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ORIGINAL ARTICLE

Association of Arterial Events With the Coexistence of Metabolic Syndrome and Primary Antiphospholipid Syndrome

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Objective. **Metabolic syndrome (MetS) is highly prevalent in rheumatic diseases and is recognized as a new independent cardiovascular risk factor. This study was undertaken to determine the clinical significance of MetS in patients with primary antiphospholipid syndrome (APS).**

Methods. **Seventy-one primary APS patients and 73 age- and sex-matched healthy controls were included. Serum samples were tested for lipid profile, Lp(a), glucose, insulin, thyroid-stimulating hormone, free T4, erythrocyte sedimentation rate, C-reactive protein level, and uric acid. MetS was defined by the International Diabetes Federation criteria, and insulin resistance was established using the homeostasis model assessment index.**

Results. **The prevalence of MetS was 33.8%, and further comparison between primary APS patients with and without MetS revealed that the former had a higher frequency of arterial events (79.2% versus 42.6%; $P = 0.003$), angina (29.2% versus 2.1%; $P = 0.002$), and positive lupus anticoagulant antibody (95.8% versus 76.6%; $P = 0.049$). In addition, primary APS patients with MetS, as expected, had a higher prevalence of cardiovascular risk factors. On multivariate analysis, only MetS was independently associated with arterial events in primary APS.**

Conclusion. **Coexistence of primary APS and MetS seems to identify a subgroup of patients with higher risk of arterial events, suggesting that MetS may aggravate existing endothelial abnormalities of primary APS.**

INTRODUCTION

Metabolic syndrome (MetS) is rapidly increasing, and this is a major public health issue worldwide (1). It is recognized as a new independent cardiovascular risk factor characterized by visceral adiposity, insulin resistance, low titers of high-density lipoprotein (HDL) cholesterol, and a systemic proinflammatory state (1,2). MetS has been shown to be highly prevalent in rheumatic diseases. Pereira et al (3) observed that the prevalence of MetS in rheumatic diseases varies from 14–62.8%, suggesting that either the presence or the treatment of those conditions seems to influence the risk of developing MetS. In primary antiphospholipid syndrome (APS) patients, a high frequency of this metabolic condition was also reported (4).

APS is an autoimmune thrombophilic disease characterized by venous and/or arterial thrombosis associated or not to pregnancy complications in the presence of antiphospholipid antibodies (aPL) (5). In the absence of any evidence of other autoimmune diseases, it is named primary APS. Of note, APS and MetS display similarities in their pathogenesis regarding endothelial dysfunction and increased thrombogenicity (6–9), raising the possibility that disease expression would be either distinct or more severe in patients with the coexistence of these 2 conditions. There is, however, only 1 study in the literature comparing the overall frequency of MetS in primary APS, and this study shows a high prevalence of MetS in primary APS (4). Therefore, the objective of this study was to evaluate whether MetS in primary APS would determine a subgroup of patients with peculiar clinical and laboratorial manifestations.

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Significance & Innovations

- This study highlights the important relationship between metabolic syndrome (MetS) and primary antiphospholipid syndrome (APS) clinical characteristics.
- Primary APS patients with MetS have higher frequency of lupus anticoagulant and arterial events.
- Coexistence of primary APS and MetS seems to identify a subgroup of patients with higher risk of arterial events.

PATIENTS AND METHODS

Patients. A cross-sectional study was conducted including 71 consecutive adult patients with primary APS (10) followed at the Antiphospholipid Outpatient Clinic of the Rheumatology Division of Clinics Hospital, University of São Paulo, Brazil, from August 2009 to July 2010 (Figure 1). Exclusion criteria were secondary APS and patients age <18 years. A total of 73 age- and sex-matched healthy individuals comprised the control group. All participants underwent a clinical evaluation with a standardized interview, and all medical charts were extensively reviewed. A blood sample after a 12-hour fasting period was also collected. Current or previous clinical parameters evaluated were venous thrombosis (documented deep vein thrombosis and/or pulmonary embolism), arterial thrombosis (clinically documented stroke, transient ischemic attacks, peripheral artery occlusion, acute myocardial infarction, or angina), livedo reticularis, thrombocytopenia (<100,000 platelets/mm^3 in at least 2 distinct occasions), recurrent spontaneous abortions, and "in uterus" fetal loss. Pregnancy and puerperium were evaluated. Waist circumference was measured and body mass index (BMI) was calculated based on the formula weight/$height^2$ (kg/m^2).

