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Insulin Resistance is Associated with Gallstones Even in Non-obese, Non-diabetic Korean Men

It remains unclear as to whether insulin resistance alone or in the presence of well-known risk factors, such as diabetes or obesity, is associated with gallstones in men. The aim of this study was to determine whether insulin resistance is associated independently with gallstone disease in non-diabetic men, regardless of obesity. Study subjects were 19,503 Korean men, aged 30-69 yr, with fasting blood glucose level <126 mg/dL and without a documented history of diabetes. Gallbladder status was assessed via abdominal ultrasonography after overnight fast. Body mass index and waist circumference were measured. Insulin resistance was estimated by the Homeostasis Model Assessment of insulin resistance (HOMA-IR). The prevalence of obesity, abdominal obesity, and metabolic syndrome in the subjects with gallstones were higher than in those without. The prevalence of elevated HOMA (>75 percentile) in subjects with gallstones was significantly higher than in those without, and this association remained even after the obesity stratification was applied. In multiple logistic regression analyses, only age and HOMA proved to be independent predictors of gallstones. Insulin resistance was positively associated with gallstones in non-diabetic Korean men, and this occurred regardless of obesity. Gallstones appear to be a marker for insulin resistance, even in non-diabetic, non-obese men.

Key Words : *Gallstones; Insulin Resistance; Body Mass Index; Obesity*

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INTRODUCTION

Gallstone disease (GD) remains an important public health problem, due to its extraordinary frequency (1). Despite its common occurrence and profound impact, the pathogenesis of gallstones remains incompletely understood. The reported risk factors are obesity, female gender, childbearing, and family history. New risk factors continue to be identified (2). One of the most prominent risk factors in this regard is insulin resistance. Many studies have implicated diabetes as a risk factor of GD (3-6), but not all population-based epidemiological studies have come to this conclusion (7, 8), and the strength of this association varied markedly across studies. The explanations of the inconsistent findings are due to limitations in design or statistical power, and also that the insulin resistance that characterized most individuals who develop non-insulin-dependent diabetes mellitus may be the primary factor involved in GD formation. A role for insulin in GD has been identified by population-based studies in univariate (9-11), but not multivariate analyses (9-11). Few reports have thus far evaluated the association between gallstones and insulin resistance in non-diabetic and non-obese subjects (12). Therefore, it remains unclear as to whether insulin resistance alone or in the presence of well-known risk factors, including diabetes or obesity, is associated with gallstones.

Obesity is currently the best established predictor of GD; this is significantly more consistent in women than in men. Women have been shown to run a greater risk of GD than men in the majority of studies. This pattern predominates when subjects are younger, and the difference between sex narrows with increasing age, particularly following menopause. Female sex hormone is regarded as the reason for gender differences (13). Obese men generally secrete more bile acids and phospholipids into bile than do obese women; consequently, the bile of obese men is less lithogenic, and they tend to harbor fewer gallstones. In a few studies of men, obesity *per se* was a weaker risk (14). Rather, gallstone disease is more closely related with abdominal obesity, diabetes mellitus, and insulin resistance in white, black, and Hispanic populations (4, 9, 15). However, from the representative data, Ruhl et al., determined that both hyperinsulinemia and diabetes are independent risk factors in women, and that only diabetes appears to be a risk factor in men. The principal reason for the lack of an association may be the relatively low prevalence of gallstones in men (3). The risk of gallstones in men needs to be evaluated more thoroughly in a large population.

The association between cholesterol gallstones and metabolic syndrome or insulin resistance syndrome has been the subject of many recent reports (16). Although the Asian population has a particular metabolic profile that differentiates them from Western populations (17), there is currently only minimal data regarding the relationship among GD and insulin resistance syndrome in apparently healthy Asian men.

Therefore, the present cross-sectional study of non-diabetic Korean men was conducted to determine whether insulin resistance was associated with GD, regardless of obesity.

