BRIEF REPORT

Impaired ankle-brachial index in antiphospholipid syndrome: Beyond the traditional risk factors

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Introduction: The patients with antiphospholipid syndrome (APS) associate an increased risk of atherosclerosis.

Objective: To determine the predictors of an abnormal ankle-brachial index (ABI), surrogate measure of atherosclerosis, in patients with APS.

Methods: The ABI was measured according to standard recommendations in 106 patients. Traditional cardiovascular risk factors were assessed in all cases. A large spectrum of APS antibodies was determined in 73 patients.

Results: A total of 106 patients diagnosed with APS were included. 28.3% patients included were found to have low ABI. Anti-beta 2-glycoprotein I (aβ2GPI) IgG antibodies [4.00 (1.00-79.00) vs 3.00 (0.00-29.00) U/mL, $P = 0.02$] and antiprothrombin (aPT) IgM antibodies [4.50 (0.00-82.00) vs 3.00 (0.00-14.00) U/mL, $P = 0.05$] titers were found to be higher in patients with abnormal ABI. However, after multivariate regression analysis, only the aβ2GPI IgG titer remained predictor of low ABI ($P = 0.04$).

Conclusions: aβ2GPI IgG associated with impaired ABI in patients with APS. This relation might reflect their involvement in the atherosclerosis occurrence.

KEYWORDS

ankle-brachial index, antiphospholipid syndrome, beta-2 glycoprotein I, cardiovascular risk

1 | INTRODUCTION

The cardiovascular risk increase observed in patients with antiphospholipid syndrome (APS) is not completely explained by the traditional risk factors.¹ Thus, the cardiovascular risk factors' prevalence is similar in APS and other rheumatologic diseases or general population.²

Atherosclerosis is an inflammatory process,³ and also, in immune diseases, systemic inflammation is important⁴ and plays also a pathogenic role for atherosclerosis progression, cytokines, and autoantibodies being involved in the vascular impairment.⁵ Moreover, antiphospholipid antibodies (APLAs) positivity may be related to the vasculopathy occurrence.¹

Ankle-brachial index (ABI) is a noninvasive test that can be used to identify asymptomatic patients with peripheral arterial disease⁶ and also an efficient tool for subclinical atherosclerotic disease screening.⁷

In this research, we intended to determine the predictors of an abnormal ABI, surrogate marker for atherosclerosis in patients with APS, starting from traditional cardiovascular risk factors and continuing to diagnostic and nondiagnostic antiphospholipid antibodies (APLAs).

2 | METHODS

A total of 106 patients fulfilling the APS criteria, diagnosed with both primary and secondary APS, consecutively admitted to the Internal Medicine Department of Colentina Clinical Hospital were prospectively enrolled in the present research. All patients had previous determinations of lupus anticoagulant (LAC), anticardiolipin antibodies

Abbreviations: ABI, ankle-brachial index; aCL, anticardiolipin; aPE, antiphosphatidylethanolamine; aPL, antiphospholipid; APLAs, antiphospholipid antibodies; APS, antiphosphatidylserine; APS, antiphospholipid syndrome; aPT, antiprothrombin; aβ2GPI, anti-β2 glycoprotein I; HTN, hypertension; LAC, lupus anticoagulant; ox-LDL, oxidized low-density lipoprotein; SLE, systemic lupus erythematosus.

(aCL), and anti- β 2 glycoprotein I antibodies (a β 2GPI) as well as history of thrombotic or pregnancy events sustaining the APS diagnosis.

The following exclusion criteria were used: active malignancy (solid or hematological), acute or chronic infections, granulomatous chronic diseases, age under 18 years, pregnancy or 6 months postpartum period, and severe chronic renal failure.

Demographic characteristics and the atherosclerosis traditional risk factors were prospectively recorded for each patient, namely age, gender, body mass index (BMI), waist circumference, waist-hip ratio, disease duration, smoking history, diagnosis of arterial hypertension (HTN), dyslipidemia, diabetes, metabolic syndrome, systolic and diastolic blood pressure, pulse pressure (defined as differential between systolic and diastolic pressure), blood glucose levels, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Values of waist circumference and HDL cholesterol cutoff values were expressed according to gender as the normal ranges are different.

The ABI was assessed using a handheld Doppler-based device and a blood pressure cuff applied to both arms and ankles. The systolic blood pressure was measured twice at each brachial artery and once at each dorsalis pedis and tibialis posterior arteries after 5 minutes of supine position. The ABI was then calculated for the right, respectively, the left side as the ratio between the highest value of the ankle blood pressure and the highest value of the brachial blood pressure.

Serums of 73 patients were collected at baseline and successively stored at -70° . A large spectrum of antiphospholipid antibodies (APLAs) was then determined in one step for all serums: IgG and IgM anticardiolipin antibodies (aCL), IgG and IgM anti- β 2 glycoprotein I antibodies (a β 2GPI), IgG and IgM antiphosphatidylserine antibodies (aPS), IgG and IgM anti phosphatidylethanolamine antibodies (aPE), and IgG and IgM antiprothrombin antibodies (aPT). All determinations were carried out by enzyme-linked immunosorbent assay (ELISA) from Aesku Diagnostics, Wendelsheim, Germany, and the analyzer Chemwell 2910, Awareness Technology, Palm City, Florida, USA.

2.1 | Statistical analysis

Variables were expressed as mean $\pm$ standard deviation and median (min, max) according to their distribution. T-independent, chi-square, and the Mann-Whitney test when appropriate were used to compare two groups. Parameters that proved to be statistically significant in univariate analysis were then tested in a forward conditional multivariate regression model. The cutoff of *P* probability for rejecting the null hypothesis was 0.05. SPSS 16.0 software (SPSS Inc, Chicago, Illinois, USA) was used for the statistical analysis.

