Prevalence of Atherosclerotic Vascular Disease in Cuban Patients With Systemic Lupus Erythematosus

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Atherosclerotic vascular disease-associated mortality and morbidity has increased in sick patients with systemic lupus erythematosus (SLE).
Objectives: To determine frequency of atherosclerotic vascular disease (AVD) in our patients, and to identify associations of some risk factors associated to its presence.
Method: Study included 51 patients and 51 controls paired by age, sex, and skin colour, who underwent carotid ultrasound (US) to measure thickness of the intima-medial complex, and to determine presence of plaques. In patients and controls we analyzed the presence of classic risk factors, eg, age, smoking, high blood pressure, diabetes mellitus, and hyperlipidemia. In addition in SLE we also analyzed the influencie on AVD of the clinical features of disease, as well as treatments applied.
Results: Risk factors were similar between patients and controls, except for hypertriglyceridemia, which was more frequent in patients. Presence of plaque was more prevalent in patients than in controls (59.9% vs 23.5%, *P*=.001). In multivariate analysis, age (OR, 1.31; 95% CI, 1.038-1.253; *P*=.005), diagnosis of SLE (OR, 3.872; 95% CI, 1.4-10.2; *P*=.005), and the presence of damage measured by SLICC/ACR (OR, 34.884; 95% CI, 1.1-12.9; *P*=.006) were the only variables independently associated to the presence of atherosclerosis in our patients.
Conclusions: Frequency of atherosclerosis is increased in patients presenting with SLE, risk factors independent of those classics, seem to be associated with this presence.

Key words: Prevalence. Atherosclerotic vascular disease. Systemic lupus erythematosus.

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Prevalencia de enfermedad vascular aterosclerótica en pacientes cubanos con lupus eritematoso sistémico

La morbimortalidad asociada a enfermedad vascular aterosclerótica ha aumentado en los enfermos con lupus eritematoso sistémico (LES).
Objetivos: Determinar la frecuencia con que se encuentra la enfermedad vascular aterosclerótica en nuestros pacientes, e identificar la asociación de algunos factores de riesgo con su presencia.
Método: El estudio incluyó a 51 pacientes y 51 controles identificados por edad, sexo y color de piel, a quienes se realizó ultrasonido de carótida para medir el grosor del complejo íntima-media y determinar la presencia de placa. Se identificaron, en pacientes y controles, los factores de riesgos clásicos, como edad, hábito tabáquico, hipertensión arterial, diabetes mellitus e hiperlipemia. En los pacientes con LES se analizaron además las características clínicas de la enfermedad y los tratamientos recibidos. Finalmente, se estudió la influencia de todas estas variables en la enfermedad vascular aterosclerótica de los pacientes con LES.
Resultados: Los factores de riesgo fueron similares entre pacientes y controles con la excepción de la hipertrigliceridemia más frecuente en los pacientes. La presencia de placa fue más prevalente en los pacientes que en los controles (el 56,9% frente al 23,5%, p = 0,001). En el análisis multivariable, la edad (*odds ratio* [OR] = 1,31; intervalo de confianza [IC] del 95%, 1,038-1,253; p = 0,005), el diagnóstico de LES (OR = 3,872; IC del 95%, 1,4-10,2; p = 0,005) y el daño sistémico valorado por el índice de SLICC/ACR (OR = 3,884; IC del 95%, 1,1-12,9; p = 0,006) fueron las variables que de forma independiente se asociaron a la presencia de aterosclerosis en los pacientes con LES.
Conclusiones: La frecuencia de aterosclerosis se encuentra aumentada en los pacientes con LES, y parece que podría estar asociada a otros factores de riesgo independientes a los clásicamente implicados en la aterosclerosis.

