Metabolic Syndrome Associated With Primary Biliary Cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) is characterized by a long natural history and a low incidence of cardiovascular events despite high serum cholesterol levels. The role of any metabolic conditions (obesity, hypertension, diabetes) in association with PBC has not been analyzed, however.

Aim: To assess the influence of metabolic syndrome (MS) on response to ursodeoxycholic acid (UDCA) and the survival in PBC patients.

Methods: The historical database (1975 to 2011) comprising consecutively enrolled PBC patients with a mean follow-up of 123 months (range, 12 to 425 mo) was used. All patients were treated with UDCA (15 mg/kg/d). Responders to UDCA were defined as patients achieving at least a 40% drop in their alkaline phosphatase levels after 1 year. MS was defined according to the American Heart Association criteria. Survival was analyzed by means of Kaplan-Meier curves.

Results: A total of 171 PBC patients were eligible for the study; 55 of them (32.1%) fulfilled the criteria for MS at presentation. Liver function tests and Mayo score were found comparable in PBC patients with and without MS. Histologic stages were similar in the 2 groups at the baseline. Significantly more cardiovascular events occurred in patients with MS during the follow-up ($P < 0.0001$). Response to UDCA was greater in the group without MS, but the difference was not statistically significant. The Kaplan-Meier curves were similar in the 2 groups.

Conclusions: When associated with MS, PBC should be monitored carefully due to the risk of cardiovascular events.

Key Words: PBC, metabolic syndrome, statins, fenofibrate

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Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease mainly affecting women (with a 9:1 female to male ratio). It is characterized by a long natural history and a low incidence of cardiovascular events, despite high serum cholesterol levels.[1–3] Although PBC is associated with a number of extrahepatic manifestations, the role of any metabolic conditions (obesity, hypertension, diabetes) in the natural history of PBC has yet to be analyzed.

The aim of the present study was to shed light on the influence of metabolic syndrome (MS) on response to ursodeoxycholic acid (UDCA) treatment and survival in patients with PBC.

METHODS

Our historical database (1975 to 2011) of PBC patients was used. A detailed description of our recruitment and diagnostic and follow-up criteria are available elsewhere.[4] In this study we included all consecutive PBC patients collected between 1975 and 2011 with at least 1 year of follow-up. PBC was diagnosed on the basis of an antimitochondrial antibody positivity higher than 1:40, abnormal alkaline phosphatase levels (at least 1.5 times the normal value), and/or a compatible liver histology. Patients with the antimitochondrial antibody–negative variant were excluded. All patients were treated with UDCA at the dose of 15 mg/kg/d and underwent a physical and biochemical examination every 6 months after their initial diagnosis, recording relevant data at each visit, and laboratory findings. Additional data used in the study included body mass index (BMI), waist circumference, and blood pressure, which were measured at the time of all eligible participants' physical examination. The laboratory tests included: aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase (GGT), alkaline phosphatase, fasting serum glucose, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, and serum protein profile. Patients with hepatitis B or C infection were excluded from this study. Participants with insufficient data to diagnose or rule out MS were also excluded.

Type II diabetes was defined as fasting blood glucose levels higher than 125 mg/dL or the use of hypoglycemic agents, and hypertension was defined as blood pressure (the mean of 4 readings) higher than 140/90 mm Hg or the use of antihypertensive medication. Obesity was defined as a BMI $\geq$ 30.0; visceral obesity (waist circumference $>$ 102 cm in men or 88 cm in women) was also assessed in all eligible participants.

MS was defined according to the American Heart Association, National Heart, Lung, and Blood Institute scientific statement.[5] The atherosclerotic lipid profile was defined as the presence of high serum cholesterol ($\geq$ 240 mg/dL), high LDL cholesterol ($\geq$ 140 mg/dL), and low HDL cholesterol ($<$ 40 mg/dL). Patients with an atherosclerotic lipid profile received treatment with simvastatin (20 mg/d) in addition to UDCA or with fenofibrate (200 mg/d) in the event of simvastatin intolerance.

Response to UDCA was defined according to the Barcelona criteria, that is, an at least 40% drop in alkaline phosphatase after 1 year of treatment.[6]

The biochemical variables were assayed using standard methods. Serum adiponectine was measured by sandwich

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enzyme-linked immunosorbent assays (R&D System Europe Ltd, Abingdon, UK).

The study was approved by the local Ethical Committee and all subjects gave their informed consent to their participation in the study.

