Risk factors associated with Arterial hypertension in patients with Systemic lupus erythematosus. Holguín, Cuba

Factores de riesgo asociados a Hipertensión arterial en pacientes con Lupus eritematoso sistémico. Holguín, Cuba

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ABSTRACT

Introduction: The presence of arterial hypertension in patients with systemic lupus erythematosus is a health problem that has not been studied in Holguín.

Objective: To determine the cardiovascular risk factors associated with hypertension in patients with systemic lupus erythematosus.

Material and Methods: A cross-sectional study was conducted. The universe was composed of 193 patients with lupus who were treated in the Rheumatology Consultation of the Clinical-Surgical Hospital of Holguín from March 3, 2014 to January 1, 2015. The sample was made up of 81 patients who were randomly selected according to a 95 % confidence interval, a population size of 193, an estimated proportion of arterial hypertension of 0,20, a precision of a 7 %, and a design effect of 1. The
recommendations of the American College of Rheumatology were followed for the diagnosis of lupus erythematosus, and national guidelines were used for the diagnosis of hypertension. Clinical, anthropometric, and laboratory variables were determined. Odds Ratio (OR), and 95% confidence intervals (IC95%) for risk determined factors were.

**Results:** The risk factors associated with hypertension in patients with lupus erythematosus are: age (OR=1,04; IC95%:1,01-1,08), age of the lupus onset (OR=1,04; IC95%:1,01-1,08), diabetes mellitus (OR=8,50; IC95%:1,63-44,33), metabolic syndrome (OR=5,09; IC95%:1,87-13,84), hyperuricemia (OR=4,08; IC95%:1,07-15,44), and microalbuminuria (OR=19,81; IC95%:4,24-92,39).

**Conclusions:** The patients with systemic lupus erythematosus presented cardiovascular risk factors associated with arterial hypertension, which are identifiable in the primary health care with variables of relatively easy realization.

**Keywords:** systemic lupus erythematosus, metabolic syndrome, hypertension, risk factors, adults.
INTRODUCTION
Systemic lupus erythematosus (SLE) is the autoimmune disease of greatest heterogeneity due to its clinical and immunological manifestations and evolution. It is considered a chronic inflammatory disease of multifactorial etiology; whose frequency presents some discrepancies among countries. The metabolic syndrome (MS) comprises risk factors characterized by central obesity, glucose intolerance, arterial hypertension (AHT), hypertriglyceridemia, low concentrations of high density lipoprotein (HDL), and insulin resistance (IR). This syndrome favors a proinflammatory and protrombotic state that leads to the appearance of cardiovascular diseases and Type 2 Diabetes Mellitus (DM2). As a basic component of MS, AHT is a cardiovascular risk factor, and a chronic non-communicable disease (CNCD). Its presence in patients with SLE results in a higher risk of morbidity and mortality since it accelerates atherosclerosis and cardiovascular disease, although the mechanisms remain uncertain. SLE is also associated with increased levels of cytokines, a characteristic found in IR and endothelial dysfunction, which are also related to cardiovascular diseases in the general population. Besides the inflammation markers used for the evaluation of cardiovascular risk in these patients, atherogenic indexes are also used.

At present, much research is conducted on MS, AHT, and associated factors in several countries, in Cuba, and in the province of Holguín. Research on patients with lupus is also carried out, up to a certain point. However, the studies about AHT conducted in Cuba in patients with SLE are insufficient and in Holguín there are no precedents of these studies.

Hypertensive patients with SLE present an increase on the prevalence of cardiovascular morbidity and mortality with regard to the general population, so it is important to identify the risk factors to apply promotion and prevention measures that reduce its complications.

OBJECTIVE
The objective of this research is to determine the risk factors associated with arterial hypertension in patients with systemic lupus erythematosus.

MATERIAL AND METHODS
A cross-sectional study was conducted with a total universe of 193 patients with SLE treated in the Rheumatology Consultation of the Clinical-Surgical Hospital of Holguín from March 3 to January 1, 2015.

The sample was composed of 81 patients who were selected by simple random sampling. To calculate the number of patients we used: 95 % confidence interval, a population size of 193, an estimated proportion of arterial hypertension of 0.20, a precision of a 7 %, and a design effect of 1.