Palabras clave: Prevalencia. Aterosclerosis vascular. Lupus eritematoso sistémico.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease caused by the deposit of autoantibodies and immune complexes in the target tissues, leading to the development of an inflammatory process and lesion in the affected organs. It is characterized by complex alterations and disequilibrium of the immune systems responses.[1,2] Up until the middle of the twentieth century the disease had a fatal course, but in the past few decades its prognosis has improved significantly, with survival rates that exceed 90%, 85%, and 70% at 5, 10, and 20 years, respectively,[3-5] however, this means that new complications develop and contribute to the morbidity and mortality of patients with SLE, and among them, atherosclerotic vascular disease (AVD) can be found.[6,7] Urowitz et al,[8] in 1976, described premature cardiac infarctions in this type of patients. This finding was confirmed in subsequent studies.[9,10]

Clinical events tied to atherosclerotic disease are only one part of the problem and it is considered that the latent subclinical event is much more prevalent. The use of non-invasive testing, such as carotid ultrasound, has allowed for the demonstration of the presence of atherosclerosis, which is shown as an increase in the width of the intima-media complex and the presence of plaque in patients with SLE, in a larger percentage than in healthy persons, oscillating between 17% to 65% of patients studied.[11-15]

The hypothesis that atherosclerosis is more frequent in patients with SLE can be easily understood if we take into account that conventional risk factors, such as hypertension, dislypidemia, and diabetes, can be exacerbated or caused by corticosteroid treatment, which is commonly employed in these patients[16-18]; however, traditional risk factors aren't enough to explain the elevated prevalence of acute myocardial infarction and stroke in these patients.[7-11,19] This leads to the conclusion that SLE in itself might be a risk factor for atherosclerosis.

Recently, the identification of inflammatory /immunological factors in patients with accelerated atherosclerosis suggests a common pathogenic mechanism in patients with SLE and atherosclerosis.[20-22]

The objective of this study was to know the prevalence of atherosclerosis in our patients with SLE and analyze its influence on diverse factors, both classic and disease-dependent.

Patients and Method

Of a total 206 patients with SLE who were attended from January to June in 2006 in the outpatient clinic of the Department of Rheumatology of the Hermanos Ameijeiras Hospital in Havana, Cuba, we consequently included 51 of these patients in the study. All of the patients complied with at least 4 of the criteria for classification as SLE proposed by the American College of Rheumatology.[23] Patients who were under 18 years of age, pregnant women, and patients with an important decline in renal function (creatinine value superior to 300 mmol/L or creatinine clearance lower than 30 mL/min) were excluded. Patients with renal failure were excluded because we considered that they presented metabolic alterations associated to the renal deterioration and that these could significantly influence the genesis of atheromatosis independently of the presence of SLE. Of the patients included, 7 had presented some episode associated to vascular atheromatosis; 1 a stroke, 2 a myocardial infarction, and 4, angina.

Patients who were included were each paired with a healthy control that had the same color of skin, sex, and age (with a maximum interval of 5 years). None of the included controls had any rheumatic inflammatory illness or other diseases that required permanent, or transient treatment with glucocorticoids.

Both patients and controls who participated in the study completed the same research protocol, which included documentation of the following variables: age, skin color, sex, body mass index (overweight was considered in those patients with values over 25), hypertension (diagnosed through the clinical history and/or detection of arterial pressure over 140/90), diabetes mellitus (diagnosed through the clinical history and/or fasting glucose levels exceeding 6.3 mmol), smoking status (non-smokers had either never smoked, or had smoked for less than a year and had more than 6 months since stopping), family history of premature cardiac disease (myocardial infarction before 65 years of age in the father or 55 years of age in the mother), presence of hypercholesterolemia (clinical history and/or blood concentrations (>6.7 mmol/L), and hypertriglyceridemia (clinical history data and/or blood levels in >1.88 mmol for males and 1.60 mmol/L for women).

In patients with SLE some other disease dependent variables were considered, such as: time since onset of disease, clinical disease pattern, considering disease that affected vital organs or systems as those who had presented renal affectation (proliferative lupus nephritis), cardiopulmonary (severe pericardial or pleural effusions, pneumonitis, or myocarditis), hematological (hemolytic anemia and severe trombocytopenia <50 000/mL), or neurological (psychosis, convulsions, transverse myelitis), and the rest was considered non-vital affection. We also determined the index of systemic lesion of SLE using SLICC/ACR, with lesion being the presence of at least 1 point of this score. Finally, the cumulative doses and time of use of glucocorticoids, cyclophosphamide, azathioprine, and antimalarials was documented.

