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The predictors of cholelithiasis in female patients with metabolic syndrome

Research Article

Doina-Clementina Cojocaru*[1,4], Florin Mitu[1,4], Cristina Gena Dascălu[2,4], Alina Manole[3,4], Corina Dima-Cozma[1,4]

1 Ist Medical Department, Faculty of Medicine

2 Medical Informatics and Biostatistics Department, Faculty of Dental Medicine

3 Primary Health Care and Epidemiology Department, Faculty of Medicine

4 University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Romania

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Abstract: Cholesterol gallstone disease is often associated with the metabolic syndrome. Female gender is an unmodifiable risk factor for cholelithiasis and, in its turn, the metabolic syndrome features a sexual dimorphism which warns that a global approach might overlook important discrimination. We carried out a retrospective analytical case-control study in order to perform a comparative analysis between two groups of female patients with metabolic syndrome and gallstones (n=60) or without gallstones (n=65). All the patients were investigated by abdominal ultrasound and met at least three criteria for the diagnosis of metabolic syndrome. Cases and controls were compared regarding anthropometric measurements, a complex lipid profile, and liver function tests. The risks associated with the likelihood of gallstones were estimated by means of cross-tabulation. In order to rank the significant variables we developed a binary logistic regression model which identified lean body weight ≤ 46.44 kg (OR 0.165; 95% CI 0.045-0.611; P = 0.007), total cholesterol ≥ 4.9 mmol/L (OR 15.948; 95% CI 2.700-94.205; P = 0.002), and direct bilirubin > 5.1 μmol/L (OR 0.056; 95% CI 0.013-0.235; P < 0.001), as variables with significant probability of association with the risk of gallstones in women with metabolic syndrome.

Keywords: *Gallstones • Metabolic syndrome • Female*

1. Introduction

Cholesterol gallstone disease is often associated with the metabolic syndrome [1,2]. Epidemiological association of cholelithiasis with metabolic syndrome places this seemingly trivial disease in the broader context of some complex metabolic disorders. The mechanisms underlying this association are incompletely understood; there are various common etiopathogenic links that call into question a cause-effect relationship or just an ordinary association through shared metabolic abnormalities [3].

In its turn, the metabolic syndrome features a sexual dimorphism introduced by gender differentiation for two of the diagnostic criteria: the abdominal perimeter and the HDL-cholesterol levels [4], which warns that a global approach might overlook important discrimination. A recent study [5], which used data from NHANES III trial, tried to outline some phenotypes of the metabolic syndrome, based on age and gender. In young women, the most frequent association of diagnosis criteria was represented by hypertriglyceridemia, low HDL-cholesterol level and abdominal circumference with pathologic values, while elders of both sexes were often met all five criteria for diagnosis, 8% in men and 9.2% in women.

Female gender is an unmodifiable risk factor for cholesterol gallstones manifested particularly during the fertile period, under the hormonal influences [1]. Estrogens and progesterone interfere with some of the primary lithogenic mechanisms such as hepatic hypersecretion

* *E-mail: dccojocaru@mail.umfiasi.ro, tina_rina2000@yahoo.com*

of biliary cholesterol, followed by supersaturated bile (estrogens) and the gallbladder hypomotility (progesterone), leading to impaired enterohepatic bile salts kinetics, which means increased intestinal cholesterol absorption and decreased bile salts absorption, the consequence being the reduction of bile salt pool [6,7].

An important role in the presence of both entities in women is played by the excessive adipose tissue and its disposition, as well as by the long-term weight pattern. The lithogenic risk increases in female gender along with the body mass index (BMI), the early development of obesity, and with serum leptin changes induced by weight fluctuations [8]. Compared to males, insulin resistance appears to be less involved in gallstone disease in women, which have mainly subcutaneous fat, at least in the premenopausal period [7].

In this context, the aim of our study is to perform a comparative analysis of female patients with metabolic syndrome, with and without gallstones, in order to identify several usual anthropometric measurements, lipid and hepatobiliary parameters that differentiate the two groups and are potentially significant for cholesterol gallstones in women with metabolic disorders.

