Original Article

Korean J Health Promot 2015;15(4):217-224 • pISSN: 2234-2141 • eISSN: 2093-5676
http://dx.doi.org/10.15384/kjhp.2015.15.4.217

# 담석증과 당뇨병 발생위험: 코호트 연구

**서 병 성**

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# A Cohort Study of Gallstones and Incidence of Diabetes in a Korean Population

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**Background:** Gallstones are associated with insulin resistance but the relation between gallstone disease and the risk of developing diabetes mellitus (DM) is unclear. We examined if gallstones are associated with an increased incidence of DM compared to no gallstones.
**Methods:** A cohort study was performed in 41,518 Koreans aged 30-59 without DM, who underwent a health checkup during 2005-2006 and then were followed annually or biennially until December 2011. Throughout the study period, gallstones were defined as ultrasound-documented gallstones by standard criteria and DM was defined as fasting serum glucose $\geq$7.0 mmol $l^{-1}$, A1c $\geq$6.5%, or use of DM medications.
**Results:** During 192999 person-years of follow-up, 2,232 participants developed DM (incidence rate 11.6 per 1,000 person-years). The incidence of DM was higher in subjects with gallstones or cholecystectomy than in those without gallstones for women but not for men. In multivariate-adjusted models, the hazard ratios (95% confidence intervals) for DM comparing gallstones and cholecystectomy vs. no gallstones were 0.95 (0.63-1.42) and 1.13 (0.53-2.38), respectively, in men and 1.64 (1.13-2.40) and 2.04 (1.01-4.11), respectively, in women. These associations did not differ significantly between relevant subgroups.
**Conclusions:** In an apparently healthy population, gallstones were independently and modestly associated with increased incidence for DM in women but not in men. Women with gallstones should be provided with adequate measures for preventing DM.
**Korean J Health Promot 2015;15(4):217-224**

**Keywords:** Gallstones, Diabetes mellitus, Insulin resistance, Cohort study, Incidence

## INTRODUCTION

Gallstones are a common condition worldwide whose prevalence is increasing with the increase in obesity and the westernization of the socioeconomic environment. They are associated with high financial costs for health care systems worldwide.[1] In addition to the direct complications of gallstones,[2] studies have shown a positive independent association between gallstone disease (GSD) and cardiovascular morbidity,[3] extrabiliary cancer,[4] overall, cancer, and cardiovascular mortality,[5] suggesting a possible role of GSD as a predictor for other diseases directly unrelated to gallstones.

Insulin resistance, an important pathogenic factor of cardiovascular disease and type 2 diabetes mellitus (DM), was found to promote cholesterol gallstones through an increase in biliary cholesterol secretion and lithogenic bile salt profile.[6] Epidemiologic studies also demonstrated an association between insulin resistance and gallstones.[7-9] All

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these raise a possibility that GSD as a manifestation of insulin resistance predicts incident DM. Recently, a prospective cohort study found that self-reported GSD increased the risk for self-reported DM.[10] The majority of gallstones do not develop symptoms: less than 25% of ultrasound-diagnosed gallstones eventually become symptomatic.[11] Thus, ascertainment of gallstones solely based on self-report can underestimate the gallstone status. Ultrasonography (US) is the procedure of choice for identifying gallstones, being a noninvasive and safe imaging technique that accurately detects the point prevalence of gallstones in a defined asymptomatic population.[12]

