The metabolic syndrome is associated with complicated gallstone disease

Naim Ata MD1, Metin Kucukazman MD1, Bunyamin Yavuz MD2, Hakan Bulus MD3, Kursat Dal MD1, Derun Taner Ertugrul MD1, Ahmet Arif Yalcin MD2, Mehmet Polat MD1, Numan Varol MD3, Kadir Okhan Akin MD4, Aral Karabag MD5, Yasar Nazligul MD1

BACKGROUND: Gallstone disease (GD) is a common condition worldwide. Several studies demonstrated that the presence of gallstones is strongly associated with cardiovascular disease. The metabolic syndrome is a highly prevalent cardiovascular condition.

OBJECTIVE: To examine the relationship between complicated GD (CGD) and the metabolic syndrome or its components.

METHODS: Two hundred seventeen patients with gallstones were examined. All patients underwent biliary ultrasonography after a complete medical history and laboratory examination. Data collection for the diagnosis of metabolic syndrome included measurements of waist circumference, blood pressure, and biochemical tests.

RESULTS: Of the 217 patients examined, 115 patients (53%) had CGD and 102 patients (47%) had uncomplicated GD (UCGD). There was a significant difference between the number of patients with large gallstones in the CGD and UCGD groups (n=14 [12%] versus n=2 [2%], respectively; P=0.004). Metabolic syndrome, diabetes mellitus, and large waist circumference were more prevalent in the CGD group than in the UCGD group. Homeostatic model assessment of insulin resistance scores were higher in the CGD group than in the UCGD group (2.51 [95% CI 0.57 to 23.90] versus 2.20 [95% CI 0.09 to 8.87], respectively; P=0.032). Logistic regression analysis revealed that the presence of metabolic syndrome (OR 1.434; 95% CI 1.222 to 1.846, P=0.014), diabetes mellitus (OR 1.493; 95% CI 1.255 to 1.953; P=0.035) and large gallstones (OR 1.153; 95% CI 1.033 to 1.714; P=0.017) were independent predictors of CGD.

CONCLUSION: Results of the present study demonstrated that metabolic syndrome, diabetes and gallstone size were associated with CGD. Further prospective studies are needed to understand the clinical importance of this association.

Key Words: Cholelithiasis; Gallstone disease; HOMA IR; Metabolic syndrome

Gallstone disease (GD) is a common condition worldwide. Because of its high prevalence and elevated health costs, it is an important condition for which further research is needed. Cholesterol comprises more than 80% of gallstones, which are associated with older age, pregnancy, obesity, insulin resistance, specific dietary habits, genetic background and ethnicity (1-3).

The pathogenesis of gallstones is multifactorial and involves environmental and individual factors resulting in three main consequences: bile cholesterol saturation, cholesterol nucleation and gallbladder dysmotility (4). Several studies demonstrated that gallstones are strongly associated with cardiovascular disease (5).

Metabolic syndrome is a highly prevalent cardiovascular condition. The National Cholesterol Education Program Adult Treatment Panel III report (6) provided a working definition of the metabolic syndrome on the basis of the presence of three to five quantitatively defined markers: abdominal obesity, high blood pressure, high fasting glucose level, high triglyceride levels and reduced levels of high-density lipoprotein cholesterol (HDL-C) (6). It is known that the metabolic syndrome and diabetes are risk factors for GD (7); however, there are no data regarding the association between complicated GD (CGD) and metabolic syndrome or its components.

The aim of the present study was to examine the relationship between CGD and the metabolic syndrome or its components.

METHODS

One hundred two consecutive patients with uncomplicated GD (UCGD) and 115 consecutive patients with CGD were examined in the internal medicine and surgery clinics, and emergency room of the Kecioren Teaching and Research Hospital (Ankara, Turkey). Patients were recruited between January 2008 and April 2009. All subjects were examined. All patients underwent biliary ultrasonography after a complete medical history and laboratory examination. Data collection for the diagnosis of metabolic syndrome included measurements of waist circumference, blood pressure, and biochemical tests.

RESULTS: Of the 217 patients examined, 115 patients (53%) had CGD and 102 patients (47%) had uncomplicated GD (UCGD). There was a significant difference between the number of patients with large gallstones in the CGD and UCGD groups (n=14 [12%] versus n=2 [2%], respectively; P=0.004). Metabolic syndrome, diabetes mellitus (OR 1.493; 95% CI 1.255 to 1.953; P=0.035) and large gallstones (OR 1.153; 95% CI 1.033 to 1.714; P=0.017) were independent predictors of CGD.