As the studies about risk factor of gallstone have been conducted principally among symptomatic GD or cholecystectomy patients, we focused in this study on nondiabetic Korean men with gallstones prior to becoming symptomatic or surgery in order to evaluate the effects of insulin resistance on gallstones.

MATERIALS AND METHODS

Participants

The study population was composed of Korean male workers at one of the largest semiconductor manufacturing companies in Korea, as well as its 13 affiliates (18). All of the workers were required to participate in either annual or biennial health examinations, in accordance with the Industrial Safety and Health Law in Korea. This cross-sectional study included 19,503 of 21,572 Korean men, aged 30-69 yr, who underwent medical screening at the Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, between January 1 and October 10, 2005. Our study population was comprised principally of asymptomatic subjects who were referred to the check-up unit by their companies as an annual requirement, and not for symptomatic disease.

In total, 1,792 men were excluded from this study on the basis of the following exclusion criteria that might influence insulin resistance and GD: 266 had histories of a chronic medical illness or major surgery (stomach, small intestine, and colon); 604 reported currently using antihypertensive, antidiabetic, or blood lipid-lowering agents; 824 had fasting blood glucose levels $\geq$126 mg/dL; 200 had a history of cholecystectomy ; 43 had a US finding of sequelae of *Clonorchis sinensis* infection; 34 had a US finding of other gallbladder diseases such as gallbladder polyps, sludge, equivocal lesions, or wall thickening. The Institutional Review Board at Kangbuk Samsung Hospital approved this study.

Measurements and definitions

The health examinations included a medical history, a physical examination, a questionnaire concerning health-related behavior, anthropometric measurements, and biochemical measurements. The medical history and a medication history of prescription drug use were evaluated by the examining physicians. All of the participants were instructed to respond to a questionnaire regarding health-related behavior. Questions regarding alcohol intake included the frequency of alcohol consumption on a weekly basis, and the usual amount consumed on a daily basis. Individuals who reported smoking were identified as current smokers. In addition, the participants were questioned regarding their weekly frequency of physical activity, including jogging, bicycling, and swimming that lasted long enough to generate perspiration. The blood specimens were sampled from the antecubital vein after more than 12 hr of fasting. The serum levels of fasting glucose, total cholesterol, triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were measured using Bayer Reagent Packs on an automated chemistry analyzer (ADVIA 1650™ Autoanalyzer, Bayer HealthCare Ltd., Tarrytown, NY, U.S.A.). The measurements utilized were as follows: hexokinase method for glucose, enzymatic colorimetric assay for LDL-C, HDL-C, total cholesterol, TG, and immunoradiometric assay for insulin (Biosource, Nivelles, Belgium). Insulin resistance was evaluated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): fasting blood insulin (μU/mL) $\times$ fasting blood glucose (mM/L)/22.5. The Korean Association of Quality Assurance for Clinical Laboratories assessed the quality control of the laboratory, both internally and externally, on a regular basis.

Trained nurses obtained sitting blood pressure levels using a standard mercury sphygmomanometer. The first and fifth Korotkoff sounds were utilized to estimate the systolic blood pressure (SBP) and the diastolic blood pressure (DBP). Height and weight were determined after an overnight fast with the subjects wearing a lightweight hospital gown and no shoes. The body mass index (BMI) was calculated as the patient's weight (kg) divided by the square of the patient's height (m). Waist circumference (WC) was evaluated by two trained personnel, to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest with the participants standing, their weight distributed equally on both feet, their arms at their sides, and their heads facing straight forward.

The ATP III proposed the following 5 abnormalities for the definition of metabolic syndrome (19): 1) abdominal obesity; 2) high fasting glucose $\geq$110 mg/dL; 3) hypertriglyceridemia: TG $\geq$150 mg/dL; 4) low HDL-C: HDL-C <40 mg/dL; and 5) high blood pressure: $\geq$130/85 mmHg. We substituted a Waist >90 cm for the threshold of abdominal obesity, on the basis of Asia-Pacific criteria (20). In addition, analyses were conducted using metabolic syndrome as defined on the basis of the criteria established by the International Diabetes Federation (IDF) (21).

