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• *BRIEF REPORTS* •

Metabolic syndrome as a risk factor for gallstone disease

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Abstract

AIM: To establish an association between the presence of metabolic syndrome and the development of gallstone disease.

METHODS: We carried out a cross-sectional study in a check-up unit in a university hospital in Mexico City. We enrolled 245 subjects, comprising 65 subjects with gallstones (36 women, 29 men) and 180 controls (79 women and 101 men without gallstones). Body mass index, waist circumference, blood pressure, plasma insulin, and serum lipids and lipoproteins levels were measured. Insulin resistance was calculated by homeostasis model assessment. Unconditional logistic regression analysis (univariate and multivariate) was used to calculate the risk of gallstone disease associated with the presence of at least three of the criteria (Adult Treatment Panel III). Analyses were adjusted for age and sex.

RESULTS: Among 245 subjects, metabolic syndrome was present in 40% of gallstone disease subjects, compared with 17.2% of the controls, adjusted by age and gender (odds ratio (OR) = 2.79; 95%CI, 1.46-5.33; $P = 0.002$), a dose-dependent effect was observed with each component of metabolic syndrome (OR = 2.36, 95%CI, 0.72-7.71; $P = 0.16$ with one component and OR = 5.54, 95%CI, 1.35-22.74; $P = 0.02$ with four components of metabolic syndrome). Homeostasis model assessment was significantly associated with gallstone disease (adjusted OR = 2.25; 95%CI, 1.08-4.69; $P = 0.03$).

CONCLUSION: We conclude that as for cardiovascular disease and diabetes mellitus, gallstone disease appears to be strongly associated with metabolic syndrome.

Key words: Obesity; Metabolic syndrome; Gallstones; Insulin resistance

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INTRODUCTION

The phenotype characteristic of metabolic syndrome was first described by Archard and Thiers[1] in 1921, in association with polycystic ovary syndrome. In 1956, Vague[2] systematically described the features of the metabolic syndrome and in 1966, Welborn *et al*[3], studied 19 non-diabetic patients with essential hypertension and demonstrated that these individuals had significantly higher plasma insulin concentrations compared to a normotensive control group. These observations suggest that the prevalence of resistance to insulin-mediated glucose disposal would be increased in patients with essential hypertension, and it was the first time that the implications of insulin resistance to the development of metabolic syndrome were described. In 1988, Reaven[4] coined the term syndrome X.

The importance of metabolic syndrome is increasing, especially when associated co-morbidities are considered. The prevalence of metabolic syndrome varies according to the diagnostic criteria selected. The general prevalence is 23.7%, although the prevalence varies widely in population analyses[5] and is up to 58.3% in Mexican-American women between 40- and 74-year old[6]. Recently, the prevalence of metabolic syndrome in Mexican population was determined to be 26.6% according to NCEP-III criteria[7].

There are a cluster of metabolic syndromes, that include resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very low-density lipoprotein cholesterol, triacylglycerol, diminished high-density lipoprotein cholesterol (HDL) and hypertension[4]. Furthermore, obesity, which has been progressively increasing worldwide, is closely associated with the increased morbidity and mortality caused by several of the most common diseases in the western world including diabetes, hypertension, cardiovascular diseases, cancer, and gallstone disease[4].

Gallstone disease is a major cause of morbidity in the United States[8,9], other western countries[10,11] and Latin American countries such as Chile[12] and Mexico[13]. In these countries, the economic impact of gallstone disease is high[8-11]. Epidemiological studies have identified risk -factors for cholesterol gallstones[10,14] and obesity and hyperinsulinemia

are the most related of these. In addition, hyperinsulinemia is considered to be a common factor linking cholesterol gallstone disease, diabetes mellitus and obesity[15,16]. Currently, it is thought that the pathogenesis of cholesterol gallstone disease is multifactorial and the disease probably develops from complex interactions between multiple genetic and environmental factors[17,18]. The aim of this study was to establish if there is an association between the presence of metabolic syndrome and the development of gallstone disease.