Statistical Analyses

For descriptive statistics, the χ^2d test was used to test for differences between 2 independent groups. Survival was analyzed with Kaplan-Meier curves, and Cox proportional model was applied when appropriate. Logistic regression analysis (with 95% confidence intervals) was applied, using MS as an independent variable. The statistical analysis was done using SPSS software (Chicago, IL).

RESULTS

The study involved 171 patients with PBC (160 females, 11 males; mean age, 53 y; range, 29 to 83 y). Fifty-five of them (32.1%) fulfilled the criteria for MS at presentation. The results of pairwise comparisons between the groups of patients with and without MS are summarized in Table 1. As expected, patients in the group with MS had a significantly higher BMI ($P < 0.0001$), a greater waist circumference ($P < 0.0001$), a higher frequency of type II diabetes ($P < 0.001$), higher serum triglyceride levels ($P < 0.0001$), and lower HDL cholesterol levels ($P < 0.0001$). Serum adiponectin levels were significantly lower in patients with MS than in those without MS (8568.5 vs. 14962.1 ng/mL, $P = 0.02$). The patients' mean age at presentation was also significantly higher among those with MS ($P < 0.045$). Histologic stages, liver function tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, serum bilirubin, total cholesterol), and the Mayo score prognostic index were comparable in the 2 groups.

The mean follow-up was much the same for patients with and without MS (137.3 ± 88.9 vs. 116.3 ± 83.5 mo, respectively, P = NS). Significantly more cardiovascular events occurred during the follow-up among the patients with associated MS (16/55 vs. 6/117, $P < 0.0001$). Cardiovascular events included: acute myocardial infarction in 5 patients, chronic stable angina pectoris in 6, and transient ischemic attacks (due to carotid stenosis) in 5. The mean time from the diagnosis of PBC to the occurrence of cardiovascular events was 5.29 ± 1.95 years.

Response to UDCA treatment was comparable in the 2 groups (25/55 vs. 70/117 P = NS).

Among the 55 patients with MS, 30 had an atherosclerotic profile; 24 of them were given simvastatin and 6 took fenofibrate. Subjects treated with simvastatin showed a statistically significant decrease in both serum cholesterol and alkaline phosphatase after 1 year of treatment [from 271 to 209.3 mg/dL, $P < 0.001$ (for serum cholesterol) and from 1.45 × upper normal limit to 0.97 × upper normal limit, $P < 0.001$ (for alkaline phosphatase)]. The 6 patients treated with fenofibrate showed a trend toward a decrease in both serum cholesterol and alkaline phosphatase after 1 year of treatment, but the trend was not statistically significant.

The Kaplan-Meier survival curves were also much the same for patients with and without MS (Fig. 1). Logistic regression analysis was conducted using the following variables: MS, age at presentation, Mayo score, serum bilirubin, serum adiponectin, cardiovascular morbidity, diabetes, hypertension, BMI, atherosclerotic profile, and response to UDCA; it identified age at presentation as the only parameter independently associated with mortality in PBC patients with MS (adjusted odds ratio 1.100; 95% confidence interval, 1.032-1.173; $P < 0.003$; Table 2).

TABLE 1. Clinical Details of the Study Groups

	PBC With MS (N = 55)	PBC Without MS (N = 116)	*P*
F:M ratio	13:1	16:1	NS
Age at diagnosis (y)	55.3 ± 10.1	51.6 ± 12.7	0.045
Histologic stage I-II [n (%)]	27 (49.1)	58 (50.0)	NS
Histologic stage III [n (%)]	23 (41.8)	46 (39.7)	NS
Histologic stage IV [n (%)]	5 (9.1)	12 (10.3)	NS
BMI	29.6 ± 9.1	22.6 ± 3.2	0.0001
Overweight (BMI 25-30) [n (%)]	32 (58.2)	16 (13.8)	0.001
Obesity (BMI > 30) [n (%)]	20 (36.4)	3 (2.6)	0.001
Waist circumference (cm)	109.8 ± 21.1	77.4 ± 16.6	0.0001
Hypertension [n (%)]	42 (76.4)	27 (23.3)	0.001
Type II diabetes [n (%)]	26 (47.3)	7.0 (6)	0.001
AST (IU/L)	52.2 ± 31	54.8 ± 32.8	NS
ALT (IU/L)	68.6 ± 47.5	68.9 ± 55.5	NS
GGT (IU/L)	281.1 ± 195	233.7 ± 228.2	NS
ALP (IU/L)	421.6 ± 372.1	412.7 ± 384.7	NS
Total bilirubin (mg/dL)	0.85 ± 1.15	0.88 ± 1.17	NS
Total cholesterol (mg/dL)	243.4 ± 46.7	227.3 ± 54.3	NS
HDL cholesterol (mg/dL)	51.7 ± 10.7	59.9 ± 14.4	0.0001
Triglycerides (mg/dL)	146.0 ± 66.5	94.4 ± 34.9	0.0001
Adiponectine (ng/mL)	8568.5 ± 2809.8	14962.1 ± 9772.1	0.02
Mayo score	4.1 ± 0.6	3.9 ± 0.8	NS

Biochemical parameters are expressed as mean ± SD.