The diagnosis of GD was established on the basis of the results of abdominal US using a 3.5-MHz transducer. US was conducted by three experienced radiologists, who were

unaware of the objectives of the study and blinded to laboratory values. Gallstones were defined by the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadowing).

Statistical analyses

All statistical analyses were conducted using the SPSS (version 13.0) software package. The results were demonstrated as the mean±S.D, or the absolute number (percentages). Chi-square tests, Student's t-tests, or analysis of covariance (ANCOVA) for adjusting for age, were employed in order to determine the differences between 2 proportions or means. Logarithm-transformed values of non-normal distribution variables were utilized for comparisons between 2 groups. In order to control the effects of other gallstone-associated covariates, we computed the adjusted gallstone prevalence estimates via binary logistic regression analyses. In order to clarify the relationship between gallstone and insulin resistance, regardless of obesity, analyses were conducted after the subjects were stratified by obesity. Finally, multivariate logistic regression analyses, using a backward procedure on the basis of the likelihood ratios, were conducted in order to determine the independent risk factors for gallstones in non-diabetic subjects, and then in euglycemic subjects. The criteria for variable removal and entry were established at 0.10 and 0.05, respectively. Hosmer and Lemeshow statistics were utilized in order to assess the fit of the logistic regression models. Both final models passed the goodness-of-fit test. The odds ratio (OR) with 95% confidence intervals (95%CI) was estimated. p values of <0.05 were considered to be significant.

RESULTS

Of the 19,503 subjects, 440 (2.3%) had gallstones. The subjects with gallstones were significantly older and evidenced higher measurements for BMI, waist circumference, systolic blood pressure, insulin, and HOMA than were observed in the subjects without gallstones (Table 1). As (increasing) age was identified as a potential confounder and we noted a trend toward a greater proportion in the GD group, we conducted age-adjusted ANCOVA (Table 1). Those whose alcohol intake was moderate had a lower prevalence of gallstones compared to those whose alcohol intake was low or high. Those who had participated in exercise more than 3 times had a higher prevalence of GD compared to those had less

Table 1. Characteristics of subjects based on gallstones

	All subjects n=19,503	No gallstone n=19,063	Gallstone n=440	p value
Age (yr)	42.5±8.1	42.4±8.1	45.7±9.2	<0.001
Smoking status				0.063
Never-smoked	5,683 (29.1)	5,553 (29.1)	130 (29.5)	
<20 pack-years	8,941 (45.8)	8,760 (46.0)	181 (41.1)	
≥20 pack years	4,879 (25.0)	4,750 (24.9)	129 (29.3)	
Alcohol drinking				0.048
<10 g/day	5,327 (27.3)	5,187 (27.2)	140 (31.8)	
10-40 g/day	10,917 (56.0)	106,95 (56.1)	222 (40.4)	
≥40 g/day	3,259 (16.7)	3,181 (16.7)	78 (17.7)	
Exercise, frequency/week				0.042
0	7,798 (40.0)	7,637 (40.1)	161 (36.6)	
1-2	8,065 (41.4)	7,888 (41.4)	177 (40.2)	
3-	3,640 (18.7)	3,538 (18.6)	102 (23.2)	
Body mass index (kg/m^2)	24.4±2.7	24.4±2.7	24.7±2.8	0.006
Waist circumference (cm)	83.3±7.5	83.3±7.4	84.7±7.5	0.001
Total cholesterol (mg/dL)	195.9±32.3	195.8±32.3	196.5±34.3	0.782
LDL cholesterol (mg/dL)	114.7±27.2	114.7±27.2	115.8±28.4	0.588
Triglyceride (mg/dL)*	148.4±89.2	148.5±89.3	145.1±83.9	0.406
HDL cholesterol (mg/dL)	50.4±10.4	50.4±10.3	50.0±11.0	0.213
Systolic blood pressure (mmHg)	116.0±14.4	115.9±14.4	119.3±15.9	0.001
Diastolic blood pressure (mmHg)	80.0±9.6	80.0±9.6	81.4±10.1	0.062
Glucose (mg/dL)	96.8±8.8	96.8±8.8	98.3±9.7	0.067
Insulin*	8.8±3.6	8.8±3.6	9.3±4.1	0.001
HOMA index*	2.1±0.9	2.1±0.9	2.3±1.1	<0.001

