRA: Korea Health Insurance Review and Assessment; hsCRP: high sensitivity C-reactive protein; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HRs: hazard ratios; CIs: confidence intervals; T2DM: type 2 diabetes mellitus; ACAT2: acetyl-CoA acetyltransferase 2; VLDL (very low-density lipoprotein).

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed in the current study are available from the corresponding author on reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Author contributions

YJL, BP, and DHJ designed the study; YJL, BP and DHJ assisted with data acquisition and interpretation; BP and KWH performed statistical analyses; YJL, BP, KWL, and DHJ contributed to the discussion; YJL and BP drafted the manuscript; and DHJ revised the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Flowchart for the selection of study participants.
Figure 2

Kaplan–Meier plots indicating the cumulative probability of being diagnosed with ischemic heart disease after the baseline survey.
Figure 3

Hazard ratios (95% CIs) for incident IHD according to the presence of GB polyps in the context of metabolic comorbidities after adjusting for age and sex.