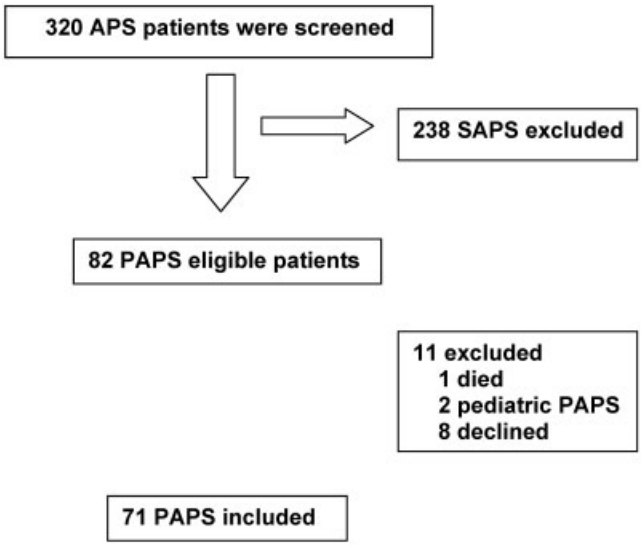

Figure 1. Trial profile of the study patients screened for inclusion according to criteria for antiphospholipid syndrome (APS). SAPS = secondary APS; PAPS = primary APS.

Blood pressure was determined as the average of 2 measurements that were recorded 5 minutes apart after subjects had rested supine for 10 minutes. Family history of premature coronary artery disease (CAD) was defined as a myocardial infarction or stroke before age 55 years in men or before age 65 years in women in a first-degree relative (11). Framingham risk score was applied in order to estimate the 10-year risk for CAD and expressed as a percentage (11). Angina was defined clinically as chest discomfort, i.e., a sensation of heaviness or pressure in the retrosternal area, with possible radiation to the ulnar aspect of the left arm, neck, jaw, midabdomen, right arm, or shoulder and relieved by rest within 1–5 minutes, or more rapidly with sublingual nitroglycerin. Episodes should have lasted from 2–10 minutes (12).

Dyslipidemia was defined as plasma total cholesterol >200 mg/dl, HDL cholesterol <40 mg/dl, low-density lipoprotein (LDL) cholesterol >130 mg/dl, triglycerides >150 mg/dl, or drug treatment for elevated LDL cholesterol or triglycerides (11). Sedentarism was defined by the absence of endurance-type physical activity at least 3 hours per week for at least 2 months (13). This study was approved by the local ethical committee, and all subjects signed an informed consent.

Laboratory evaluation. Blood samples were obtained from the participants after a 12-hour overnight fasting period. Immunologic and biochemical analyses were performed in the same serum samples. Glucose, uric acid, thyroid-stimulating hormone, free T4, and insulin were also measured. Insulin was measured by immunofluorometric assay and reported as μU/ml.

Lp(a). Lp(a) was measured by immunoturbidimetric technique, using a commercial kit (DiaSorin). The instrument calibration was performed using calibrators supplied by the kit. The levels of change were those >30 mg/dl.

Serum immunologic analysis. Anticardiolipin antibodies (aCL) were detected by enzyme-linked immunosorbent assay (ELISA), using a commercially available kit (Enzyme Immunoassay Kit). The cutoff values were <11 IgG phospholipid (GPL)/IgM phospholipid (MPL) units/ml for negative, 11–19 GPL/MPL units/ml for indeterminate, and 20 GPL/MPL units/ml for positive (14,15). Lupus anticoagulant (LAC) was detected using activated partial thromboplastin time (Diagnostica Stago) and diluted Russell's viper venom time (Trinity Biotech) according to international guidelines (10). Serum IgG and IgM anti–β_2-glycoprotein I (anti-β_2GPI) were detected by ELISA technique (ORG 521 anti-β_2GPI IgG/IgM) with cutoff values of 8 units/ml for IgM and 8 units/ml for IgG. The IgG intraassay variation was 2.1–5.0% and interassay variation was 2.6–7.95%. The IgM intraassay variation was 2.1–3.8% and interassay variation was 4.1–6.3%.