Normal values: AST < 35 U/L; ALT < 40 U/L; GGT < 65 U/L; ALP < 115 U/L; high-density cholesterol > 40 mg/dL in male and > 50 mg/dL in female; total cholesterol < 200 mg/dL; triglycerides < 150 mg/dL; total bilirubin < 1.2 mg/dL; glucose 110 mg/dL.

ALP indicates Alkaline phosphatise; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; F, female; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; M, male; MS, metabolic syndrome; PBC, primary biliary cirrhosis.

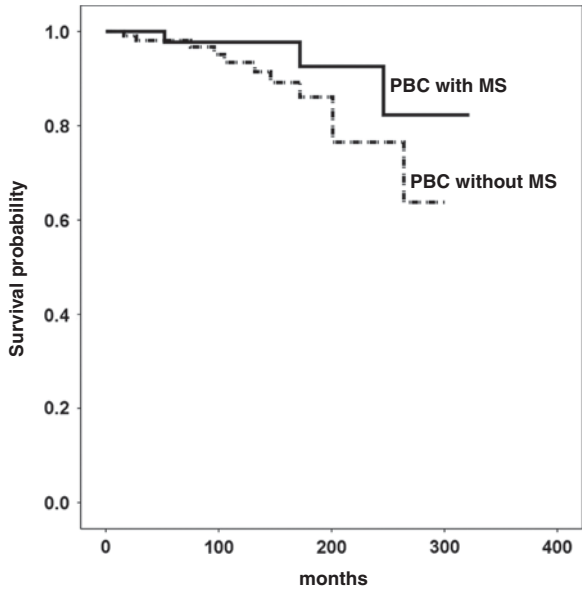

FIGURE 1. Kaplan-Meier survival curves for patients with and without metabolic syndrome (MS). PBC indicates primary biliary cirrhosis.

DISCUSSION

This study assesses MS in association with PBC, using a single-center database of patients with a long-term follow-up. MS was found associated with PBC in 32.1% of cases in our sample. Patients with MS had much the same biochemical profile as those without MS, apart from their HDL cholesterol and triglyceride levels. As expected, they had a higher BMI and waist circumference. The mean age at diagnosis of the PBC patients with MS was also significantly older. The severity of the patients' liver disease (based on histologic stage and Mayo score prognostic index) was similar in the 2 groups. During the follow-up the incidence of cardiovascular events was significantly higher in patients with MS than in those without MS, but their survival rates did not differ. These results prompt several considerations.

TABLE 2. Multivariate Analysis of Risk Factors Associated With Mortality in PBC Patients With MS

Variables	Adjusted OR		Adjusted OR CI 95%	*P*
Mayo score	0.941	0.412	2.150	0.886
Serum bilirubin	0.996	0.996	1.028	0.820
Cardiovascular morbidity	0.899	0.251	3.211	0.869
Diabetes	1.616	0.329	7.941	0.555
Hypertension	2.418	0.580	10.071	0.225
BMI	0.818	0.641	1.045	0.109
Atherosclerotic profile	0.597	0.168	2.119	0.425
Response to UDCA	1.663	0.442	6.262	0.452
Age at presentation	1.100	1.032	1.173	0.003
Metabolic syndrome	2.030	0.285	14.462	0.480
Adiponectine	1.000	1.000	1.000	0.373

BMI indicates body mass index; CI, confidence interval; OR, odds ratio; UDCA, ursodeoxycholic acid.

First of all, it is not surprising that MS should be associated with PBC in roughly 30% of cases. In 2 small studies conducted on PBC patients, MS was found in 30.9% and 20% of cases.[7,8] The first study involved 55 patients with PBC and 44 sex-matched and age-matched healthy controls (43.2% of them diagnosed with MS). The second study enrolled 49 patients with PBC with a view to ascertaining whether MS was associated with an increase in fibrosis: the results suggested careful observation for overweight PBC patients due to a risk of advanced fibrosis,[8] and the authors recommended larger studies to assess the impact of BMI on the clinical progression of PBC and its response to therapy. Our study sheds more light on these issues.