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underwent biliary ultrasonography after a complete medical history and laboratory examination. Patients who experienced at least one acute cholecystitis attack were defined as having CGD. Data collection included the exploration for risk factors for coronary artery disease, waist circumference measurement (measured at the level of umbilicus with the patient standing), blood pressure measurement, biochemical tests, lipid measurements, lifestyle habits and medications. Patients receiving statins or fibrates before lipid measurement were excluded because of the possibility of introducing bias in the determination of metabolic syndrome.

Informed consent was obtained from the study subjects before enrollment; the study protocol was approved by the ethics committee of the Kecioren Teaching and Research Hospital.

Diagnosis of metabolic syndrome
Participants were defined as having the metabolic syndrome if they fulfilled three or more of the following criteria: waist circumference greater than 102 cm for men, greater than 88 cm for women; diagnosed with hypertension or receiving antihypertensive medication, or two blood pressure measurements exceeding 130/85 mmHg; diagnosed with diabetes mellitus or receiving anti-diabetic treatment, or a fasting blood glucose level of greater than 6.105 mmol/L; HDL-C level lower than 40.136 mmol/L for men, lower than 1.295 mmol/L for women; and triglyceride levels above 1.695 mmol/L.

Biliary ultrasonography
Patients underwent real-time ultrasonographic studies after an overnight fast. Gallstones were defined by the presence of strong intraluminal echoes that were gravity dependent or that attenuated ultrasound transmission (acoustic shadowing). At the completion of each patient’s participation in the study, all ultrasonographic studies were evaluated again by the same radiologist. A gallstone size of 2.5 cm or larger was defined as large, whereas a gallstone size smaller than 2.5 cm was defined as small.

Biochemical analysis
Blood samples were drawn from an antecubital vein from participants after they had fasted for more than 12 h. Total cholesterol and triglyceride levels were measured with commercially available enzymatic colorimetric tests (Konelab, Finland). Low-density lipoprotein cholesterol and HDL-C levels were also measured with commercially available homogeneous enzymatic colorimetric tests (Konelab, Finland).

Fasting serum glucose concentrations were measured enzymatically with an automatic chemistry analyzer (Konelab 60i, Thermo Scientific, Finland). Fasting serum insulin and C-peptide levels were measured using an immunoluminometric assay (Liaison, DiaSorin, USA). Homeostasis model assessment – insulin resistance (HOMA-IR) was calculated using the updated model available from the Oxford Centre for Endocrinology and Diabetes (8).

Statistical analysis
Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test. Data are reported as mean ± SD for normally distributed continuous variables, median (minimum-maximum) for skewed distributed continuous variables and categorical variables are reported as frequencies. Comparisons of categorical variables were performed using the Pearson χ² test. Then means of normally distributed continuous variables were compared by ANOVA. Skewed distributed continuous variables were compared using the Mann-Whitney U test. Skewed variables were log transformed before performing regression analysis. Multivariate logistic regression analyses using a backward procedure on the basis of likelihood ratios were conducted to determine the independent risk factors for CGD. The criteria for variable removal and entry were established at P≤0.10. The OR with 95% CI was estimated. SPSS version 10.0 (SPSS Inc, USA) for Windows (Microsoft Corporation, USA) was used for the analysis, with P<0.05 considered to be statistically significant.

RESULTS
Of 217 patients with gallstones, 115 (53%) had CGD (mean age 54.6±10.2 years) and 102 patients (47%) had UCGD (mean age 55.2±9.6 years). GD duration was (13.6±4.3 years versus 12.6±5.3 years; P=0.108) and the age at diagnosis of cholelithiasis (41.0±9.3 years versus 42.7±6.2 years; P=0.115) were similar between the CGD and UCGD groups, respectively. There was a significant difference between the number of patients with large gallstones in the CGD and UCGD groups (n=14 [12%] versus n=2 [2%], respectively; P=0.004). The number of patients with metabolic syndrome in the CGD group was significantly higher than in the UCGD group (n=54 [47%] versus n=22 [22%], respectively; P=0.001). When the components of metabolic syndrome were compared between groups, diabetes mellitus (54 patients [47%] versus 24 patients [24%]; P<0.001) and large waist circumference (82 patients [71%] versus 59 patients [58%]; P<0.001) were more prevalent in the CGD group than in the UCGD group, respectively. Low HDL-C (35 patients [30%] versus 29 patients [28%]; P=0.747) and high triglyceride levels (53 patients [46%] versus 41 patients [40%]; P=0.382) were not different between the CGD and UCGD groups. Insulin resistance calculated according to the homeostatic model assessment of insulin resistance (HOMA-IR) was higher in the CGD group than in the UCGD group (2.51 [95% CI 0.57 to 23.90] versus 2.20 [95% CI 0.99 to 8.87]; P=0.032). Demographic, clinical and biochemical characteristics of the patients are summarized in Table 1.