Lipid profile. Total cholesterol and triglycerides in serum samples were measured enzymatically (Boehringer Mannheim and Merck, respectively) on a Technicon RA 1000 Analyser (Technicon Instruments) (16,17). HDL

cholesterol was obtained after precipitation of very low-density lipoprotein (VLDL) cholesterol from serum and LDL cholesterol by phosphotungstic acid and magnesium chloride (18), and serum levels were determined by the colorimetric method (Roche Diagnostics). Levels of VLDL cholesterol and LDL cholesterol were estimated since all samples had triglyceride levels <400 mg/dl (19). VLDL cholesterol levels were estimated using the triglyceride level/5 ratio (TG/5) (19), and LDL cholesterol levels were estimated using the following equation:

Total cholesterol = HDL + TG/5 + LDL (19).

Inflammation markers. C-reactive protein levels of all participants were determined by nephelometry, and results were expressed as mg/liter. Erythrocyte sedimentation rate (ESR) was evaluated using the modified Westergren method, and results were expressed as mm/first hour.

MetS definition. MetS was defined according to the International Diabetes Federation criteria as follows: central obesity with ethnic-specific values (waist circumference 80 cm in women and 90 cm in men) plus any 2 of the following 4 factors: 1) fasting glucose >100 mg/dl or previously diagnosed type 2 diabetes mellitus; 2) fasting triglycerides >150 mg/dl or specific treatment for this lipid abnormality; 3) HDL <40 mg/dl in men and <50 mg/dl in women or specific treatment for this lipid abnormality; and 4) systolic pressure 130 mm Hg and/or diastolic 85 mm Hg or treatment of previously diagnosed hypertension (20). On the basis of the Study of Inherited Risk of Coronary Atherosclerosis data, we defined a homeostasis model assessment (HOMA) index with >2.114 as representing the top quartile of a population without diabetes mellitus (21).

Statistical analysis. Demographics and clinical characteristics are expressed as means and SDs for continuous variables or as frequencies and percentages for categorical variables. Median (interquartile range) was calculated for continuous variables not normally distributed. Comparisons between patients and controls and between patients with and without MetS were made using Student's *t*-test or the Mann-Whitney test for continuous variables. Pearson's chi-square test or Fisher's exact test was used for categorical variables.

A logistic regression analysis was performed to determine which variables of MetS and primary APS were independently associated to the higher frequency of arterial events (dependent variable) in patients with the coexistence of these 2 conditions. The independent variables

Table 1. Characteristics of primary APS patients and controls*

Characteristics	Patients with primary APS (n = 71)	Control subjects (n = 73)	*P*
Age, years	41.6 ± 11.6	38.3 ± 11.6	0.089
Female sex, no. (%)	59 (83.1)	60 (82.2)	0.886
White race, no. (%)	62 (87.3)	63 (86.3)	0.856
Disease duration, months	85.7 ± 63.5	NA	NA
Family history of CAD, no. (%)	23 (32.4)	2 (2.7)	< 0.001
Framingham score, %†	4.59 ± 4.56	2.47 ± 2.48	0.001
History of diabetes mellitus, no. (%)	5 (7)	0	0.027
History of hypertension, no. (%)	30 (42.3)	0	< 0.001
Dyslipidemia, no. (%)	40 (56.3)	33 (45)	< 0.001
Tobacco use, no. (%)	10 (14.1)	9 (12.3)	0.756
Current statin therapy, no. (%)	18 (25.4)	0	< 0.001
BMI, kg/m^2	27.35 ± 5.61	23.9 ± 3.17	< 0.001
Waist circumference, cm	90.5 ± 15.9	81.0 ± 8.43	< 0.001
HOMA-IR index	2.0 ± 1.9	1.2 ± 0.8	0.007
Glucose, mg/dl	80.8 ± 18.42	75.0 ± 10.7	0.03
Uric acid, mg/dl	4.8 ± 1.81	4.4 ± 1.1	0.12
Triglycerides, mg/dl	118.6 ± 63.2	103.7 ± 58.6	0.11
Total cholesterol, mg/dl	185.7 ± 43.1	195.2 ± 44.7	0.173
HDL cholesterol, mg/dl	51.3 ± 14.7	60.5 ± 15.7	< 0.001
LDL cholesterol, mg/dl	110.9 ± 35.4	112.4 ± 41.0	0.854
VLDL cholesterol, mg/dl	22.8 ± 11.6	19.5 ± 9.2	0.110
Insulin, μU/ml	9.85 ± 9.0	6.8 ± 4.3	0.006
CRP level, median (range) mg/liter	4.71 (0.2–20.7)	2.96 (0.1–17.6)	0.058
ESR, mm/first hour	12.8 ± 12.0	6.3 ± 4.3	< 0.001
MetS, no. (%)‡	24 (33.8)	5 (6.8)	< 0.001