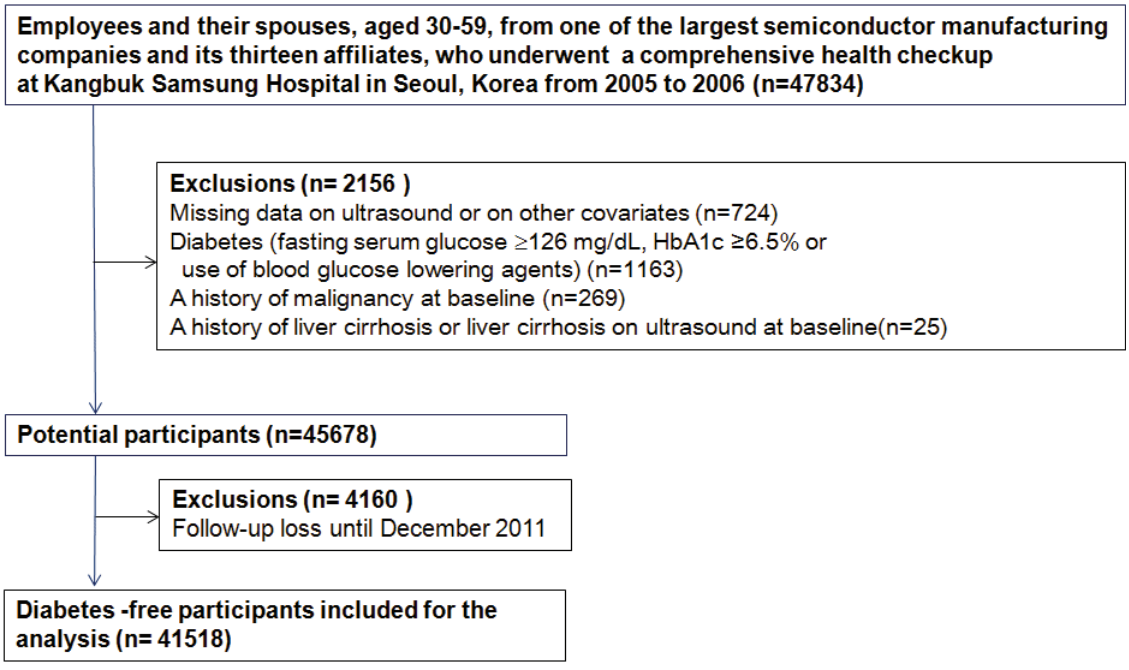
To our best knowledge, no study has examined whether US-documented gallstones are associated with an increased incidence of DM. If the previously documented relationship of gallstones with incident DM was also observed in asymptomatic population, it would indicate that individuals with gallstones should be supported with adequate prevention measures, regardless of gallstone-related symptoms or complications. We hypothesized that gallstones, as a manifestation of insulin resistance, increase the development of DM even in an asymptomatic individuals. The aim of our study was to examine whether GSD based on US is associated with incident DM compared with no gallstones in an apparently healthy population.

## METHODS

### 1. Study population

The study population comprised workers and their spouses from one of the largest companies in Korea and its 13 affiliates. In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. These companies also support health screening program of spouses of their employees according to their welfare policies. Study subjects included all workers 30-59 years of age and their spouses participating in comprehensive health examinations at Kangbuk Samsung Hospital in Seoul, Korea from 2005 to 2006 (n=47,834), then followed annually or biennially until December 2011. Of the 47,834 subjects, 2,156 were excluded for any of the following reasons: missing data on abdominal US or other covariates, DM, a history of malignancy, and a history of liver cirrhosis or US finding suggestive of cirrhosis (Figure 1). As some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 45,678 at baseline. Further, 4,160 subjects (9.1%) were excluded for not attending any follow-up visits by December 2011. Finally, 41,518 subjects were included in the analysis. Those not attending any follow-up visits were, on average,

**Figure 1.** Flow diagram for the selection of study subjects.



0.3 years younger and tended to have more favorable metabolic profiles at baseline than the remaining participants (data not shown).

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent as we only retrospectively accessed data that were de-identified.

## 2. Measurements

Abdominal ultrasounds were performed using the Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI, USA) by 11 experienced radiologists who were unaware of the aims of the study. Gallstones were defined as US-documented gallstones by the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadowing).[13] Cholecystectomy was defined as evidence of a cholecystectomy, a right upper quadrant or epigastric scar and the absence of a gallbladder, by standard criteria.[13] GSD was defined as either having gallstones or having had a cholecystectomy. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma.[14]

To assess the intra- and inter-observer reliability of the ultrasound diagnosis of gallstones, a random sample of 200 stored ultrasonographic images were re-read at least two weeks apart by the eleven radiologists. All radiologists were blinded to clinical information. The inter-observer reliability and intra-observer reliability for gallstones diagnosis were substantial (kappa statistic of 0.75) and excellent (kappa statistic of 0.96), respectively.