The prevalence and incidence of MS have been increasing over the last 10 years in developed countries.[9] Epidemiological studies on the general population undoubtedly have a great impact on public health strategies designed to prevent mortality related to cardiovascular events and liver cirrhosis. Judging from population-based studies on the prevalence of fatty liver in the general population (using ultrasound combined with a battery of biochemical liver function tests and metabolic performance), it has been estimated that 20% to 30% of the adult population has fatty liver.[10–13] The clinical and histologic features of MS may coexist with other chronic liver diseases, however, and this warrants further investigation.[14]

The problem is that MS has never been considered as a risk factor for survival in clinical studies on PBC patients, nor as a condition correlating with the symptoms of their liver disease. Serum cholesterol is the only biomarker to have been studied in epidemiological and clinical studies.

In a cohort of 312 PBC patients observed for 7.4 years, the incidence of atherosclerotic diseases did not differ statistically from that of age-matched and sex-matched controls.[1] Severe hypercholesterolemia (typical of severe and longstanding cholestasis) was not associated with any increased risk of vascular disease in an Italian cohort of 400 PBC patients followed up for 6.2 years.[2] The same Italian researchers recently conducted ultrasound imaging studies on the carotid artery of 103 PBC patients (38% of them with hypercholesterolemia), 37 controls with hypercholesterolemia, and 141 matched controls with normal cholesterol levels. The controls with hypercholesterolemia, but not PBC patients with high serum cholesterol had an increased risk of intima-media thickness. These results suggest that hypercholesterolemia is not consistently associated with subclinical atherosclerosis in PBC.[3]

Our study is the first to have identified a significantly higher frequency of cardiovascular events in PBC patients with associated MS than in those without the MS. This is probably attributable to factors associated with metabolic conditions, namely age, hypertension, and obesity. In fact, the mean age at presentation of PBC patients with MS was significantly higher than for those without MS. Smoking was not considered in our sample because $< 5\%$ of patients reported smoking (2 to 5 cigarettes/d).

We found no significant difference between the survival of our patients with and without MS. Older age at presentation was the only factor associated with a shorter survival. The medication given to treat MS included antihypertensive drugs, antidiabetes treatment, and statins/fenofibrate in cases presenting with an atherosclerotic profile. Treatment with simvastatin significantly improved serum cholesterol, as observed previously in pilot studies.[15,16] We also found a statistically significant reduction in

alkaline phosphatase in patients treated with simvastatin, but we cannot speculate on any effect of simvastatin in improving survival. Unfortunately, the majority of the published studies on PBC patients given cholesterol-lowering agents, even the controlled trials, do not consider the effect of these agents on lipids, because their main endpoints are to ameliorate liver function test results and improve the efficacy of UDCA.

Our study suffers from some limitations, in that we did not record patients' adherence to dietary recommendations or how much physical exercise they routinely engaged in.

Finally, response to UDCA was similar in patients with and without MS. This can probably be explained by the fact that patients' UDCA dosage was adjusted to their body weight. It may be that MS influences response to UDCA, but we have no explanation for this for the time being. Indeed, high body weight, insulin resistance, or MS have never been considered in analyses on PBC patients' biochemical response to UDCA.[17–19] A cross-sectional study using the United Kingdom-PBC cohort of 2353 patients was recently conducted to analyze the determinants of the clinical phenotype of PBC in relation to the response to UDCA, but here again body weight was not included in the statistical analysis.[20] MS may also exacerbate liver disease by a number of mechanisms, including an increase in free radicals and induction of lipid peroxidation with consequent ability to stimulate the synthesis of the extracellular matrix in stellate cells.[21]

In conclusion, an associated MS increases the cardiovascular morbidity rates in PBC patients and, even if it is not associated with shorter survival rates, this can potentially change the natural history of the disease. An important question arises of whether or not the lipid profile in patients with PBC is antiatherogenic and protects against cardiovascular risk. Our present results do not entitle us to offer a definite answer to this question, because of the limited size of our sample of patients with MS, but a high adiponectin concentration should be regarded as a factor potentially protecting against atherosclerosis,[22] and the results of our study confirm that PBC patients with MS have significantly lower serum levels of adiponectin than those without MS. In addition to seeking protective factors against atherosclerosis, efforts should be made to identify subgroups of PBC patients at high risk of atherosclerotic complications—that is, those with high serum cholesterol levels, and with low HDL cholesterol and high LDL cholesterol levels. In addition to lifestyle measures, a pharmacological approach with cholesterol-lowering agents may be appropriate in these cases, and clinical trials with such agents are warranted in PBC patients at risk of cardiovascular events.

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