The metabolic syndrome and its criteria affecting CGD (diabetes mellitus, high waist circumference), age, HOMA-IR, gallstone size and body mass index were entered into a logistic regression analysis equation to determine the independent factors affecting the CGD patients. Results revealed that the presence of the metabolic syndrome (OR 1.434; 95% CI 1.222 to 1.846; P=0.014), diabetes mellitus (OR 1.493; 95% CI 1.255 to 1.953; P=0.035) and having large gallstones (OR 1.153; 95% CI 1.033 to 1.714; P=0.017) were independent predictors of CGD. Waist circumference, low HDL-C levels, hypertension, high triglyceride levels, HOMA-IR and body mass index were not independently associated with the presence of CGD (Table 2).

DISCUSSION
In the present study, we found that the presence of metabolic syndrome, diabetes and large gallstones were independent predictors of CGD. The current study is the first to demonstrate metabolic syndrome as an independent risk factor for CGD. There are several studies (7,9,10) that examined the association between the metabolic syndrome or its components and the prevalence of gallstones. Mendez-Sanchez et al (7) concluded that GD appeared to be strongly associated with metabolic syndrome. Chang et al (9) reported that the prevalence of obesity, abdominal obesity and the metabolic syndrome in subjects with gallstones were higher than in those without. Shaffer (10) reported obesity as a major risk factor for GD (10). Nakeeb et al (11) demonstrated that insulin resistance alone may be responsible for gallbladder dysmotility, which may result in acalculous cholecystitis or gallstone formation. Most of these studies included asymptomatic patients with gallstones or acalculous cholecystitis, CGD and its association with metabolic syndrome was not studied.

Almost 10% of individuals with asymptomatic cholelithiasis in the general population can be expected to develop symptoms or complications that require treatment within five years (12). Acute cholecystitis, which is acute inflammation of the gallbladder, is a complication that develops in 1% to 3% of patients with symptomatic gallstones (13,14). The primary etiology of acute cholecystitis is obstruction of the cystic duct secondary to an impacted gallstone.

There are certain factors that predict a more serious course in patients with asymptomatic gallstones, which warrant a prophylactic cholecystectomy when they are present. These factors include patients with large (larger than 2.5 cm) gallstones, patients with congenital hemolytic anemia or nonfunctioning gallbladders, or during bariatric surgery.
TABLE 1
Demographic, clinical and biochemical characteristics of the study subjects

|                      | Complicated (n=115) | Uncomplicated (n=102) | P     |
|----------------------|---------------------|-----------------------|-------|
| Age, years           | 54.6±10.2           | 55.2±9.6              | 0.621 |
| Sex, female/male     | 86/27               | 71/31                 | 0.251 |
| Gallstone size†      | 14 (12)/101 (88)    | 2 (2%)/100 (98)       | 0.004 |
| Body mass index, kg/m²| 30.15±5.7          | 31.06±4.3             | 0.845 |
| Systolic blood pressure, mmHg | 130±11          | 127±12                | 0.563 |
| Diastolic blood pressure, mmHg | 82±8           | 79±10                 | 0.678 |
| Total cholesterol, mmol/L | 4.92±1.076       | 4.99±1.153            | 0.631 |
| High-density lipoprotein cholesterol, mmol/L | 1.22±0.326       | 1.25±0.414            | 0.936 |
| Low-density lipoprotein cholesterol, mmol/L | 3.00±0.826       | 3.07±0.901            | 0.541 |
| Triglycerides, mmol/L | 1.76±0.415         | 1.75±0.359            | 0.954 |

Data presented as mean ± SD unless indicated otherwise. *Patients who experienced at least one acute cholecystitis attack were defined as complicated; †Gallstones measuring 2.5 cm or larger in size were defined as large; gallstones measuring smaller than 2.5 cm in size were defined as small.

TABLE 2
Multivariate logistic regression analyses* of complicated gallstone disease as the dependent variable (n=217)

|                      | Multivariate OR | 95% CI       | P     |
|----------------------|-----------------|--------------|-------|
| Metabolic syndrome   | 1.434           | 1.222–1.846  | 0.014 |
| Diabetes mellitus    | 1.493           | 1.255–1.953  | 0.035 |
| Large gallstone†     | 1.153           | 1.033–1.714  | 0.017 |

*Metabolic syndrome, diabetes mellitus, large waist circumference, age and Homeostatic model assessment – insulin resistance, gallstone size and body mass index were entered into the equation for logistic regression analysis. The presence of metabolic syndrome, diabetes mellitus and large gallstones were independent predictors of complicated gallstone disease; †Gallstones measuring 2.5 cm or larger in size were defined as large.

CONCLUSION
Results of the present study demonstrated that the metabolic syndrome, diabetes and gallstone size were associated with CGD. These results suggest that the metabolic syndrome can be regarded as another indication for prophylactic surgery in patients with GD. Further prospective studies are needed to understand the clinical importance of this association.