Metabolic syndrome (MetS) was defined using the modified National Cholesterol Education Program Adult Treatment III as the presence of three or more of the following criteria: 1) abdominal obesity; 2) fasting blood glucose ¤ 5.6 mmol $l^{-1}$; 3) triglycerides $\geq$1.7 mmol $l^{-1}$; 4) HDL-cholesterol $<$1.0 mmol $l^{-1}$ for men and $<$1.3 mmol $l^{-1}$ for women; and 5) BP$\geq$130/85 mmHg. Since waist circumference measurements were not available for all subjects, we substituted overall adiposity (i.e., body mass index [BMI] $\geq$25 kg $m^{-2}$, a proposed cut-off for the diagnosis of obesity in Asians) for abdominal obesity. Hypertension was defined as systolic BP$\geq$140 mmHg or diastolic BP$\geq$90 mmHg or the use of anti-hypertensive medications. Diabetes mellitus was defined as fasting serum glucose $\geq$7.0 mmol $l^{-1}$, A1c $\geq$6.5%, or the use of blood glucose lowering agents. Anthropometric measurements and procedures for obtaining the blood samples were described in detail elsewhere.[15] The glycated hemoglobin determination using the Cobas Integra 800 (Roche Diagnostics, Rotkreuz, Switzerland) was based on the turbidimetric inhibition immunoassay for hemolyzed whole blood. The intra- and inter-assay coefficient of variation was 2.3% and 2.4%.

## 3. Statistical analyses

The $\chi^2$-test and student t-test were used to compare the characteristics of the study participants at baseline between GSD and no GSD groups. The distribution of continuous variables was evaluated and log-transformations for right-skewed variables were done during analyses.

Incidence density was expressed as the number of cases divided by person-years. Follow-up extended from the baseline exam until the development of DM, or the last health exam conducted for each participant. Since we knew that the gallstones had occurred between two visits but did not know the precise time of diabetes development, we used a parametric Cox model to take into account this type of interval censoring (*stpm* command in Stata).[16] In these models, the baseline hazard function was parameterized with restricted cubic splines in log time with four degrees of freedom. We estimated the adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for incident diabetes comparing gallstones and cholecystectomy to the no GSD group. For time-dependent analyses, we used a pooled logistic regression model that closely approximates a Cox model when the risk of outcome between intervals is low.

The models were initially adjusted for age, and then, for smoking, alcohol intake, exercise, BMI, total cholesterol, triglyceride, HDL-cholesterol, and HOMA-IR. To determine linear trends of risk, the number of categories was used as a continuous variable and tested on each model. We assessed the proportional hazards assumption by examining graphs of estimated log(-log) survival.

In addition, we performed stratified analyses in pre-specified subgroups defined by gender, age ($<$40, $\geq$40 years), MetS (yes, no), BMI ($<$25, $\geq$25 kg $m^{-2}$), HOMA-IR ($<$2.5 vs. $\geq$2.5),[17] and fatty liver (yes, no); and the interactions

by subgroups were tested.

Statistical analyses were performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). All *P* values were 2-tailed, and statistical significance was set at $P<0.05$.

## RESULTS

The baseline characteristics of subjects by GSD are presented in Table 1. The prevalence of GSD was 1.9% in men and 2.5% in women. In both genders, age, BMI, diastolic BP, glucose, GGT, and HOMA-IR were associated positively with GSD, whereas HDL-C was associated negatively. The proportions of obesity, MetS, and fatty liver were also positively associated with GSD in both men and women. Triglycerides, systolic BP, and hypertension were associated with GSD in women, whereas ALT and CRP were associated with GSD in men.

The average follow-up period for participants who did not develop DM was 4.7 years. During 192,999 person-years of follow-up, 2,232 participants developed DM (for men, incidence rate 11.0 per 1000 person-years; for women, incidence rate 12.6 per 1000 person-years) (Table 2). Incidence of DM was higher in subjects with gallstones or cholecystectomy than those without gallstones in women but not in men; but the association between GSD and DM did not differ statistically by sex (*P* for interaction >0.05). In multivariate-adjusted models, the HR (95% CI) for DM comparing gallstones and cholecystectomy vs. no GSD were