The Scientific Commission, which is part of the Health Ministry of the Republic of Cuba, approved the research protocol and the participants stated their agreement in writing.

Ultrasonographic Study

The radiology department of our center carried out the ultrasonographic studies. It employed a Doppler carotid ultrasound in B mode, with a 7.5 MHz transducer. The same researcher, who was unaware of the patients' diagnosis, performed all of the measurements. Measurements were performed in a supine position with the evaluation of the common carotid in 3 different places: first, the bulb; second, 1 cm in a downward direction; and third, between the 2 previous sites. The final variable was whichever point had the highest reading.

In agreement with previously published data, the intima-media complex was considered pathological when it exceeded 1 mm, ant the presence of plaque was established when the complex measured >1.3 mm.[11-14]

Statistical Analysis

Descriptive statistics were used to determine Student *t* test for quantitative variables, and for dichotomous variables we employed Fishers' exact test, and χ^2 for variables with more than 2 categories. The influence of the different variables on the presence of atherosclerosis was analyzed through logistical regression. A *P* value less than .05 was considered significant. Data was processed using SPSS 11.0 software.

Results

Comparison Between Patients and Controls

As shown in Table 1, patients and controls had similar sociodemographic variables (age, sex, and race). As for the classical cardiovascular risk factors, patients were overweight in a larger percentage (78.4% vs 64.7%; *P*=.0094), and elevated serum concentrations of tryglicerides (60.8% vs 25.5%; *P*=.0001). The frequency of hypertension was also found in patients in a larger percentage when compared to controls, though this did not reach a statistical significance (39% vs 23.5%; *P*=.067). For the rest of the evaluated risk factors (diabetes mellitus, family history of myocardial infarction, smoking, hypercholesterolemia) did not show significant differences between patients and controls.

The thickness of the intima-media complex at the carotid level was larger in the group of patients than in controls (1.56 vs 1.21 mm; *P*=.002). Besides, the prevalence of atheromatosis (carotid plaque) was also significantly higher in patients when compared to controls (29/56.9% vs 12/23.5%; *P*=.001).

These differences were maintained in all age groups and especially around the fifth decade of life.

TABLE 1. Characteristics of the Patients With Systemic Lupus Erythematosus and Controls[a]

Characteristics	Patients (n=51)	Controls (n=51)	*P*
Age, mean (SD), y	37.88 (11.04)	37.76 (11.91)	NS
Women, %	46 (90.2)	46 (90.2)	NS
Race, %			
White	41 (80.4)	41 (80.4)	NS
Black	3 (5.9)	3 (5.9)	NS
Mestizo	7 (13.17)	7 (13.17)	NS
Overweight, %[b]	40 (78.4)	33 (64.7)	.0094
Hypertension, %	20 (39.2)	12 (23.5)	.067
Smoking status, %	24 (47.1)	21 (41.2)	NS
Familiar history of myocardial infarction, %	8 (15.7)	10 (19.6)	NS
Diabetes, %	4 (7.8)	6 (11.8)	NS
Elevated cholesterol, %	7 (13.7)	2 (3.9)	NS
Elevated triglycerides, %	31 (60.8)	13 (25.5)	.000
Plaque, mm	29 (56.9)	12 (23.5)	.001
Intima-media width, mm	1.56 (0.69)	1.21 (0.39)	.002

[a]NS indicates not significant.
[b]Patients with a body mass index >25.
Data are presented as mean (standard deviation) or n (%).

Comparison Between Patients With and Without Atherosclerotic Plaque

In the unvaried analysis (Table 2) patients with SLE and atherosclerotic plaque had a mean age that was significantly higher (41.9 vs 32.3 years; *P*=.001). The presence of systemic damage measured using the SLICC/ACR index was also significantly more frequent in patients with plaque (13/44.8%) than in those without it (3/13.6%) (*P*=.017). With respect to the time since the onset of disease, this was slightly superior in patients with SLE and atherosclerosis, but the differences did not reach statistical significance.