2. Materials and methods

2.1. Population and sample

We carried out a retrospective analytical case-control study, in female patients with metabolic syndrome and gallstones (n = 60) or without gallstones (n = 65). The two groups were composed of patients consecutively admitted to Medical Clinic of Iasi Clinical Rehabilitation Hospital, from January 2007 to December 2008 and who met the study inclusion criteria. The methodology of this study and data collection has been approved by the ethics committee of Iasi Clinical Rehabilitation Hospital.

The inclusion criteria were female gender and meeting at least three of the following five conditions necessary for the diagnosis of metabolic syndrome, according to International Diabetes Federation (IDF), National Heart, Lung, and Blood Institute (NHLBI), and American Heart Association (AHA) consensus from 2009 [4]: waist circumference ≥ 80 cm, triglycerides ≥ 1.7 mmol/L, HDL-cholesterol < 1.3 mmol/L, blood pressure ≥ 17.3/11.3 kPa, impaired fasting glucose ≥ 5.55 mmol/L.

All the patients were investigated by abdominal ultrasound. Diagnosis of uncomplicated gallstones was made by the characteristic image of gallbladder intraluminal mobile formations, with distal acoustic shadowing.

Patients suffering from diseases associated with pigment gallstones, such as infection, hemolytic anemia, toxic or viral chronic hepatitis, and liver cirrhosis, or those with missing values that may affect statistical results were also excluded. In order to study the potential influence of uncomplicated gallstones on liver function tests we have excluded all the patients with biliary lithiasis complicated through infective or obstructive mechanisms, resulting in cholecystitis, cholangitis, choledocholithiasis or biliary pancreatitis and thus being associated with abnormal bilirubin levels, high liver transaminases (caused by inflammatory injury of the adjacent liver), high cholestasis enzymes (alkaline phosphatase, gamma-glutamyl transpeptidase) or leukocytosis.

2.2. Studied parameters

The data were collected from medical records, the following parameters being included: age, height, weight, abdominal perimeter, basal glucose, lipid profile (HDL–cholesterol, total cholesterol, serum triglycerides, LDL–cholesterol), the values of blood pressure on admission or previous diagnosis of hypertension under treatment, and liver function tests: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALKP) and the bilirubins (total, direct and indirect). The values of biological parameters expressed in conventional units were converted to international units.

Based on height and weight we have calculated, for each patient, the body surface area (BSA) (according to Mosteller's formula): BSA (m^2) = [(Height $_{(cm)}$ * Weight $_{(kg)}$) / 3600] ½ [9], the lean body weight (LBW) according to the formula: Lean Body Weight (women) = (1.07 * Weight $_{(kg)}$) – 148 * [$Weight^2$ / (100 * Height $_{(m)}$)^2] and the body mass index (BMI): Body Mass Index = Weight $_{(kg)}$ / Height $_{(m)}^2$ [10,11].

Considering the link between insulin resistance, metabolic syndrome and gallstones, we have calculated some atherogenic and insulin resistance indexes, derived from the regular lipid parameters, defined as follows:

Castelli I risk index = total cholesterol / HDL–cholesterol (normal values < 4.4); Castelli II risk index = LDL- cholesterol / HDL- cholesterol (normal values < 2.9) [12,13].

The lipid accumulation product (women) (LAP) = (waist circumference $_{(cm)}$ – 58) * serum triglycerides $_{(mmol/l)}$ [14].

Reaven insulin resistance index = serum triglycerides / HDL-cholesterol (values ≥ 3.5 mean insulin resistance) [15].

2.3. Statistical methods

The statistical calculations were performed by the SPSS 16.0 software (SPSS Inc., Chicago, IL). The descriptive statistics parameters for the two groups (cases and controls) were determined for all the variables included in the study and the significance was tested using t-Student test for those which follow the normal distribution and Mann–Whitney U test in the case of variables which do not respect the normal distribution law. Moreover, the risks associated with the likelihood of gallstones were estimated by means of cross-tabulation, calculating the odds ratios (OR), with the independent variables encoded in a binary form. The normal standard values were used as reference values, but the lower limit of the 95% confidence interval of the mean values was also tested within the cases (metabolic syndrome with gallstones), in order to find a better cut-off value for significant risks, considering the fact that both groups had metabolic syndrome with consequently increased values for most of the analyzed parameters. In order to rank the variables which were identified as being significant, we developed a binary logistic regression model, and we tested the multicollinearity problems using covariance matrix.