**Table 1.** Baseline characteristics of study population according to gallstone diseases (GSD)

| Characteristics | Men | | *P* value | Women | | *P* value[d] |
|---|---|---|---|---|---|---|
| | No GSD | GSD | | No GSD | GSD | |
| Number | 26,057 | 498 | | 14,587 | 376 | |
| Age ,y[a] | 37.0 (4.6) | 38.3 (4.9) | <0.001 | 36.4 (4.2) | 37.5 (4.4) | <0.001 |
| BMI, kg $m^{-2}$[a] | 24.3 (2.8) | 24.9 (3.1) | <0.001 | 21.7 (2.7) | 22.8 (3.3) | <0.001 |
| Current smoke, % | 48.1 | 45.0 | 0.171 | 2.2 | 2.7 | 0.505 |
| Alcohol intake, %[c] | 43.1 | 37.6 | 0.014 | 9.4 | 9.6 | 0.930 |
| Regular exercise, %[c] | 45.9 | 47.2 | 0.554 | 35.3 | 39.1 | 0.125 |
| Obesity, % | 38.9 | 45.8 | 0.002 | 11.0 | 23.9 | <0.001 |
| Hypertension, % | 11.9 | 14.1 | 0.150 | 2.7 | 5.1 | 0.005 |
| Metabolic syndrome, % | 17.7 | 21.7 | 0.021 | 3.9 | 8.0 | <0.001 |
| Fatty liver on ultrasound,% | 37.8 | 44.8 | 0.001 | 6.8 | 15.7 | <0.001 |
| Systolic BP, mmHg[a] | 115.9 (12.4) | 116.4 (12.0) | 0.446 | 105.9 (11.2) | 108.9 (11.9) | <0.001 |
| Diastolic BP,mmHg[a] | 75.3 (8.7) | 76.4 (8.7) | 0.006 | 67.3 (7.9) | 69.1 (8.3) | <0.001 |
| Glucose, mmol $l^{-1}$[a] | 5.2 (0.4) | 5.3 (0.5) | 0.028 | 5.0 (0.4) | 5.1 (0.4) | <0.001 |
| HbA1c, % | 5.3 (0.3) | 5.4 (0.3) | 0.880 | 5.4 (0.3) | 5.4 (0.3) | 0.283 |
| Total cholesterol, mmol $l^{-1}$[a] | 5.0 (0.8) | 4.9 (0.9) | 0.159 | 4.6 (0.8) | 4.6 (0.8) | 0.733 |
| LDL-C, mmol $l^{-1}$[a] | 2.9 (0.7) | 2.9 (0.8) | 0.415 | 2.5 (6.4) | 2.6 (0.7) | 0.283 |
| HDL-C, mmol $l^{-1}$[a] | 1.3 (0.3) | 1.3 (0.2) | 0.001 | 1.5 (0.3) | 1.5 (0.3) | 0.004 |
| Uric acid, μmol $l^{-1}$[a] | 370.0 (70.2) | 371.2 (71.4) | 0.758 | 245.7 (49.4) | 249.8 (48.8) | 0.137 |
| Triglycerides, mmol $l^{-1}$[b] | 1.4 (1.0-2.0) | 1.4 (1.0-1.9) | 0.271 | 0.9 (0.7-1.2) | 0.9 (0.7-1.3) | 0.027 |
| AST, U $l^{-1}$[b] | 24 (20-29) | 25 (20-29) | 0.310 | 20 (17-23) | 20 (17-24) | 0.808 |
| ALT, U $l^{-1}$[b] | 26 (19-37) | 27 (19-39) | 0.011 | 16 (13-20) | 16 (13-21) | 0.622 |
| GGT, U $l^{-1}$[b] | 27 (18-44) | 29.5 (20-55) | 0.049 | 11 (8-15) | 12 (9-17) | <0.001 |
| hsCRP, mg $l^{-1}$[b] | 0.50 (0.30-1.10) | 0.60 (0.30-1.40) | 0.007 | 0.30 (0.20-0.70) | 0.40 (0.20-1.00) | 0.903 |
| HOMA-IR[b] | 1.98 (1.58-2.55) | 2.15 (1.67-2.80) | <0.001 | 1.79 (1.45-2.28) | 1.95 (1.57-2.63) | <0.001 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; GGT, 약어풀이; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance. LDL-C, low-density lipoprotein cholesterol.

Data are [a]Mean (standard deviation), [b]Median (interquartile range), or percentage.