3 | RESULTS

3.1 | Study cohort

A total of 106 patients with APS were included. The majority was female gender, with a female-to-male ratio of 92:14. The mean ABI value was 0.91 ± 0.18 . According to the ABI value, two groups were defined: first group (30 patients) with an ABI value lower than 0.9

(low ABI) and a second one (76 patients) with ABI values equal or higher than 0.9. Only one patient had high ABI (>1.40).

General characteristics of the patients as well as the risk factors traditionally associated with atherosclerosis are listed in Table S1.

When compared to patients with normal ABI, those with low ABI were older both at inclusion (51.1 ± 13.2 vs 42.1 ± 11.1 years, $P = 0.001$) and at the APS diagnosis (42.9 ± 13.4 vs 36.1 ± 10.6 years, $P = 0.07$).

In regard to the traditional cardiovascular risk factors, the presence of HTN (63.3% vs 32.9% , $P = 0.008$) and diabetes (23.3% vs 6.6% , $P = 0.02$) was significantly higher in patients with low ABI. Also, the values of the pulse pressure (53.8 ± 12.4 vs 48.7 ± 9.8 mm Hg, $P = 0.02$) and the fasting glucose levels (95.3 ± 17.6 vs 84.6 ± 15.9 mg/dL, $P = 0.004$) were higher in the low ABI group.

3.2 | Antiphospholipid antibodies

In 73 patients—86% of feminine gender, age at inclusion 44.9 ± 0.18 years, and disease duration 3.0 (1.0-29.0) years—an extended APLA was searched.

For this group of patients, the prevalence of cardiovascular risk factors was as follows: smoking (31.5%), HTN (35.6%), dyslipidemia (53.4%), diabetes (8.2%), and metabolic syndrome (8.2%). Moreover, the pulse pressure value was 48.7 ± 9.5 mm Hg, waist-hip ratio 0.9 ± 0.1 , fasting glucose 88.7 ± 17.4 mg/dL, total cholesterol 191.1 ± 41.3 mg/dL, LDL cholesterol 115.6 ± 33.4 mg/dL, HDL cholesterol 58.7 ± 13.2 mg/dL, and triglycerides 98.8 ± 51.2 mg/dL.

Of the tested APLAs, only the titers of IgG a β 2GPI and IgM aPT were significantly higher in the group of patients with low ABI when compared with normal ABI: 4.0 (1.0-79.0) vs 3.0 (0.0-29.0) U/mL, $P = 0.02$; and 4.5 (0.0-82.0) vs 3.0 (0.0-14.0) U/mL, $P = 0.05$, respectively. No significant differences were found for the other APLAs tested (Table S2).

3.3 | Multivariate analysis

In a forward stepwise regression model analyzing parameters associated with ABI in univariate analysis, only the IgG a β 2GPI titer remained predictor of a low ABI ($P = 0.04$). None of the traditional risk factors of subclinical cardiovascular atherosclerosis analyzed proved to be independent risk factor for impaired ABI in the patients with APS included.

4 | DISCUSSION

Ankle-brachial index is a useful screening tool for subclinical atherosclerosis and a facile method for the global cardiovascular risk evaluation.⁶ Impaired ABI is seven times more frequent in patients with APS than controls,⁸ and APLAs presence might be directly involved in the vasculopathy development.¹

In patients with SLE, the occurrence of APS has an additive deleterious effect, determining more aggressive arterial atherosclerosis, especially in young patients.⁹ Also, the abnormal low ABI was identified in patients with APS presenting pregnancy pathology and it was hypothesized that a diffuse vascular impairment might contribute to

pregnancy loss in patients with APS.¹⁰ There are also data that did not show any correlation of the abnormal ABI neither with the cardiovascular risk factors nor with the APLAs positivity.¹¹ To might have final conclusions, there is also the need of standardized testing in APS.¹²

Starting from these data, we evaluated the ABI in patients with primary and secondary APS. The group of APS patients with low ABI presented significant higher age, associated HTN and diabetes, higher blood glucose levels, higher pulse pressure values, and lower HDL cholesterol levels in males. Regarding the ten diagnostic and nondiagnostic APLAs tested, we found statistically significant higher titers of aPT IgM and a β 2GPI IgG in patients with low ABI. However, after multivariate analysis, only the a β 2GPI IgG titer was identified as predictor for an impaired ABI in patients with APS.

The a β 2GPI IgG is diagnostic criteria antibodies,¹³ have pathogenic role in APS,¹⁴ and proved good discriminating accuracy for the APS diagnosis.¹⁵ The interaction between the oxidized low-density lipoprotein (ox-LDL), β 2GPI, and a β 2GPI is proposed as pathogenic mechanism for atherogenesis development. Ox-LDL, an important component of the atherosclerotic lesions,¹⁶ is localized in the atherosclerotic plaque in the proximity of β 2GPI and lymphocytes.¹⁷ The β 2GPI probably has antiatherogenic properties, and so the a β 2GPI antibodies might have proatherogenic effects after inclusion in complexes with ox-LDL and β 2GPI.¹⁸ However, there are other conflicting data showing that the APLAs have no relation with atherosclerotic plaques,¹⁹ but only with the APS thrombotic phenomenon.²⁰

The present research has several limitations. It is a cross-sectional study without prospective follow-up of the patients included. The LAC was not determinate as all determinations were carried out on conserved serum. Nevertheless, a large number of APLAs were tested, ten criteria and noncriteria APS antibodies.

In conclusion, we found a high prevalence of an abnormal ABI in the patients with APS tested. The a β 2GPI IgG titer was independently associated with impaired ABI, possibly reflecting the role of disease itself in the vasculopathy pathogenesis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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