* Values are the mean ± SD unless indicated otherwise. APS = antiphospholipid syndrome; NA = not applicable; CAD = coronary artery disease; BMI = body mass index; HOMA = homeostasis model assessment; IR = insulin resistance; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MetS = metabolic syndrome.
† Assesses cardiovascular risk within the next 10 years; calculated using the Framingham risk equation.
‡ According to the International Diabetes Federation criteria.

Table 2. Demographics, clinical features, and treatment of primary APS patients with and without MetS*

Variable	MetS present (n = 24)	MetS absent (n = 47)	*P*
Demographic characteristics			
Age, mean ± SD years	47.1 ± 12.0	38.8 ± 10.5	0.004
White race	19 (79.2)	43 (91.5)	0.256
Primary APS duration, mean ± SD months	88.4 ± 57.2	84.3 ± 67.1	0.527
Cardiovascular risk factors			
Family history of CAD	9 (37.5)	14 (29.8)	0.511
Framingham score, mean ± SD (%)†	6.7 ± 5.2	3.5 ± 3.8	0.004
BMI, mean ± SD kg/m^2	30.4 ± 5.0	25.8 ± 5.3	0.001
Waist circumference, mean ± SD cm	99.9 ± 14.6	85.7 ± 14.4	< 0.001
Angina	7 (29.2)	1 (2.1)	0.002
Myocardial infarction	1 (4.2)	0 (0.0)	0.338
Hypertension	20 (83.3)	10 (21.3)	< 0.001
Diabetes mellitus	4 (16.7)	1 (2.1)	0.042
Dyslipidemia	19 (79.2)	21 (44.7)	0.006
Thyroid dysfunction	6 (25.0)	3 (6.4)	0.053
Tobacco use	3 (12.5)	7 (14.9)	> 0.999
Primary APS characteristics			
Arterial events	19 (79.2)	20 (42.6)	0.003
Venous events	14 (58.3)	30 (63.8)	0.652
Pregnancy morbidity	11 (45.8)	16 (34.9)	0.333
Livedo reticularis	8 (33.3)	18 (38.3)	0.681
Thrombocytopenia	3 (12.5)	11 (23.4)	0.355
Stroke	11 (45.8)	15 (31.9)	0.250
Sneddon syndrome	5 (20.8)	8 (17.0)	0.751
Pulmonary embolism	3 (12.5)	12 (25.5)	0.203
Peripheral occlusion	6 (25.0)	3 (6.4)	0.053
Deep venous thrombosis	12 (50.0)	25 (53.2)	0.799
Treatment			
Current statin therapy	12 (50.0)	6 (12.8)	0.001
Oral anticoagulant	21 (87.5)	44 (93.6)	0.399
Chloroquine	9 (37.5)	23 (48.9)	0.360
Low-dose aspirin	13 (54.2)	19 (40.4)	0.271

* Values are the number (percentage) unless indicated otherwise. APS = antiphospholipid syndrome; MetS = metabolic syndrome; CAD = coronary artery disease; BMI = body mass index.
† Assesses cardiovascular risk within the next 10 years; calculated using the Framingham risk equation.

included in the model, according to the univariate analysis, were MetS, LAC, and age.

Measures were presented as odds ratios (ORs) with 95% confidence intervals. *P* values less than 0.05 were considered significant. All analyses were undertaken with SPSS statistics software, version 15.0.