Data are mean±standard deviation (SD) or frequency (%). T-test for age; chi-square test for smoking, drinking, and exercise habits; age-adjusted ANCOVA for all other variables; *logarithm transformed values were used for comparison.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA, Homeostasis Model Assessment Index.

Table 2. Prevalence of gallstone disease based on the components of metabolic syndrome (n=19,503)

	Gallstones n (%)	Age-adjusted odds ratios	95% CI (*p* value)	Multivariate-adjusted odds ratios*	95% CI (*p* value)
Body mass index ≥25 (kg/m²)	191 (2.5)	1.21	1.00-1.47 (0.050)	1.22	1.00-1.47 (0.047)
Waist circumference ≥90 (cm)	102 (2.9)	1.27	1.02-1.60 (0.036)	1.29	1.03-1.61 (0.030)
Glucose ≥100 (mg/dL)	179 (2.7)	1.16	0.96-1.42 (0.129)	1.17	0.96-1.43 (0.112)
Glucose ≥110 (mg/dL)	54 (3.3)	1.28	0.96-1.72 (0.099)	1.29	0.96-1.73 (0.090)
SBP ≥130 or DBP ≥85 (mmHg)	180 (2.7)	1.20	0.99-1.46 (0.069)	1.21	0.99-1.47 (0.058)
HDL cholesterol <40 (mg/dL)	61 (2.5)	1.15	0.87-1.51 (0.323)	1.15	0.87-1.51 (0.335)
Triglyceride ≥150 (mg/dL)	167 (2.4)	1.02	0.84-1.24 (0.852)	1.04	0.85-1.27 (0.698)
Metabolic syndrome (ATPIII)†	65 (2.9)	1.24	0.95-1.62 (0.116)	1.26	0.96-1.65 (0.096)
Metabolic syndrome (IDF)	151 (3.1)	1.45	1.12-1.89 (0.006)	1.47	1.13-1.92 (0.004)

Data are expressed as frequency (%) and odds ratios at 95% confidence Interval (*p* value). *Multivariate-adjusted odds ratios were for age, smoking habit, exercise habit, and alcohol drinking habit; †Criteria of abdominal obesity were defined as waist circumference >0.9 m (based on the Asia-Pacific criteria), and the other criteria were defined based on ATP III (the Third Report of the National Cholesterol Education Program Adult Treatment Panel).
SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IDF, International Diabetes Federation.

Table 3. Prevalence ratios for gallstones based on insulin resistance stratified by obesity (n=19,503)

	Age-adjusted odds ratios	95% CI (*p* value)	Multivariate-adjusted odds ratios*	95% CI (*p* value)	*p* value for interaction
Glucose (mg/dL)					0.708
Body mass index <25 (kg/m²)	1.01	1.00-1.02 (0.186)	1.01	1.00-1.02 (0.223)	
Body mass index ≥25 (kg/m²)	1.01	0.99-1.02 (0.366)	1.01	0.99-1.03 (0.262)	
HOMA index					0.482
Body mass index <25 (kg/m²)	1.16	0.98-1.36 (0.081)	1.16	0.98-1.36 (0.078)	
Body mass index ≥25 (kg/m²)	1.18	1.06-1.31 (0.003)	1.18	1.06-1.31 (0.003)	
HOMA 75 percentile					0.577
Body mass index <25 (kg/m²)	1.37	1.04-1.80 (0.024)	1.38	1.05-1.82 (0.021)	
Body mass index ≥25 (kg/m²)	1.52	1.12-2.07 (0.008)	1.53	1.12-2.09 (0.007)	

Data are expressed as odds ratios at 95% Confidence Interval [CI] (*p* value). *Multivariate-adjusted Odds Ratios were adjusted for age, cigarette smoking, alcohol consumption, and exercise habit.
HOMA, Homeostasis Model Assessment Index; HOMA 75 percentile of subjects <25 (kg/m²): 2.22-10.50 units; HOMA 75 percentile of subjects with ≥25 (kg/m²): 3.08-18.59 units.