MATERIALS AND METHODS

Population and sample

We conducted a cross-sectional study in the check-up unit of the Diagnostic Clinic at the Medica Sur Clinic and Foundation. This hospital provides care for mainly middle- and high-income individuals from Mexico City and surrounding metropolitan areas. Our sample population was formed from a series of consecutive asymptomatic subjects who were referred to the check-up unit by their companies as an annual requirement and not for symptomatic disease. The study included 245 subjects who agreed to participate (no one neglected our invitation to participate), 65 subjects found to have gallstones (36 women, 29 men) and 180 controls (79 women and 101 men without gallstones). Gallstones cases and controls were a series of consecutive asymptomatic subjects from the check-up unit. Real-time ultrasonographic studies were done while the subjects were fasting (as part of usual procedures in check-up unit). 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. No discrepancies were found between the results of the first and second evaluations. In the second evaluation, all studies for each subject were viewed side-by-side in a masked fashion. The study was approved by the Medica Sur Clinic and Foundation Ethics Committee.

Questionnaire

Subjects were asked to complete a questionnaire that asked for information on demographic data, age, gender, alcohol consumption, smoking habits, diabetes mellitus, hypertension, chronic liver disease, hyperlipidemia, gastrointestinal surgery (vagotomy gastrectomy for peptic ulcer, ileal resection for inflammatory bowel disease, or any other disease or cause), gravidity, and the use of oral contraceptives.

Metabolic syndrome

Participants, having three or more of the following criteria, were defined as having the metabolic syndrome[19]. The waist to hip >0.85 and high body fat were defined according to previous definitions[20,21]. The other criteria were defined according to the Executive Summary of the Third Report of the National Cholesterol Education Program[19]. (1) Abdominal obesity: waist circumference >102 cm in men and >88 cm in women; (2) Hypertriglyceridemia: triacylglycerol $\geqslant$1.7 mmol/L; (3) Low high-density lipoprotein cholesterol: HDL <1.03 mmol/L in men and <1.3 mmol/L in women; (4) High blood pressure: $\geqslant$17.3/11.3 kPa; (5) High fasting glucose: $\geqslant$6.1 mmol/L.

Physical examination

Body weight was measured, in light clothing and without shoes, to the nearest 0.10 kg. Height was measured to the nearest 0.5 cm. Body mass index was calculated as weight (kg) divided by height (m) squared. Waist circumference (at the nearest 0.1 cm) was measured at the midpoint between the lower border of the rib cage and the iliac crest, and hip circumference was similarly obtained at the widest point between hip and buttock. Body fat percentage was measured using bipolar electric impedance (OMRON model HBF-306INT).

Three blood pressure readings were obtained at 1-min intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analyses.

Analytical procedures

Insulin levels were measured using an immunoenzymometric assay (MEIA; Abbott Diagnostics), with inter- and intra-assay coefficients of variation less than 3%. Plasma glucose in the fasting state was measured in duplicate with an automated analyzer. The coefficient of variation for a single determination was 1.5%. Cholesterol, HDL-cholesterol, and triacylglycerol were measured by enzymatic colorimetric methods, using CHOL, HDL-C plus (second generation) and TG assays (Roche Diagnostics Co., Indianapolis, IN). Low-density lipoprotein cholesterol (LDL) concentrations were calculated using the Friedewald formula[22].

Assessment of insulin resistance using the homeostasis model assessment (HOMA-IR)

HOMA-IR was calculated using the following formula: HOMA index = [fasting insulin (μU/mL) ·fasting glucose (mmol/L)] ·22.5^{-1}, high index of insulin resistance a value >2.5[23]. HOMA-IR has a close correlation with the insulin sensitivity index by the standard euglycemic hyperinsulinemic clamp, as shown by Matthews *et al*[23].