The diagnosis of SLE was made according to the recommendations of the American College of...
Rheumatology of 1997. The patients should fulfill at least 4 of the 11 following requirements:

1. Malar exanthema: flat or raised fixed erythema over the malar eminences on the nasolabial folds.
2. Discoid lupus: raised erythematous plaques with adherent keratotic scales and follicular plugs with presence of atrophic scars in old lesions.
3. Photosensitivity: skin rash as an abnormal reaction to sunlight.
4. Painless ulcers: oral or nasopharyngeal.
5. Arthritis: non erosive in ≥ two peripheral joints.
7. Renal affection: proteinuria> 500 mg / 24 h greater than 3 crosses if not quantified; or cylinders composed of red blood cells or hemoglobin, granular, tubular or mixed.
8. Neurological disorders: convulsions or psychoses which are not explained by other causes.
9. Hematologic disorders: hemolytic anemia, leukopenia, <4x10⁹/L in, at least, two determinations; lymphopenia <1,5x10⁹/L in, at least, two determinations; thrombocytopenia <100x10⁹ /L without drugs.
10. Immunological alterations: anti-native DNA to positive or anti-Sm positive titers or positive antiphospholipid antibodies: antcardiolipin, lupus anticoagulant, or false positive lueticserology during six months, confirmed by the immobilization of Treponema pallidum or Treponema I antibody-absorption[FTA-ABS] fluorescent test

Operationalization of the variables:
Cuban guidelines were followed for the determination of arterial hypertension. The patients who presented figures of blood pressure ≥ 140/90 mmHg were considered hypertensive. The patients should fulfill at least three criteria of the National Cholesterol Education Program (ATPIII) for the diagnosis of MS.

- Abdominal obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women.
- Hypertriglyceridemia: serum triglycerides ≥ 1.70 mmol/L.
- Low levels of HDL-cholesterol: men <1,02mmol/L and women <1,29 mmol/L.
- Fasting blood glucose level ≥ 5.55 mmol/L.
- Diabetes Mellitus was diagnosed according to the criteria of the American Diabetes Association:
  - Fasting blood glucose level ≥ 7 mmol/L with symptoms of diabetes.
  - Casual glycemia ≥ 11.1 mmol/L with symptoms of diabetes.
  - Glycemia ≥ 11.1 mmol/L at 2h of an oral load.
- Ischemic heart disease: Patients had a history of angina, acute myocardial infarction or other manifestations of ischemic heart disease and electrocardiographic signs of ischemic heart disease, assessed by a specialist in Cardiology.

Body mass index (BMI) according to weight(kg) /height (m2).

Obesity was considered if BMI ≥ 30. The abdominal diameter or waist circumference was determined at the level of the median axillary line and the upper border of the iliac
The hip perimeter was measured at the level of the greater trochanter. Anthropometric duplicate measurements were made and an average was taken to determine the values. The waist/hip Ratio and waist/height Ratio were determined by dividing the respective values. The skinfolds were measured on the right side, after a previous marking of the area with a crystallographic pencil, with a Holtain® brand caliper with a precision between 0.1-0.2 mm. X1: Bicipital fold: at the mid-point of the radial acromion, in the anterior part of the arm, measured vertically in the meso-brachial ridge. X2: Triceps fold: at the mid-acromion radial point, measured vertically on the posterior side of the arm. X3: Subscapular fold: measured in the direction of the ribs on the inferior angle of the scapula. X4: Suprailiac fold: measured above the iliac crest in the mid-axillary line. To calculate the fat percentage, Siri’s equation was used: \[ \text{% of body fat} = \left[ (4.95/ \text{density}) - 4.5 \right] \times 100, \]
where:

\begin{align*}
\text{Density} &= 1.1776 - 0.0744 \times \log (\text{biceps + triceps + subscapular + suprailiac}) \text{ for males.} \\
\text{Density} &= 1.1567 - 0.0717 \times \log (\text{biceps + triceps + subscapular + suprailiac}) \text{ for women.}
\end{align*}