RESULTS

Comparison between patients and controls. Patients with primary APS and control subjects had similar age (mean ± SD 41.6 ± 11.6 versus 38.3 ± 11.5 years; $P = 0.09$), frequency of female sex (83% versus 82.2%; $P = 0.86$), and white race (87.3% versus 86.3%; $P = 0.86$). Higher frequencies of the following cardiovascular risk factors were found more frequently in patients than in controls: family history of CAD (32.4% versus 2.7%; $P < 0.001$), Framingham score (4.59 ± 4.56% versus 2.47 ± 2.48%; $P = 0.001$), BMI (mean ± SD 27.35 ± 5.61 versus 23.9 ± 3.17 kg/m^2; $P < 0.001$), diabetes mellitus (7% versus 0%; $P = 0.027$), systemic arterial hypertension (42.3% versus 0%; $P < 0.001$), dyslipidemia (56.3% versus 45%; $P < 0.001$), with lower HDL cholesterol (mean ± SD 51.3 ± 14.7 versus 60.5 ± 15.7 mg/dl; $P < 0.001$). No differences were observed regarding tobacco use (14.1% versus 12.3%; $P = 0.75$) and sedentarism (59.2% versus 68.5%; $P > 0.24$). Waist circumference was also higher in primary APS patients than controls (mean ± SD 90.5 ± 15.9 versus 81 ± 8.43 cm; $P < 0.001$), as well as glucose levels (mean ± SD 80.8 ± 18.4 versus 75 ± 10.7 mg/dl; $P = 0.03$) and HOMA index (mean ± SD 2.0 ± 1.9 versus 1.23 ± 0.8 units; $P = 0.007$). ESR was significantly higher in primary APS patients in comparison to controls (mean ± SD 12.8 ± 12.0 versus 6.3 ± 4.3 mm/first hour; $P < 0.001$) (Table 1). None of the patients were pregnant, in puerperium, or taking oral contraceptives.

Venous thrombosis was observed in 61.9% of the patients and the majority (84.1%) had deep venous thrombosis; 34.1% had pulmonary embolism. Arterial events were observed in 54.9% of the patients as follows: 66.7% stroke, 23% peripheral occlusion, 20.5% angina, and 2.5% myocardial infarction. Obstetric events occurred in 38.0%,

Table 3. Laboratory findings of primary APS patients with and without MetS*

Variable	MetS present (n = 24)	MetS absent (n = 47)	*P*
Cardiovascular risk factors, mean ± SD			
HOMA-IR index	3.16 ± 2.7	1.42 ± 1.1	< 0.001
Glucose, mg/dl	90.1 ± 24.3	76.0 ± 12.4	0.003
Insulin, μU/ml	14.4 ± 12.9	7.5 ± 5.0	0.001
Uric acid, mg/dl	5.4 ± 1.9	4.4 ± 1.7	0.010
Lipid profile, mean ± SD mg/dl			
Triglycerides	155.8 ± 73.0	99.6 ± 49.0	0.001
Total cholesterol	187.1 ± 36.9	185 ± 46.3	0.447
HDL cholesterol	46.3 ± 14.7	53.7 ± 14.3	0.025
LDL cholesterol	110.4 ± 33.5	111.2 ± 36.6	0.952
VLDL cholesterol	29.7 ± 12.9	19.3 ± 9.3	0.001
Inflammatory markers, median (range)			
C-reactive protein level, mg/liter	2.8 (0.7–17.1)	3.2 (0.2–20.7)	0.688
ESR, mm/first hour	8 (2–58)	9 (2–48)	0.950
Antiphospholipid antibodies, no. (%)			
aCL IgM, MPL units/ml	5 (20.8)	6 (13.3)	0.496
aCL IgG, GPL units/ml	10 (41.7)	19 (42.2)	0.964
Anti-β_2GPI IgM, units/ml	6 (25.0)	6 (12.8)	0.315
Anti-β_2GPI IgG, units/ml	7 (29.2)	18 (38.3)	0.446
Lupus anticoagulant	23 (95.8)	36 (76.6)	0.049
Single positivity	14 (58.3)	27 (57.4)	1.00
Double positivity	2 (8.3)	6 (12.8)	0.708
Triple positivity	8 (33.3)	14 (29.8)	0.790