Statistical analysis

By means of cross-tabulations, the risks associated with the probability of developing gallstone disease were estimated. Odds ratios (OR) were calculated with the independent variables coded in a binary form. Statistical significance was determined by exact Fisher's test (two-tailed) and 95% confidence intervals and Mann-Whitney *U* test was used to determine non-normal distribution variables. To derive adjusted OR (by age and gender) associated with the probability of gallstone disease, multivariate unconditional logistic regression analyses were conducted. Multicollinearity in the adjusted models was tested by deriving the covariance matrix. All statistical analyses were carried out with the SPSS/PC v 10.0 program (SPSS Inc., Chicago, IL). The sample size for the study was chosen so that by assuming a prevalence of metabolic syndrome in cases (40%) and controls (17.2%), in a posthoc power calculation was analyzed to get statistically significant differences among cases and controls with >99% power, Table 2.

RESULTS

There were significant differences in the mean of clinical, laboratory and anthropometric data in relation to cases and controls. Cases were older, had greater waist and hip circumferences, body mass index, % body fat, and higher systolic and diastolic blood pressure, blood glucose and HOMA-IR (Table 1). Table 2 shows the crude (non-controlled) risks. In general terms, when anthropometric variables were tested, a higher obesity grade was associated with a higher probability of gallstone disease; however, non-statistical differences were showed related to gender. Waist circumference was also statistically associated with a higher risk of gallstone disease. Hypertension, which is a variable included within the definition of metabolic syndrome, was associated statistically with gallstone disease. An important fact is that none of the lipid variables (total cholesterol, LDL-cholesterol, low HDL-cholesterol and triacylglycerol) was statistically associated with the risk of gallstone disease (Table 2).

Table 1 Mean differences of continuous variables between cases and controls (mean±SD)

Variable	Cases *n*=65		Controls *n*=180		*P*
Age (yr)	51.6	13.7	45.0	11.2	<0.0001
Waist (cm)	97.0	15.6	89.9	13.2	<0.0001
Hip (cm)	105.0	12.9	99.7	11.6	0.001
Waist to hip ratio	0.92	0.07	0.91	0.14	0.08
Body mass index (kg/m²)	28.4	5.7	26.3	4.8	0.001
% body fat	33.1	7.8	28.8	7.5	<0.0001
Systolic blood pressure (kPa)	15.7	2.2	14.4	1.9	<0.0001
Diastolic blood pressure (kPa)	10.0	1.36	9.4	1.3	0.002
Glucose (mmol/L)	5.9	2.3	5.3	1.5	0.01
Insulin (μU/mL)	7.1	4.3	6.1	3.9	0.10
Total cholesterol (mmol/L)	5.3	1.2	5.3	1.0	0.80
HDL-cholesterol (mmol/L)	1.0	0.3	1.1	0.3	0.35
LDL-cholesterol (mmol/L)	3.3	0.9	3.42	0.9	0.53
Triacylglycerol (mmol/L)	1.9	0.9	1.8	1.2	0.18
Cholesterol/HDL ratio	5.3	1.4	5.1	1.6	0.34
HOMA index	1.9	1.2	1.5	1.5	0.02

Table 2 Clinical, demographic, anthropometric and biochemical variables associated with the probability of gallstone disease in univariate logistic regression analysis