Of the 51 patients, only 7 (14%) had presented some clinical vascular event (6, cardiovascular and 1, cerebrovascular); in 6/7 (85%) of these, ultrasound demonstrated the presence of atherosclerotic plaque. Finally, no differences were observed regarding the traditional risk factors between patients with and without atherosclerotic plaque (Table 2), nor with respect to the accumulated dose of each one of the drugs used (Table 3).

In the multivariate analysis (Table 4) of the possible factors associated to the presence of atheromatous plaque in patients with SLE, only age (OR, 1.31; 95% CI, 1.038-1.233; *P*=.005), the presence of systemic damage as measured by SLICC/ACR (OR, 3.82; 95% CI, 1.16-12.95; *P*=.005), and the diagnosis of SLE itself (OR, 3.82;

TABLE 2. Characteristics of the Patients With Systemic Lupus Erythematosus According to the Presence or Not of Atherosclerotic Plaque[a]

Characteristic	Without Plaque (n=22)	With Plaque (n=29)	*P*
Age, mean (SD), y	32.3 (8.5)	41.9 (11.1)	.001
Women, %	21 (95.6)	25 (86.2)	NS
Race, %			NS
White	20 (90.9)	21 (72.4)	
Black	1 (4.5)	2 (6.9)	
Mestizo	1 (4.5)	6 (20.7)	
Body mass index	26.8 (1.5)	26.7 (1.7)	NS
Smoking status	10 (45.5)	14 (48.3)	NS
Hypertension, %	7 (31.8)	13 (44.8)	NS
Diabetes, %	1 (4.5)	3 (10.3)	NS
Atherosclerotic vascular disease, %	1 (4.5)	6 (20.7)	NS
Family history of myocardial infarction, %	3 (13.6)	5 (17.2)	NS
Affection of vital organs, %	14 (63.6)	11 (37.9)	NS
Elevated cholesterol, %	1 (4.5)	6 (20.7)	NS
Elevated triglycerides, %	13 (59.1)	18 (62.1)	NS
SLICC/ACR, %	3 (13.6)	13 (44.8)	.017
Time since onset of disease, mean (SD), y	9.1 (4.8)	10.8 (6.9)	NS

[a]NS indicates not significant.
Data are presented as mean (standard deviation) or n (%).

TABLE 3. Patients With Systemic Lupus Erythematosus, With and Without Plaque, Regarding Accumulated Dose of Drugs[a]

Accumulated Dose	Without Plaque (n=22), n (%)	With Plaque (n=29), n (%)	*P*
Prednisone			NS
20 g	9 (40.9)	11 (37.9)	
20-40 g	7 (31.8)	8 (27.6)	
40-60 g	6 (27.3)	10 (34.5)	
Cyclophosphamide			NS
0 g	11 (50)	18 (62.1)	
<6 g	0 (0)	3 (10.3)	
6-12 g	5 (22.7)	4 (13.8)	
>12 g	6 (27.3)	14 (13.8)	
Antimalarial			NS
0 g	14 (63.6)	15 (51.7)	
<90 g	5 (22.7)	4 (13.8)	
90-270 g	3 (13.6)	3 (10.3)	
>270 g	0 (0)	7 (24.1)	
Azathioprine			NS
0 g	11 (50)	12 (41.4)	
<36 g	5 (22.7)	7 (24.1)	
36-72 g	2 (9.1)	3 (10.3)	
>72 g	4 (18.2)	7 (24.1)	

[a]NS indicates not significant.

TABLE 4. Logistical Regression Analysis of Independent Predictors of Atherosclerosis in Patients With Systemic Lupus Erythematosus (SLE)

	Adjusted OR	95% CI	*P*
Age	1.131	1.038-1.233	.005
Group (SLE/control)	3.872	1.468-10.211	.006
SLICC/ACR (damage index)	3.884	1.165-12.951	.027

95% CI, 1.46-10.21; *P*=.006) were independently associated to the presence of atherosclerosis.