* MetS diagnosed according to International Diabetes Federation criteria. APS = antiphospholipid syndrome; MetS = metabolic syndrome; HOMA = homeostasis model assessment; IR = insulin resistance; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; ESR = erythrocyte sedimentation rate; aCL = anticardiolipin antibodies; MPL = IgM phospholipid; GPL = IgG phospholipid; anti-β_2GPI = anti–β_2-glycoprotein I.

livedo reticularis in 36.5%, and thrombocytopenia in 19.7% of the cases. LAC positivity was seen in 83.1%, IgG aCL in 42%, IgM aCL in 15.9%, IgG anti-β_2GPI in 35.2%, and IgM anti-β_2GPI in 16.9%.

Comparison of patients with primary APS with and without MetS. The prevalence of MetS in primary APS patients was 33.8%. Comparative analyses between primary APS patients with and without MetS revealed the following in patients with MetS: higher mean age ($P = 0.004$), an expected higher frequency of cardiovascular risk factors, such as percentage of Framingham score ($P = 0.004$), higher BMI ($P = 0.001$), higher frequency of systemic arterial hypertension ($P < 0.001$), and higher frequency of diabetes mellitus ($P = 0.042$). With regard to primary APS characteristics, arterial events (79.2% versus 42.6%; $P = 0.003$) and angina (29.2% versus 2.1%; $P = 0.002$) were more prevalent in patients with concomitant MetS. The use of statins was more common in primary APS ($P = 0.001$) (Table 2).

Table 3 illustrates the laboratory findings in primary APS patients with and without MetS. As anticipated, all evaluated cardiovascular laboratorial risk factors ($P < 0.05$) and dyslipidemia ($P < 0.05$) were more prevalent in those with MetS, whereas no difference was observed for inflammatory markers. The analysis of aPL demonstrated that LAC antibodies were present in 23 of 24 of patients with MetS, which is a higher frequency than in those without this complication ($P = 0.049$), while the other antibody specificities tested occurred in similar frequency in both groups (Table 3).

Association between arterial events and MetS in primary APS. Once a higher frequency of arterial events and LAC in patients with primary APS with MetS was identified, a logistic regression analysis was performed to determine which variables were independently associated with the development of arterial events (dependent variable). Analyzing primary APS with and without arterial events, we found that the presence of LAC represented a major chance for arterial events (OR 4.7, $P = 0.031$). Similarly, patients with MetS had a 5-time greater chance for arterial events (OR 5.13, $P = 0.005$). In logistic regression, MetS remained the only factor independently associated with arterial events (Table 4).

Table 4. Logistic regression arterial events in primary APS with MetS*

Variable	OR	95% CI	*P*
With MetS	3.60	1.08–12.02	0.037
LAC	2.87	0.65–12.53	0.161
Age, years	1.02	0.98–1.08	0.252

* APS = antiphospholipid syndrome; MetS = metabolic syndrome; OR = odds ratio; 95% CI = 95% confidence interval; LAC = lupus anticoagulant.

DISCUSSION

Coexistence of primary APS and MetS seems to identify a subgroup of patients with higher risk of arterial events, suggesting that the latter may aggravate existing endothelial abnormalities of primary APS.

The strength of this study was the simultaneous evaluation of several cardiovascular risk factors, disease, and laboratorial parameters, since the restricted evaluation performed by previous studies may preclude a definitive conclusion about their findings (4,22). In addition, the inclusion of a homogeneous APS group of patients regarding primary APS criteria is essential, since secondary APS might hamper data interpretation. This latter group of patients is usually receiving corticosteroids and/or cytotoxic drugs that can interfere with the development of MetS (23), in addition to the underlying disease pathophysiology that can itself increase the cardiovascular risk in them.

It is important to be aware of the fact that the coexistence of these 2 conditions may be associated with an increased cardiovascular morbidity that may be even greater than the risks associated with each individual component (24). Our study has identified that primary APS patients with and without MetS have distinct CAD emerging risk factors.