Variable	Cases, *n* = 65		Controls, *n* = 180		OR	95%CI	*P*
	n	%	*n*	%			
Gender							
Men *vs* women	29	44.6	101	56.1	0.63	0.34–1.12	0.15
Age (yr)							
⩾45 men; ⩾55 women	38	58.5	69	38.3	2.26	1.27–4.03	0.006
Waist circumference (cm)							
>102 men; >88 women	34	52.3	40	22.2	3.84	2.11–7.00	<0.0001
Waist to hip ratio							
>0.85	55	84.6	139	77.2	1.62	0.76–3.46	0.29
Body mass index (kg/m²)							
⩾25	52	80.0	103	57.2	2.99	1.52–5.88	0.001
Body fat (%)							
⩾30	41	63.1	79	43.9	2.18	1.22–3.91	0.009
Glucose (mmol/L)							
⩾6.1	15	23.1	22	12.2	2.16	1.04–4.47	0.04
Triacylglycerol (mmol/L)							
⩾1.7	32	49.2	76	42.2	1.33	0.75–2.34	0.38
Triacylglycerol (mmol/L)							
⩾2.3	20	30.8	42	23.3	1.46	0.78–2.74	0.25
Total cholesterol (mmol/L)							
⩾6.2	13	20.0	31	17.2	1.20	0.59–2.47	0.71
LDL-cholesterol (mmol/L)							
⩾4.1	16	24.6	38	21.1	1.22	0.63–2.38	0.60
HDL-cholesterol (mmol/L)							
<1.03 male; <1.3 female	43	66.2	110	61.1	1.24	0.69–2.56	0.55
HDL-cholesterol (mmol/L)							
<0.9	19	29.2	51	28.3	1.05	0.56–1.95	0.87
HDL-cholesterol (mmol/L)							
<1.3	54	83.1	135	75.0	1.64	0.79–3.40	0.23
Total cholesterol/HDL-cholesterol							
>7	8	12.3	20	11.1	1.12	0.47–2.69	0.82
Systolic blood pressure (kPa)							
⩾17.3	21	32.3	18	10.0	4.30	2.11-8.76	<0.0001
Diastolic blood pressure (kPa)							
⩾11.3	12	18.5	14	7.8	2.69	1.17–6.16	0.03
Blood pressure (kPa)							
⩾17.3/⩾11.3	21	32.2	23	12.8	3.26	1.65–6.43	0.001
Metabolic syndrome (ATPIII)							
yes *vs* no	26	40.0	31	17.2	3.20	1.71–6.01	<0.0001
Metabolic syndrome (ATPIII)							
0 criterion	4	6.2	39	21.7	1		
1 criterion	16	24.6	58	32.2	2.69	0.84–8.65	0.10
2 criteria	19	29.2	52	28.9	3.56	1.12–11.31	0.03
3 criteria	16	24.6	17	9.4	9.18	2.67–31.55	<0.0001
4 criteria	7	10.8	12	6.7	5.69	1.42–22.80	0.01
5 criteria	3	4.6	2	1.1	14.63	1.86–115.2	0.01
HOMA index							
>2.5	17	26.2	24	13.3	2.30	1.14–4.64	0.03

Metabolic syndrome was associated with a more than three-fold risk of gallstone disease (OR = 3.20; 95%CI, 1.71-6.01; $P = 0.0001$), and the HOMA-IR with a risk of 2.30 (95%CI, 1.14-6.64; $P = 0.03$) (Table 2). Because age was identified as a potential confounder and there was a trend towards a greater proportion of women in the gallstone disease group, compared to the control group (Table 2), we adjusted the risks by both variables (age and gender) in multivariate models (Table 3). Metabolic syndrome increased its risk, with an OR of 2.79 (95%CI, 1.46-5.33; $P = 0.002$). Other anthropometric variables remained statistically associated. Low HDL-cholesterol had a borderline risk (OR = 2.32; 95%CI, 1.05-5.11; $P = 0.04$) in this adjusted analysis.

Table 3 Adjusted[1] risks associated with the probability of gallstone disease in multivariate logistic regression analysis

Model	OR	95%CI	*P*
Glucose (mmol/L)			
≥6.1	2.05	0.96–4.39	0.06
Metabolic syndrome (ATPIII)[2]			
Yes *vs* no	2.79	1.46–5.33	0.002
Metabolic syndrome (ATPIII)			
0 criterion	1		
1 criterion	2.36	0.72–7.71	0.16
2 criteria	3.89	1.20–12.59	0.02
3 criteria	7.89	2.25–27.73	0.001
4 criteria	5.54	1.35–22.74	0.02
5 criteria	7.46	0.89–62.85	0.07
HOMA index			
>2.5	2.25	1.08–4.69	0.03
Waist circumference (cm)			
>102 male; >88 women	3.61	1.95–6.71	<0.0001
Body mass index (kg/m^2)			
25–29.9 *vs* <25	2.35	1.09–5.09	0.03
≥30 *vs* <25	5.84	2.47–13.83	<0.0001
Body mass index (kg/m^2)			
≥25 *vs* <25	3.23	1.57–6.62	0.001
HDL-cholesterol (mmol/L)			
<1.3	2.32	1.05–5.11	0.04
Waist to hip ratio			
>0.85	2.20	0.95–5.12	0.07

[1]All of the models adjusted by: age (≥45 men; ≥55 women) and gender (men *vs* women). [2]Yes = 3 or more criteria of ATPIII. No = 0–2 ATPIII criteria.