3. Results

The mean age was 55.58 ± 10.40 years for gallstones group and 55.23 ± 6.07 years for controls (P = NS), which indicated perimenopausal women for both groups. Statistically significant differences were found between the two groups for the mean values of the following variables: BMI and waist circumference, total cholesterol, LDL-cholesterol, Castelli I risk index, LAP, ALAT, bilirubin and its components, and alkaline phosphatase. Among these, the BMI values, abdominal perimeter, LAP, total and direct bilirubin, alkaline phosphatase, and ALAT levels were significantly higher within the cases (female patients with metabolic syndrome and cholelithiasis) (Table 1).

All the variables included in the study have been tested, keeping track especially of those in which there were identified statistical significant differences in the mean values between cases and controls.

As regards to the crude risk assessment, we found several variables that were significantly associated with lithogenic risk (OR > 2; P < 0.05): anthropometric measurements, lipid accumulation product, bilirubins (direct and indirect), and cholestasis enzymes (ALKP, GGT) (Table 2).

The results showed that, among the anthropometric measurements, the pathologic waist circumference and a low value of the LBW were the most strongly associated parameters with the risk of gallstones in female patients with metabolic syndrome, also the risk being significantly from BMI values corresponding to the first-degree obesity (BMI ≥ 31.2 kg/m^2).

Other variables which indicated a high lithogenic risk were the liver function tests ALAT, direct bilirubin and cholestatic enzymes (gamma-glutamyl transpeptidase and alkaline phosphatase), which had significant differences in the favour of women with gallstones (cases).

Among the lipid parameters and their derivatives, only high LAP values (≥ 80 cm.mmol/L) were significantly associated with increased risk of cholelithiasis in women with metabolic syndrome; other variables, such as total cholesterol, LDL-cholesterol, Castelli I, and Castelli II risk indexes, registered statistically significant differences between cases and controls, but the values were higher in controls, with apparently protective effect against the biliary disease (OR < 1).

We developed a binary logistic regression model which identified as significant predictors LBW ≤ 46.44 kg (OR = 0.165; 95% CI 0.045-0.611; P = 0.007), total cholesterol ≥ 4.9 mmol/L (OR = 15.948; 95% CI 2.700-94.205; P = 0.002), and direct bilirubin > 5.1 μmol/L (OR = 0.056; 95% CI 0.013-0.235; P < 0.001), as variables with significant probability of association with the risk of gallstones in women with metabolic syndrome (Table 3). The model used the binarized variables, normal reference values being used for their differentiation. Hosmer and Lemeshow Goodness–of-Fit Test, applied to the regression model, showed that it represents a good approximation (P = 0.185), and the classification table showed a 78.4% overall accuracy in characterizing the real situation.

4. Discussion

A number of studies focused on insulin resistance and its effects raised the question of the association between various components of the metabolic syndrome and cholelithiasis [16,17], being followed by studies which proved the significant association of cholesterol gallstones and the metabolic syndrome, as defined by the Adult Treatment Panel III (ATPIII) criteria, in various populations [2,18].

The population of Romania, in which the studied sample is included, has a high prevalence of cholesterol biliary stones, the necroptic and ultrasound studies highlighting an average prevalence of 11-12% in the general population [19,20]. For the definition of

Table 1. Mean differences of continuous variables between cases and controls

Variable	Controls (MS[a] – GS[b]) n = 65		Cases (MS + GS) n = 60		P
	m	SD	m	SD	
BMI[c] (kg/m^2)	30.23	4.33	32.63	5.22	0.006
Waist circumference (cm)	94.78	12.98	106.99	12.59	0.000
BSA[d] (m^2)	1.87	0.15	1.89	0.15	0.54
LBW[e] (kg)	48.36	3.62	47.69	4.85	0.38
Total cholesterol (mmol/L)	6.25	1.19	5.59	1.43	0.006
HDL-cholesterol (mmol/L)	1.21	0.24	1.18	0.2	0.70
LDL-cholesterol (mmol/L)	4.11	1.18	3.56	1.37	0.001
Triglycerides (mmol/L)	1.88	0.74	1.85	0.71	0.80
Castelli I risk index	5.33	1. 53	4.85	1.55	0.005
Castelli II risk index	3.53	1.37	3.12	1.46	0.11
Reaven index	3.75	1.82	3.65	1.42	0.74
LAP[f] (cm.mmol/L)	71.52	45.92	89.65	37.27	0.017
ASAT[g] (U/L)	22.77	9.21	25.55	10.24	0.07
ALAT[h] (U/L)	23.26	11.78	27.75	12.24	0.012
Total bilirubin (μmol/L)	14.12	3.54	15.96	5.23	0.024
Direct bilirubin (μmol/L)	3.63	1.72	7.78	5.41	0.000
Indirect bilirubin (μmol/L)	10.33	2.78	8.17	5.48	0.007
Alkaline phosphatase (U/L)	113.23	36.05	186.78	49.23	0.000
GGT[i] (U/L)	29.28	14.37	37.37	37	0.95