Accordingly, there is strong evidence that aPL may have a deleterious effect in endothelium both in vitro (25) and in experimental animal models by inducing vasculopathy and an endothelial proinflammatory/coagulant phenotype (26–28). The higher frequency of aPL in primary APS patients with MetS is of particular concern because these antibodies have a role in endothelial dysfunction (26), which may ultimately contribute to further amplify the accelerated atherosclerosis and thromboembolic complications present in these patients due to MetS (29). In this regard, 2 studies suggested that LAC is a major risk factor for arterial thrombotic events in young women and aPL carriers (30,31), and 2 other studies reported that aPL was associated with higher risk of myocardial infarction (32,33) in an unselected population of young women.

We have found that, beyond the clustering of CAD risk factors that comprise MetS, this syndrome in primary APS patients is also independently associated with high titers of VLDL cholesterol. Likewise, in systemic lupus erythematosus (SLE), MetS was found to be associated with other traditional risk factors for coronary heart disease, mainly obesity and LDL cholesterol >100 mg/dl (34), reinforcing the idea of risk factor clustering in autoimmune diseases. Of note, one-fourth of our patients were taking statins, a drug with known antiinflammatory, anticoagulant, and immunoregulatory effects (35). Its possible contribution to thrombosis prevention in our APS patients deserves further studies, since statins have multiple profound effects in monocyte activity by a significant inhibition on the protein expression of tissue factor (35).

An unexpected higher proportion of angina in patients with MetS and primary APS was observed in spite of a low Framingham score stratification cardiovascular risk (36). This finding may be explained by the limitations of the Framingham algorithm, which does not include other risk factors such as obesity or family history for CAD, as well as emerging risk factors such as inflammatory markers, insulin resistance, and probably underestimates it, especially in women and young adults (23). In fact, a higher risk for atherosclerotic cardiovascular events was reported in APS patients regardless of comparable Framingham risk factors of the general population (37). Reinforcing this finding, Sacré et al (38) showed that the prevalence of occult myocardial ischemia was more than 7 times higher in patients with APS ($P = 0.0006$ versus controls), despite the low Framingham scores. In SLE patients, the Framingham risk scoring model also does not adequately predict the risk of clinical (39) and subclinical (23) atherosclerosis, and a MetS diagnosis seems to more appropriately identify women at risk for cardiovascular disease (36).

aPL are associated with a spectrum of cardiovascular manifestations, including accelerated atherosclerosis, valvular heart disease, intracardiac thrombi, myocardial involvement, and peripheral vascular disease (40–42). This antibody seems to exert proinflammatory and procoagulant effects directly on endothelial cells, and the inflammatory and immune components of autoantibody-mediated thrombosis may play an indirect role in atherogenesis (43). We observed an increased rate of LAC-positive patients, although the overall aPL profile did not discriminate a population at the highest risk of thrombosis, as reported recently (44). Based on this, we speculated that this finding may be due to the fact that these patients are followed in a tertiary care center, and they have generally more severe clinical manifestations with arterial events.

The endothelial dysfunction induced by MetS in patients with primary APS is probably responsible for the higher probability of developing arterial events compared to primary APS patients without metabolic syndrome, strengthening a synergic action of these 2 conditions in determining endothelial dysfunction, accelerated atherosclerosis, and thromboembolic phenomena. Reinforcing these findings, Cugno et al (26) showed that APS patients display an endothelial dysfunction in the absence of other detectable traditional risk factors for atherosclerosis, amplifying the atherothrombotic risk in these patients.

In this context, our findings of higher frequency of hypertension in patients with primary APS and MetS is of major concern since previous studies have demonstrated that this complication is the most important factor for the occurrence of arterial events in primary APS (23,32,33). On the other hand, this is a modifiable condition, and treatment of hypertension may be the most important intervention to reduce arterial thrombosis in these patients (45).

In conclusion, the mutual occurrence of primary APS and MetS seems to identify a subgroup of patients with a distinct autoantibody and lipid profile with a consequent increased risk of arterial events, suggesting that MetS may exacerbate existing endothelial alterations of primary APS.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bonfá had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rodrigues, Bonfá, Caleiro, Vendramini, Bueno, Carvalho.
Acquisition of data. Rodrigues, Caleiro, Vendramini, Bueno, Carvalho.
Analysis and interpretation of data. Rodrigues, Bonfá, Caleiro, Vendramini, Bueno, Lopes, Carvalho.

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