[c]≥ once time per week.

[d]$\chi^2$-test and student *t*-test were used.

**Table 2.** Development of type 2 diabetes according to gallstone diseases (GSD)

| | Number | Person-years | Incident case | Incidence density (1000 person-year) | Age-adjusted HR (95% CI) | Multivariate HR[a] (95% CI) | | HR (95% CI)[b] in the model using time-dependent variables |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1 | Model 2 | |
| Men | 26,555 | | | | | | | |
| No GSD | 26,057 | 122,403.3 | 1,343 | 11.0 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| GSD | 498 | 2,377.1 | 31 | 13.0 | 1.10 (0.77-1.58) | 0.97 (0.68-1.38) | 0.98 (0.69-1.40) | 0.88 (0.63-1.23) |
| Gallstone | 406 | 1,945.6 | 24 | 12.3 | 1.06 (0.71-1.59) | 0.96 (0.64-1.44) | 0.95 (0.63-1.42) | 0.88 (0.60-1.29) |
| Cholecystectomy | 92 | 431.5 | 7 | 16.2 | 1.26 (0.60-2.65) | 0.98 (0.46-2.07) | 1.13 (0.53-2.38) | 0.87 (0.43-1.77) |
| *P* for trend | | | | | 0.520 | 0.866 | 0.975 | 0.456 |
| Women | 14,963 | | | | | | | |
| No GSD | 14,587 | 66,578.6 | 821 | 12.3 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| GSD | 376 | 1,640.3 | 37 | 22.6 | 1.88 (1.35-2.62) | 1.66 (1.14-2.42) | 1.74 (1.24-2.43) | 1.73 (1.24-2.42) |
| Gallstone | 300 | 1,312.2 | 29 | 22.1 | 1.83 (1.26-2.64) | 1.66 (1.14-2.42) | 1.64 (1.13-2.40) | 1.67 (1.14-2.44) |
| Cholecystectomy | 76 | 328.1 | 8 | 24.4 | 2.14 (1.06-4.29) | 2.08 (1.03-4.18) | 2.04 (1.01-4.11) | 2.00 (1.003-3.97) |
| *P* for trend | | | | | <0.001 | 0.001 | 0.001 | 0.001 |
| *P* for interaction by gender | | | | | 0.124 | 0.202 | 0.236 | 0.202 |

Abbreviations: CI, confidence intervals; HR, hazard ratio.
[a]Estimated from Parametric Cox models
[a]Model 1: adjusted for age, smoking status, alcohol intake regular exercise, and BMI; model 2: model 1 plus adjusted for total cholesterol, triglyceride, HDL-cholesterol, and HOMA-IR.
[b]Estimated from a pooled logistic regression models with GSD as a time-dependent categorical variable adjusted for other covariates (smoking status, alcohol intake, regular exercise, triglyceride, HDL-cholesterol, and HOMA-IR over time as time-dependent variables).

0.95 (0.63-1.42) and 1.13 (0.53-2.38) in men and 1.64 (1.13-2.40) and 2.04 (1.01-4.11) in women. After adjustment for glucose and insulin instead of HOMA-IR in multivariate-adjusted models, the results were virtually unchanged. For women, this association persisted after introducing GSD and metabolic risk factors as time-dependent exposures. There was not a significant difference between the association of diabetes with gallstones and cholecystectomy among women when cholecystectomy is compared with gallstones as the reference group (*P* value=0.55).

The association between GSD and the risk of incident DM were similar across the subgroups of study participants with no statistically significant interactions with age (<40, ≥40 years), MetS (yes, no), BMI (<25, ≥25 kg $m^{-2}$), HOMA-IR (<2.5 vs. ≥2.5), and fatty liver (yes, no).

## DISCUSSION

We found that GSD was associated with increased incidence of DM in women but not in men. In women, both gallstones and cholecystectomy were significantly associated with the development of DM, and these associations persisted after adjusting for age, BMI, lipid profiles, HOMA-IR, and possible confounders, suggesting that GSD is an independent risk factor for the development of DM in women.