[a] MS – metabolic syndrome [b] GS – gallstones [c] BMI – body mass index
[d] BSA – body surface area [e] LBW – lean body weight
[f] LAP – lipid accumulation product [g] ASAT–aspartate aminotransferase
[h] ALAT–alanine aminotransferase [i] GGT – gamma glutamyl transpeptidase

Table 2. Variables significantly associated with the probability of gallstones

Variable	Controls (MS – GS) n = 65		Cases (MS + GS) n = 60		OR	95% CI		P
	n	%	n	%		Lower	Upper	
BMI ≥ 31.2 kg/m^2	22	33.8%	33	55.0%	2.38	1.15	4.92	0.017
Waist circumference ≥ 103 cm	18	27.7%	39	65.0%	4.84	2.26	10.36	0.000
LBW ≤ 46.44 kg	18	27.7%	31	51.7%	2.79	1.32	5.86	0.006
LAP ≥ 80 cm.mmol/L	21	32.3%	35	58.3%	2.93	1.41	6.09	0.003
ALAT ≥ 24.5 U/L	20	30.8%	29	48.3%	2.10	1.014	4.370	0.044
Direct bilirubin > 5.1 μmol/L	9	13.8%	30	50.0%	6.222	2.615	14.806	0.000
Indirect bilirubin >11.9 μmol/L	24	36.9%	35	58.3%	2.392	1.165	4.909	0.017
Alkaline phosphatase ≥ 174 U/L	4	6.2%	39	65.0%	28.32	9.03	88.75	0.000
Gamma-glutamyl transpeptidase ≥ 36 U/L	13	20.0%	22	36.7%	2.31	1.03	5.17	0.038

the metabolic syndrome, we have chosen the 2009 IDF, NHLBI & AHA consensus definition [4], because it brings populational differentiation in what concerns the cut-off value for the waist circumference, defining element which is very important for studies emerging from different geographical areas.

As far as we know, there are no studies on the correlation between the uncomplicated cholelethiasis and the hepatobiliary functional parameters. The results of our study showed a very significant difference (P < 0.001) between cases and controls in terms of direct bilirubin, also normal mean values for total bilirubin (15.96 ± 5.23

μmol/L), but pathological ones for direct bilirubin (7.78 ± 5.41 μmol/L), as well as the modification of the normal subunit direct to indirect bilirubin ratio, in the sense of the equalization, only in the group with metabolic syndrome and gallstones (Table 1). Furthermore, high values of the direct bilirubin were significantly associated with the risk of lithiasis (OR = 2.8; 95% CI 2.15-3.64; P < 0.001) (Table 2). Moreover, the alkaline phosphatase had the same behaviour in terms of statistical values, having higher values in the group of cases, but within the reference range (< 240 U/L) for our hospital laboratory; GGT had higher mean values for the cases, but it did not reach the level of significance (P = 0.95) (Table 1). Both cholestasis enzymes – GGT and ALKP – were significantly associated with the risk of calculi, but the risk was much higher for ALKP which, from the statistical point of view, was the strongest tested parameter, for high normal values ≥ 174 U/L (OR = 28.32; 95% CI 0.03-88.75; P < 0.001) but not for values above the upper limit of the reference range (OR = 2.12; 95% CI 1.75-2.55; P = 0.13) (Table 2).