Table 4. Multivariate logistic regression analyses with gallstones as the dependent variable (n=19,503)

	Multivariate-adjusted odds ratio*	95% CI (*p* value)
Age (yr)	1.045	1.034-1.056 (<0.001)
Waist circumference (cm)	1.013	0.999-1.027 (0.073)
HOMA index	1.140	1.036-1.254 (0.007)

Data are expressed as odds ratios at 95% Confidence Interval (*p* value). *Multivariate models using the backward likelihood method were adjusted for age, smoking habit, drinking habit, exercise habit, body mass index (as a continuous variable; and then substituting abdominal obesity as a categorical variable; substitution made no difference), waist circumference, total cholesterol, glucose, and HOMA as independent variables.
HOMA, Homeostasis Model Assessment Index.

frequent exercise. After subgroup analyses for exercise, frequent exercisers were older, and likely to have higher BMI: after controlling for age and BMI, there was no significant association between the prevalence and exercise frequency (data not shown). However, due to the possibility that habitual smoking, drinking, and exercise were all potential confounders, we adjusted the prevalence ratios for these factors in multivariate models (Table 2-4).

In our age-adjusted logistic regression analyses, a higher prevalence was observed with obesity, abdominal obesity, and metabolic syndrome as defined by IDF (Table 2). After considering hyperglycemia as fasting glucose ≥100 mg/dL (8), the age-adjusted odds ratio of metabolic syndrome (defined by ATPIII) for gallstones was 1.40 (95% CI, 1.14-1.71) (not shown in Table 2). None of the other components, with the exception of abdominal obesity, was associated significantly with the risk of GD. Two obesity indices (BMI and WC) were moderately correlated with the log-transformed HOMA values (age-adjusted r=0.466 for BMI; and age-adjusted r=0.473 for WC).

In our age-adjusted analysis, higher HOMA indices were associated with increased prevalence of gallstones (Table 3).

As compared with those in lower quartiles, increased gallstone prevalence was observed for those in the 4th quartile of the HOMA, and this persisted even after the subjects were stratified by obesity.

Finally, our multiple logistic regression included age, smoking habit, drinking habit, exercise habit, BMI (as a continuous variable and then substituting abdominal obesity as a categorical variable; substitution made no difference), waist circumference, total cholesterol, glucose, and HOMA as independent variables and gallstones as the dependent variable. In multivariate models using the backward likelihood method, only age and HOMA were associated significantly with gallstones (Table 4).

DISCUSSION

In the current study of non-diabetic Korean men, age and the HOMA index were associated with gallstones. Even after obesity stratification was applied, the positive association between gallstones and insulin resistance, as defined by the 4th quartile of HOMA, remained. To the best of our knowledge, this study is the first to demonstrate that the relationship between insulin resistance and gallstone persisted in non-obese subjects.

Scragg et al. were among the first to evaluate the relationship between plasma insulin levels and gallstone risk. In a 1984 hospital-based case control analysis, they determined the fasting insulin means to be higher in gallstone cases of both sexes, regardless of age and triglyceride levels (22). In a small case-control study, fasting insulin was higher in the gallstone group (23). However, in a large, population-based survey, the prevalence of clinical gallbladder disease rose with increasing insulinemia among nondiabetic women; however, this relationship was no longer significant after adjustment for potential confounders (10). In a population-based biliary ultrasonographic survey, Heaton et al. determined that nondiabetic British men with the highest levels of insulin had twice the risk of gallstones as those with low levels, but the relationship proved insignificant after the subjects were matched for waist-to-hip ratio (9). An ultrasonographic survey from Mexico City found that the mean fasting insulin levels in women with gallstones were higher than those of the controls, although no such relationship was detected in men (11). Ruhl and Everhart have clarified the relationship of insulinemia to gallstones in the large scale, NHANES III in women, but not in men. The Asian population was not included in this study (3).