To our knowledge, this is the first cohort study demonstrating a prospective relationship of US-diagnosed gallstones on the incidence of DM while accounting for possible confounders. Our results agree with prior cross-sectional studies[18] and a recent prospective cohort study.[10] Contrary to the prospective study where gallstones and DM were based on self-report, which could introduce misclassification bias,[7] we were able to use objective measures for defining exposure and outcome status. Throughout the study period, gallstones based on US, an ideal method to identify gallstone disease,[12] and DM based on the levels of fasting glucose and A1c, recently adopted criteria for diagnosing diabetes,[19] as well as self-reported history were assessed repeatedly over time, along with other confounders, allowing us to evaluate the association between US-diagnosed gallstones, even in the case of silent gallstones found incidentally during health checkup, and the development of DM even though individuals were unaware of having DM. Additionally, after introducing gallstones and other confounders as time-dependent exposures, the association between gallstones and incident DM persisted in women. For

women, when analyzed in the model using time-dependent variables, the HR of GSD categories did not change much compared to the previous multivariate-adjusted model, which could suggest that both baseline and recent GSD status similarly predicts incident DM, after taking into account all other factors.

Like a previous cross-sectional study in the general population,[18] we found no significant association between gallstones and DM in men. This may be explained possibly by a greater heterogeneity of gallstones in men.[18] Even in a population where gallstones are mainly composed of cholesterol stones, the proportion of cholesterol stones differs by sex and is lower in men than in women.[20] Moreover, in Asia, pigment stone diseases are relatively common.[21] The greater heterogeneity of gallstones in Asian men could explain this gender difference in the association between gallstones and DM seen in our study. Alternatively, the pathogenesis of gallstones might be different by sex. Female sex hormones have been implicated as contributory factors to the promotion of gallstones by increasing the hepatic secretion of biliary cholesterol, diminishing bile salt secretion, and increasing gallbladder stasis.[12] Estrogen and progesterone receptors have been documented in gallbladders of gallstone patients, and the proportion of gallbladders expressing estrogen receptors is higher in women than in men.[22] Further, obese men generally secrete more bile acids and phospholipids into bile than do obese women; consequently, the bile of obese men is less lithogenic.[23] Also, in a study addressing the relationship between adiponectin and type of gallstones, decreased adiponectin levels were associated with cholesterol gallstones, whereas increased adiponectin levels were associated with pigment gallstones.[24] The heterogeneity of gallstones in men and its different pathogenesis by sex and stone type may be responsible for the differences between men and women in this study. Therefore, for establishing that gallstones are risk factors or risk markers for DM, further studies addressing gallstone type and sex difference are needed.

We hypothesized that gallstones, as a manifestation of insulin resistance, possibly mainly cholesterol stones predict incident DM. In East Asians, pigment stones still comprise some portion of gallstones,[12] but gallstone composition has changed over the past decades in East Asian countries,[11] and epidemiological and composition characteristics of gallstone disease have become similar to that seen in Western countries.[25] If pigment stones are included, the association between gallstones and DM may be attenuated.

Compared with previous findings, in this study, the prevalence of GSD at baseline was 2.1% (95% CI, 2.0-2.2), which is lower than in the general population.[5] Since GSD increases with increasing age, this smaller prevalence of GSD can be explained by age and ethnic differences. The frequency of gallstones increases with age, escalating markedly after age 40 to 4-10 times more likely[1]. In our study, 75% of the subjects were younger than 40 years old. Additionally, in Asian population, a lower prevalence of GSD has been reported than in Western countries.[26] Despite the lower prevalence of GSD and a healthy young population, a large sample size made it possible to show a significant association between gallstones, cholecystectomy, and incident DM in women.

The association between gallstones and incident DM can be explained by the relationship of gallstones with insulin resistance.[7,8] An in vitro study suggested that insulin resistance could play a major role in the pathogenesis of gallstone by favoring the production of cholesterol-supersaturated bile and inducing gallbladder inflammation with increased mucus production and by altering gallbladder function.[27] Another experimental animal study indicated that mice with only hepatic insulin resistance, created by liver-specific disruption of the insulin receptor, were markedly predisposed toward cholesterol gallstone formation due to an increase in biliary cholesterol secretion and lithogenic bile salt profile.[6] And epidemiological studies have demonstrated that insulin resistance was independently associated with gallstone disease even in individuals without diabetes.[18,28] Therefore, gallstones as a manifestation of insulin resistance, a key pathogenic factor in DM, can predict increased incidence of DM.