These findings drew our attention, because the selected female patients had uncomplicated gallstones, without any evidence of migrated calculi or of pancreatitis and without dilatation of the biliary tract during the abdominal ultrasound. Furthermore, in this biochemical context, the assumption that female patients with uncomplicated biliary lithiasis and metabolic syndrome normally conjugate the bilirubin at the hepatic level, but there are perturbations at the level of intrahepatic biliary excretion, in the sense of an existent subclinical cholestasis, appears plausible. However, larger studies are needed and also the removal of a possible confounding factor represented by osteoporosis, common in elder women and which induces the increase of alkaline phosphatase, irrespective of the cholestasis, is needed. In addition, binary logistic regression model showed that among the liver function tests, only direct bilirubin maintained its association with gallstones.

The lipid profile parameters have provided conflicting results since, except for LAP, which is dependent on the abdominal circumference, lower mean values–sometimes significantly–were recorded in cases compared to controls (Table 1). There are several possible interpretations: one is the indirect confirmation of the fact that there is no parallelism between the values of serum lipid fractions and those of the biliary excreted lipids which contribute directly to the cholesterolic lithogenesis, except for the total cholesterol; another explanation might be that the female patients with gallstones and metabolic syndrome were more carefully monitored before admission due to a higher background cardiometabolic risk, received properly dietary and lipid-lowering treatment, resulting in partial correction of the pathological values of lipid metabolism.

For these reasons, we believe that the lipid parameters with the greatest usefulness in the analysis of lithogenic risk in women with metabolic syndrome are the lipid accumulation product (LAP) ≥ 80 cm.mmol/L (OR = 2.93; 95% CI 1.41-6.09; P = 0.003) and the total cholesterol, starting from normal high values (≥ 4.9 mmol/L), the latter being also validated by the logistic regression model (Table 3).

Our results regarding the anthropometric measurements are supported by the literature, which ascertained the association of cholesterol gallstones with BMI in women [8] and with waist circumference, particularly for male patients [17]. We found a strong association of both abdominal circumference ≥ 103 cm and BMI ≥ 31.2 kg/m^2, as well as lean body weight (LBW) ≤ 46.44 kg with probability of gallstones in female patients with metabolic syndrome. Corroborating these data, we can conclude that excessive fat, reproducing the android pattern of obesity at the expense of lean body mass, would have the highest risk for developing gallstones in women with metabolic syndrome. The fact that the logistic regression model preserves only the LBW as variable associated with the cholelithiasis for this category of patients means that a simple pathological BMI or waist circumference is not sufficiently to predict the development of gallstones in women with metabolic syndrome, without the association of a low ratio of the lean body mass.

In conclusion, following the model developed by our study, the predictors of cholesterol gallstones in female patients with metabolic syndrome are the lean body weight, the total cholesterol and the direct bilirubin. It should be noted that the lipid parameter is subject to iatrogenic fluctuations induced by the lipid-lowering treatment, while increased direct bilirubin correlates with a degree of subclinical cholestasis in these women, whose significance deserves further investigation.

Gallstone disease is an apparently trivial condition but its evolution in time is not completely predictable and it becomes costly when complications arise. Total cholesterol, direct bilirubin and especially lean body weight might provide simple stratification tools for obese women, outlining a high risk profile for developing gallstones so that these patients should preferentially undergo abdominal ultrasound screening and monitoring over time.

Table 3. The variables associated with cholelithiasis in a binary logistic regression model

Variable	OR	95% CI		P
		Lower	Upper	
BMI ≥ 25 kg/m²	0.592	0.044	7.986	0.693
Waist circumference ≥ 80 cm	0.000	0.000	.	0.999
LBW ≤ 46.44 kg	0.165	0.045	0.611	0.007
Total cholesterol ≥ 4.9 mmol/L	15.948	2.700	94.205	0.002
LDL-cholesterol ≥ 3.4 mmol/L	1.112	0.193	6.408	0.905
Castelli I risk index ≥ 4.4	1.106	0.182	6.712	0.913
Castelli II risk index ≥ 2.9	2.668	0.300	23.765	0.379
LAP ≥ 80 cm.mmol/L	0.604	0.185	1.976	0.405
ALAT ≥ 35 U/L	0.362	0.081	1.622	0.184
Direct bilirubin > 5.1 μmol/L	0.056	0.013	0.235	0.000
Indirect bilirubin >11.9 μmol/L	1.077	0.325	3.573	0.903
Alkaline phosphatase ≥ 240 U/L	0.000	0.000	.	0.999
Gamma-glutamyl transpeptidase ≥ 36 U/L	0.382	0.104	1.410	0.149

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