Body density was calculated with the Durnin & Womerley (1974) equation.\(^{46}\) The venous blood needed to determine duplicate laboratory variables was taken to the patients after 12-14 hours of fasting, and after diets low in lipids for 3 days. The reagents used were from national production (Finlay Laboratories, Havana): Glycemia: Rapiglucotest. Triglycerides: Triglitest for the enzyme determination of serum triglycerides. Total cholesterol: Colestest. The patient had hypercholesterolemia when the concentrations were > 5.2 mmol / L. HDL-cholesterol: homogeneous essay for HDL-C ImmunoFS. C-reactive protein: turbidimetric method with high values > 8 mg / L. Microalbuminuria: Microalb-Latex using a qualitative method with positive result if an agglutination occurs. Uric acid: uric acid mono SL. Hyperuricemia when values were > 428 μmol /L in men and > 357 μmol /L in women. Low-density lipoprotein cholesterol (LDL-cholesterol) according to the Friedewald formula: \(^{47}\) \[ \text{LDL-cholesterol} = \text{Total cholesterol} - \left[ \frac{\text{triglycerides}}{2.1} \right] - \text{HDL-cholesterol} \]
For high values of atherogenic indexes, recommendations for secondary prevention were considered: High Total cholesterol / HDL-cholesterol Ratio > 4.0 for men and > 3.5 for women. High LDL/HDL-cholesterol Ratio > 3.0 for men and > 2.5 for women. High Triglycerides / HDL-cholesterol Ratio > 2.75 for men and > 1.65 for women according to the recommendations of Cordero et al.\(^{49}\) for the diagnosis of MS. The atherogenic index of plasma was calculated as the logarithm of the molar Ratio between the concentration of serum triglycerides and HDL-cholesterol, according to: \(^{50}\)
= log (triglycerides/HDL-cholesterol). It was considered high if > 0.21.
The waist / height Ratio for identifying risk ≥ 0.53.51
Menopause when women were > 45 years and had consecutive absence of menstruations for at least one year.
Smoking habit was considered as a dichotomous variable: smoker and non-smoker.
Hypothyroidism when they presented clinical symptoms and hormonal alterations (TSH, T3 and T4) 30

Statistical analysis:
Quantitative variables were expressed as mean ± standard deviation.

RESULTS
Of the 81 patients with SLE, 75 were female for a 92.59%. The prevalence of AHT was 34.56%.
The mean comparisons were madewith the Mann-Whitney U test or t-test. Odds Ratio (OR) and their 95% confidence intervals (IC95%) of risk factors were calculated. The level of significance chosen was 5%.
The EPIDAT program V. 4.1 was used (Xunta de Galicia, Spain, PAHO, CES University, Colombia, 2014).

Ethical aspects:
The patients gave their informed consent in written form to participate in this research, which was approved by the Scientific Council and Ethics Committee of the University of Medical Sciences of Holguín, Cuba. The authors did not present conflict of interests.

Some clinical and anthropometric variables differed between patients with AHT and without AHT. (Table 1)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Arterial Hypertension</th>
<th>Total (n=81)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=28)</td>
<td>No (n=53)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.45 ± 11.49</td>
<td>40.69 ± 12.23</td>
<td>42.69 ± 12.22</td>
</tr>
<tr>
<td>Age of diagnosis SLE (years)</td>
<td>36.50 ± 12.29</td>
<td>30.75 ± 11.65</td>
<td>32.74 ± 12.24</td>
</tr>
<tr>
<td>Time of Evolution SLE (years)</td>
<td>9.95 ± 9.90</td>
<td>9.94 ± 8.47</td>
<td>9.95 ± 8.23</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124 ± 11.03</td>
<td>115 ± 11.70</td>
<td>118 ± 12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 ± 6.61</td>
<td>73 ± 8.59</td>
<td>76 ± 8.0</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>69.07 ± 15.36</td>
<td>64.87 ± 11.75</td>
<td>66.32 ± 13.17</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>160 ± 7.87</td>
<td>161 ± 7.19</td>
<td>160 ± 7.40</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.88 ± 5.05</td>
<td>24.95 ± 4.32</td>
<td>25.62 ± 4.56</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.95 ± 10.63</td>
<td>90.13 ± 11.10</td>
<td>91.71 ± 10.24</td>
</tr>
<tr>
<td>Hip perimeter (cm)</td>
<td>103 ± 10.33</td>
<td>106 ± 9.54</td>
<td>107 ± 9.85</td>
</tr>
<tr>
<td>Waist/hip Ratio</td>
<td>0.85 ± 0.07</td>
<td>0.84 ± 0.07</td>
<td>0.85 ± 0.07</td>
</tr>
<tr>
<td>Waist/height Ratio</td>
<td>0.58 ± 0.07</td>
<td>0.55 ± 0.06</td>
<td>0.57 ± 0.06</td>
</tr>
</tbody>
</table>
Table 2 shows the significantly associated risk factors or not associated ones to AHT in patients with Systemic Lupus Erythematosus.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.01-1.08</td>
<td>0.04*</td>
</tr>
<tr>
<td>Age of onset of SLE</td>
<td>1.04</td>
<td>1.01-1.08</td>
<td>0.04*</td>
</tr>
<tr>
<td>Time of evolution of SLE</td>
<td>1.00</td>
<td>0.94-1.05</td>
<td>0.99</td>
</tr>
<tr>
<td>Total cholesterol /HDL-cholesterol Ratio</td>
<td>1.49</td>
<td>0.59-3.75</td>
<td>0.39</td>
</tr>
<tr>
<td>LDL-cholesterol/HDL-cholesterol Ratio</td>
<td>1.49</td>
<td>0.57-3.90</td>
<td>0.49</td>
</tr>
</tbody>
</table>
**DISCUSSION**