Obesity is a well-established, major risk factor for the development of gallstones, with the basis being an increased hepatic secretion of cholesterol. This risk is particularly high in obese women than in obese men.

In men, obesity *per se* was a weaker risk (14). Rather, GD is more closely related with abdominal obesity, diabetes mellitus, and insulin resistance (4, 9, 15). In this study of Korean men, obesity was not determined to be a significant predictor for gallstones; rather, age and insulin resistance were associated with gallstones.

As has been documented in previous studies, other risk factors, including the presence of metabolic syndrome as an insulin resistance phenotype was associated with an increased prevalence of gallstones (24). However, in these non-diabetic men, among all of the characteristics of metabolic syndrome, waist circumference was the only factor that was significantly associated with the risk of developing gallstones. Several studies have indicated that abdominal adiposity or waist circumference is associated with GD (4, 9, 14, 15). Metabolic syndrome in accordance with IDF criteria predicted gallstones better than did metabolic syndrome as defined by NCEP criteria, because waist circumference was a better predictor of gallstones than cholesterol or fasting glucose.

Waist circumference was a better predictor for gallstones than BMI in men in our study. Another study corroborated that waist circumference predicted gallstones better than did BMI in men (9, 15). Waist circumference is a better indicator of total body fat than is BMI (25). In addition, waist circumference, which is essentially an indicator of abdominal fat, proved to be rather predictive for metabolic complications (19).

The pathogenesis of cholesterol GD is known to be multifactorial, with an interaction of genetic and environmental factors resulting in bile supersaturation, gallbladder hypomotility, and the precipitation/nucleation of cholesterol microcrystals (26).

Insulin levels have been correlated with biliary cholesterol saturation (27). Insulin has been shown previously to augment the activity of hydroxymethylglutaryl coenzyme A reductase, the rate-limiting step in cholesterol synthesis (28). The risk of GD attributable to insulin resistance may not be solely explained by insulin. However, at least in part, it remains simply a surrogate for other pathophysiological factors.

This study had several limitations. First, abdominal adiposity was not evaluated by more accurate methods, including computed tomography (CT), dual-energy radiography absorptiometry (DEXA), and magnetic resonance imaging (MRI), as these are costly and impractical for routine clinical practice. They have, thus far, been used principally for research purposes. Second, the definition of insulin resistance in this study was predicated on only a single insulin measurement. We estimated insulin resistance on the basis of insulin levels and HOMA analyses, not on euglycemic insulin clamp analyses, which are impossible to use for large populations. Third, we were unable to include dietary information, which could be possible confounders for gallstones. Forth, the exact types of gallstones were not determined. Pigment stones proved to be more frequent in the Korean population 30 to 40 yr ago, but the pattern changed rapidly (29, 30). More than half of gallstones were cholesterol stones

by 1990, and cholesterol stones are thought to represent a common condition, especially in younger individuals. In the present study, we tried to minimize by excluding subjects with *Clonorchis sinensis*-related sequelae (parasites causing infectious stones) on the basis of ultrasonic findings, and we excluded subjects in postcholecystectomy states due to the possibility of misclassification from other causes. At present, it is unknown whether insulin resistance might be associated with pigment stones. The heterogeneity of gallstones, if present, would tend to reduce the strength of the association between HOMA and gallstones.

In conclusion, the findings of this study lead us to the conclusion that even in an Asian, non-diabetic male population, insulin resistance appears to be an independent predictor of gallstones, regardless of obesity. Therefore, gallstones appear to be a marker for insulin resistance, even in non-diabetic, non-obese men.

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