DISCUSSION

This is the first study to show an association between gallstone disease and metabolic syndrome in a population with a high prevalence of both diseases[13,24]. The presence of metabolic syndrome was associated with an increased risk of gallstone disease (OR = 3.20; 95%CI, 1.71-6.01; $P = 0.0001$). Of all the characteristics of metabolic syndrome, the presence of high waist circumference was the most important factor associated with the risk of having gallstone disease (OR = 3.84; 95%CI, 2.11-7.00; $P<0.0001$), followed by body mass index (OR = 2.99; 95%CI, 1.52-5.88; $P = 0.001$). This observation coincides with the importance of obesity as a pathophysiological phenomenon in both the conditions[18,25,26]. Obesity is an important risk factor for gallstone disease, more so for women than for men, especially considering that women with a body mass index of 30 kg/m^2 or more have at least twice the risk of gallstone disease as women with a body mass index of less than 25 kg/m^2[27-33]. In our study, the presence of high waist circumference was common in patients with gallstone disease compared with the controls (52.3% *vs* 22.2%). The cornerstone of metabolic syndrome is the presence of obesity, especially considering its increasing prevalence, reaching 20.9% of the United States population[34]. In Mexican-Americans, the prevalence of high waist circumference in patients with metabolic syndrome is higher (62.7%)[35]. Furthermore, in the present study, the presence of insulin resistance in patients with gallstone disease is 26.2%, compared with 13.3% in controls ($P = 0.03$), which confers an increased risk of having gallstone disease (OR = 2.30; 95%CI, 1.14-4.66; $P = 0.03$). This increased risk could be attributed to the presence of obesity, which is a major risk factor for developing gallstone disease, mainly by the presence of lithogenic bile, a consequence of excessive synthesis of cholesterol[35,36]. In addition, increases in the plasma insulin levels seen in obesity could be a determinant in developing gallstone disease. Scragg *et al*[37], show that mean plasma insulin concentration was higher in patients with gallstone disease, independent of triglyceride levels, and the presence of a state of increased plasma insulin levels associated with obesity increases the bile cholesterol saturation index[38,39]. In fact, an increase in insulin concentration of 10 μU/mL was associated with an increased relative risk of developing gallstone disease in women (OR = 1.9; 95%CI, 1.1-4.2). The mechanism by which insulin may increase gallstone formation could be by increasing the activity of hydroxy-3-methylglutaryl-coenzyme A reductase[40], and insulin has been reported to stimulate the bile acid-independent flow of bile in whole animals[41], and in perfused liver[42]. In our multivariate analysis, the increased risk of having metabolic syndrome was maintained in all variables, and show the influence of low HDL cholesterol (OR = 2.32; 95%CI, 1.05-5.11; $P = 0.004$) on developing gallstone disease. One of the main metabolic characteristics of metabolic syndrome is diminished levels of HDL cholesterol[19], with this pattern having an increased risk of cardiovascular morbidity and mortality[43]. The importance of HDL cholesterol in developing gallstone disease has been shown in different analyses, which show that the bile cholesterol saturation index is negatively correlated with HDL cholesterol. Considering the high association between gallstone disease and metabolic syndrome in this study, the fact that blood pressure, especially systolic blood pressure, was associated with metabolic syndrome and gallstone disease appears logical. With more insulin resistance and higher levels of plasma insulin, this association could be explained by the action of insulin in hypertension. Finally, the presence of three criteria of metabolic syndrome confers a 7.89-fold increased risk of having gallstone disease. These data support the strong relationship between the entities that share the cornerstone phenomena of obesity and insulin resistance.

In conclusion, as in cardiovascular disease and diabetes mellitus, gallstone disease appears to be strongly associated with metabolic syndrome. These results are also consistent with the hypothesis that insulin resistance plays an important role in the pathogenesis of such diseases and that gallstone disease may be a part of metabolic syndrome.

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