Age constituted a significant cardiovascular risk factor in patients with AHT and SLE; that is, the older you get, the greater your risk; which is due to the ageing process that favors atherosclerosis, inflammation, oxidative stress, and endothelial dysfunction.\(^{52}\)

On the other hand, SLE affects the arterial walls and causes atherosclerosis due to its systemic and chronic nature. Also, some medications administered such as steroids retain water and electrolytes at a kidney level, which favors the venous return and cardiac output, factors that influence on the elevation of blood pressure.\(^{8}\) This explains, at least, part of the role of the onset age of SLE as a risk factor strongly associated with AHT.
Diabetes Mellitus increased the risk of AHT (about 8.5 times), which is explained by the close links between DM2 and AHT, which coincides with the majority of researchers who find higher levels of blood pressure in diabetic patients.33,54 MS includes a group of cardiovascular risk factors characterized by AHT, dyslipidemias, glucose intolerance, and a proinflammatory and prothrombotic state that favors atherosclerosis and its long-term sequelae, and the appearance of DM2. 3As high levels of blood pressure constitute a basic feature of MS; it is not surprising that MS constitutes a risk factor associated with hypertension in patients with lupus.

Serum concentrations of uric acid are increased in MS and IR; 55 this metabolite is associated with AHT, 55 which partially explains that hyperuricemia constitutes a risk factor associated with AHT in patients with SLE. The concentration of uric acid is related to autoimmune diseases as it was demonstrated in a Peruvian study that found an association between age, fat percentage, and uric acid with MS in patients with lupus.56 Besides, this metabolite is a circulating marker of oxidative damage in diseases such as hepatic ischemia, hyperlipemia, atherosclerosis, and Diabetes Mellitus.57 This means that its determination in patients with SLE is of great importance to assess the risk of presenting cardiovascular and other complications.

Patients with SLE and cardiovascular risk factors also present a low-grade chronic inflammatory state due to the quantity of adipokines synthetized by the visceral adipose tissue, among which the tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6) stand out. In the health care, two markers of inflammation are used: microalbuminuria, which is considered an early marker of kidney damage, and C-reactive protein. In this research, positive microalbuminuria was considered a risk factor associated with AHT in patients with lupus, but not high C-reactive protein, without presenting significant differences between both groups of patients.

The role of C-reactive protein in SLE is still unclear. Generally, when there is no infection, the C-reactive protein concentrations are lower or normal than in other systemic diseases like rheumatoid arthritis, despite the high levels of activity of the disease.58 The smoking habit did not constitute a risk factor associated with AHT due to the low number of smoking patients (7, 41% of the total). Other risk factors and CNCDs, such as ischemic cardiopathy, obesity, abdominal obesity, hypothyroidism, and risk lipid profile did not indicate a significant association; which could be due to the influence of factors that were not studied, and the prolonged evolution of SLE.

The identification of cardiovascular risk factors in patients with SLE is a challenge because of the close links established among them, the long period of evolution of the disease, the use of steroids and immunosuppressive drugs, and the appearance of complications that make the cause-effect more complex.

The identification of risk factors in patients with CNCDs is important for the evaluation of the risk of cardiovascular morbidity and mortality; for the prevention, diagnosis, and effective treatments of these disorders; and for the calculation and distribution of material human resources.59,60 The main limitations of this study are related to the cross-sectional design of this research, which
limits the cause-effect analysis; and the small number of patients. However, the authors consider that this fact does not demerit the extrapolation of this research which has the merit of studying AHT in patients with SLE in the province of Holguín.

CONCLUSIONS

The patients with SLE presented cardiovascular risk factors associated with AHT, which were identifiable in primary health care with relatively easy variables.

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