Discussion

The main result of the study is the demonstration that atherosclerotic is clearly more frequent in patients with SLE than in patients without the disease but of the same age and gender (57% vs 24%; *P*=.001). In addition, the presence of atherosclerosis in these patients with SLE does not seem to be associated to classical cardiovascular risk factors. In this sense, the behavior of our patients is similar to that of those in other parts of the world, though different in their prevalence values.[11-13]

The presence of atherosclerosis in patients with SLE evaluated through ultrasound varies between 17% and 65% in different studies depending especially on the presence of previous clinical cardiovascular events, age, and the echographic technique employed.[11-14] Therefore, in our study we have used the classical criteria previously published in order to define atherosclerosis.[11-14]

The prevalence of atherosclerosis (54%) that we have found is among the highest reported, however, in a study done in Brasil[24] with a population significantly younger than ours (mean age, 34 years), but with similar genetic factors and exposure to toxins, the reported prevalence was 50% and resulted similar to ours.

In our study, hypertriglyceridemia was the only classical risk factor that showed significant differences when comparing patients with controls, something that has already been reported by other authors.[11,25,26]

This result, next to the observation that the diagnosis of SLE in itself is independently associated to the presence of atherosclerosis, reinforces the hypothesis that in patients with SLE, there are possibly risk factors different from the classic ones that influence the appearance of atherosclerosis.

In this sense, the recent identification of mechanisms that are common to inflammatory and cardiovascular illness constitute areas of great interest for research, because of the possible therapeutic implications that advances in the knowledge of these aspects could have.[27,28] In our study,

factors independently associated to the presence of atherosclerosis in patients with SLE were: age and systemic damage as measured by the SLICC/ACR index.

Age is a classical risk factor of atherosclerotic vascular disease that has been found associated to it in several studies of patients with SLE.[12,24,27,29,30]

On the other hand, the presence of systemic damage, which is considered an indicator of severe disease as well as an irreversible process, has also been previously reported by other study groups.[12,27,31,32]

In contrast, neither the affection of vital organs nor the accumulated doses of glucocorticoids were shown to be variables independently associated to the presence of atherosclerosis in our patients with SLE. The lower prevalence of atherosclerosis in affected vital organs coincides with a previous study that suggests that 2 different patterns of patients with SLE could exist, one chronic, with less severe disease that boosts atherosclerosis due to a low degree of persistent inflammation, and another pattern, of more aggressive autoimmune disease in which atherosclerosis is less evident due to aggressive treatment with steroids and immunosupressants.[27] On the other hand, the atherogenic influence of steroid treatment has been linked, over all, to the alterations caused on the plasma lipid profiles, to the increase of arterial pressure and to its association to hyperglycemia. However, recent findings of a lack of association between steroid use and the presence of atherosclerosis in patients with SLE suggest that inflammatory mechanisms associated to endothelial lesion could be involved in the genesis of atherosclerosis. In this sense, it has been suggested that treatment with steroids could prevent their development in these patients who have chronic inflammatory processes such as the ones with SLE. Two recently published studies showed high rates of atherosclerosis in patients with SLE which were not associated to accumulated doses of corticosteroids,[27,28] and one of them even showed a lower rate of atherosclerosis than in patents with higher mean doses of steroids and immunosupressants, lending credence to the inflammatory hypothesis in the genesis of atherosclerosis.[27]

Among the limitations of our work we must emphasize the lack of evaluation, due to technical problems, of the influence of inflammatory activity in itself (inflammatory mediators and/or the global activity index of SLE) with the presence of atherosclerosis. In conclusion, the prevalence of AVD is elevated in our patients with SLE and seems to be more associated to factors related to SLE itself than those factors classically implicated in atherosclerosis.

In this sense it is necessary to design studies with SLE patients that evaluate the influence of inflammatory activity and the repercussions that anti-inflammatory treatments to reduce atherosclerosis might have over it.

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