There were several limitations in this study. First, even though abdominal ultrasound is an ideal method to identify gallstone disease,[12] we did not have information on the intra- or interobserver variability of gallbladder ultrasound examinations. However, all examinations were interpreted by experienced radiologists, unaware of the aims of the study, using widely established methods and criteria. Second, values of fasting glucose and A1c were based on single measurements, but should have been repeated to determine the individual's status.[19] However, for defining DM, we included A1c which has good pre-analytical stability and is

not affected by acute perturbations including stress, exercise and smoking.[29] If ascertaining DM was misclassified due to a single measurement, the association between gallstones and DM could be attenuated. Third, indications for cholecystectomy were not available, which can be other reason unrelated to gallstones.[30] For example, cholecystectomy can be performed by acalculous gallbladder diseases such as gallbladder polyps, tumor, acalculous cholecystitis, and biliary dyskinesia, which represent between 5% and 30% of laparoscopic cholecystectomies.[30] In this study, the association between gallstones and DM in women was similar to that between cholecystectomy and DM. However, due to the unavailability of cholecystectomy indications, we cannot conclude that symptomatic gallstone disease or cholecystectomy is a stronger predictor for DM than asymptomatic gallstones. Finally, we studied a young, healthy working Korean population with only low prevalence of gallstones and moderate prevalence of obesity and insulin resistance; thus our findings may not be generalizable to other populations. However, the major strength of our study was that gallstones based on ultrasound and laboratory measures were assessed repeatedly over time, along with other confounders, allowing us to evaluate the association between gallstones and the development of DM.

This cohort study demonstrated that gallstone disease is independently associated with increased incidence of DM compared with no gallstone disease in apparently healthy women, supporting the role of insulin resistance in the pathogenesis of gallstones in human population. Gallstones, regardless of gallstone-related complications, as a risk factor for incident DM, may provide physicians with an opportunity to implement adequate preventive measures in women with gallstone disease.

## 요 약

연구배경: 담석과 인슐린저항성이 관련이 있다고 밝혀져 있으나, 담석증이 있는 환자에서 당뇨병 발생위험이 더 높은지 본 연구는 희박하다. 본 연구는 담석증이 없을 때보다 담석증이 있는 경우 당뇨병 발생위험이 증가하는지 알아보고자 코호트 연구를 수행하였다.

방법: 2005년 1월부터 2006년 12월까지 건강검진 수검자 중에서 30-59세의 당뇨병이 없는 남녀성인 41,518명을 대상으로 2011년 11월까지 추적 관찰하였다. 담석증은 상복부초음파를 통하여 진단되었고, 당뇨병은 공복혈당(≥7.0 mmol $l^{-1}$), 당화혈색소(≥6.5%), 당뇨병약 복용력이 있는 경우로 정의하였다. 담석증에 따른 당뇨병 발생 위험도는 Cox proportional hazard model을 이용하여 분석하였다.

결과: 총 192,999인·년(person-years) 추적 관찰 기간 동안, 2,232명에서 당뇨병 발생이 관찰되었다(발생률, 11.6/1000인·년). 담석증이 없을 때보다, 담석증 또는 담낭절제술을 받은 군에서 당뇨병 발생률이 유의하게 높았고, 이러한 관련성은 여성에서만 관찰되었다. 혼란변수를 보정한 다변량 분석결과, 담석증이 없는 경우와 비교하여, 당뇨병 발생 상대위험도(95% 신뢰구간)는 남자에서는 담석증군 0.95배(0.63-1.42), 담낭절제술을 받은 경우 1.13배(0.53-2.38) 높았고, 여자에서는 담석증군 1.64배(1.13-2.40), 담낭절제술군에서 2.04배(1.01-4.11) 당뇨병 발생위험이 높았다.

결론: 건강한 성인 여성에서 담석증이 있는 경우, 당뇨병 발생위험이 유의하게 높았으나, 남성에서는 이러한 관련성이 없었다. 담석증이 있는 여성에서 당뇨병 발생 예방을 위한 노력이 필요하겠다.

중심 단어: 담석증, 당뇨병, 인슐린저항성, 코호트연구, 발생

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