Is Systemic Lupus Erythematosus a New Risk Factor for Atherosclerosis?

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Objective

To evaluate the prevalence of cardiovascular events (CVE) secondary to atherosclerosis in lupus patients and correlate them to the traditional risk factors, disease duration and drug therapy used.

Methods

A retrospective study was carried out based on data obtained from patients' charts. Patients included were those who had a lupus diagnosis confirmed at least two years before inclusion in the study and had been followed since 1992. CVE were characterized as MI, angina pectoris and stroke non-related to lupus activity. Risk factors and drugs used for treatment were recorded.

Results

Seventy-one charts were analyzed. Patients' mean age was 34.2±12.7 years; 68 were women and three were men; 58 were Caucasian (81.6%). Ten (14.08%) presented CVE. Patients in whom CVE were observed were older (42.7 vs. 32.8 years p=0.0021) and presented longer disease duration (10.8 vs. 7.2 years p=0.011). The traditional risk factors, daily and cumulative doses of steroids, immunosuppressive drugs and antimalarial drugs were not significant when patients with and without CVE were compared.

Conclusion

The prevalence of CVE secondary to atherosclerosis in systemic lupus erythematosus (SLE) was 14.08%. The traditional risk factors were not associated with the development of CVE in lupus patients. Patients that presented cardiovascular events were older and presented longer disease duration. It is a premature conclusion to establish SLE as an independent risk factor for atherosclerosis development.

Key words

Systemic lupus erythematosus, atherosclerosis, cardiovascular disease.

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Systemic Lupus Erythematosus (SLE) is a systemic, inflammatory and autoimmune disease that diffusely affects conjunctive tissue in a chronic way. It presents a worldwide distribution with a prevalence of 14.8 to 50.8 cases per 100,000 inhabitants and an incidence of 1.8 to 7.6 per 100,000 inhabitants in American studies[1].

The initial manifestations of the disease can be acute or insidious. Symptoms are usually non-specific and include myalgia, nausea, vomiting, headaches, depression, adinamy, weight loss and fever, in several combinations. They can present as mild or severe, intermittent or persistent symptoms. All organs can be affected, with the preferential involvement of the joints, skin, serous membranes, and vessels[2].

The degree of morbidity is high and can be mainly represented by the renal involvement that occurs in almost all patients at some time during the course of the disease. The most common causes of death are renal involvement and infectious complications[3].

Studies carried out in the 70's in developed countries, where death due to infection was uncommon, started to show that myocardial infarction was an important cause of death among lupus patients. The first of such studies was published by Urowitz et al in 1976, which showed that 45% of the deaths that occurred among SLE patients were due to cardiovascular diseases secondary to an atheromatous process[4]. The pattern of the mortality curve was bimodal. The first peak, considered an early one (less than 2 years of disease duration) occurred due to the acute activity of the disease and/or infection. The second peak, considered a late one (more than two years of disease duration) also included the deaths due to acute disease and/or infections, however, 30% of them were related to cardiac and cerebrovascular involvement, secondary to atherosclerosis, of moderate to severe intensity, present in several cases. Another study showed that the incidence of myocardial infarction in SLE has a 50-fold increase when compared to patients without lupus, within the same age range[5]. Most of the deaths occur in women younger than 55 years, who have often not entered menopause. Angina pectoris can occur in 6.5% to 15.8% of the cases[6]. Additionally, other studies have shown similar results, supporting the hypothesis that women with SLE have a higher probability to develop an atherosclerotic process[7,8].

Methods

The introduction of steroids in the treatment of SLE is considered by some as being fundamental in the development of early atherosclerosis in such patients, as vascular events represented less than 10% of all deaths in the pre-steroid age[9]. The study of autopsies of SLE patients showed that 42% of those who underwent steroid therapy for more than a year presented significant plaque formation in at least one coronary vessel and half of them had a history of myocardial infarction[6]. Nevertheless, other authors failed to show an association between cumulative or maximum steroid doses or therapy duration with coronary artery disease[10]. The extension and intensity of steroid use involvement in these findings is still debatable[11,12].

The presence of active disease with vasculitis, which are frequently observed in these patients, can lead to a more severe vascular involvement and endothelial dysfunction; thus, it is possible that patients who present a high relapses rate also have a higher chance of developing endothelial lesions, and, consequently, further atherosclerosis[13].

Clinical events, such as angina pectoris and myocardial infarction, are the basis for most studies in this area. However, the frequency of subclinical atherosclerosis varies from 4% to 23% in different studies, according to the different techniques employed in its detection[14]. Therefore, it is possible that the real incidence of atherosclerosis is being underdiagnosed.

Ultrasonography studies of the carotid arteries in SLE patients showed that 40% of them present at least one atheromatous plaque in these vessels. Plaque prevalence increases with age. In spite of that, 22% of the pre-menopausal women presented plaque before 45 years of age[15].

As it has been observed, the increased development of the atherosclerotic process in SLE patients is a real and unquestionable current problem, especially due to the morbidity and mortality rates of myocardial infarction, its main form of presentation.

Hence, the objective of this study was to assess the prevalence of cardiovascular events secondary to an atherosclerotic process in a population of SLE patients who are treated at a university hospital and correlate such events to the known risk factors for the development of atherosclerosis.

The study was carried out retrospectively through the collection and analysis of data obtained from SLE patients' hospital charts, who fulfilled the criteria established by the American College of Rheumatology (ACR) for SLE classification[16], whose diagnoses had been confirmed for at least two years and followed from January 1992 to December 2003. The study was approved by the Research Review Board of our Institution. The following were considered cardiovascular events (CVE) secondary to atherosclerosis: angina pectoris, acute myocardial infarction, and stroke. The diagnosis of the event was performed by clinical and laboratory assessment, and the direct causes of lesion due to the activity of the underlying disease were ruled out. Thus, the events were not taken into account when the presence of vasculitis and its complications secondary to active SLE were confirmed.

The traditional risk factors for the development of atherosclerosis were thus recorded and defined: smoking;

BMI calculated in kg/m^2; presence of renal disease was considered if the glomerular filtration was < 50 mL/min; current drug therapy: dose and duration of steroid, antimalarial, and immunosuppressive drug therapy and hormonal replacement therapy (HRT). Diabetes was defined in the presence of classic symptoms (polyuria, polydipsia and unexplained weight loss) associated to plasma glucose levels ≥ 200 mg/dL at a casual measurement; or eight-hour fast glucose levels ≥ 126 mg/dL; or two-hour plasma glucose levels ≥ 200 mg/dL during the oral-glucose tolerance test[17]. The presence of hypertension was defined when systolic arterial pressure was > 140 mmHg or diastolic arterial pressure was > 90 mmHg in at least two or more blood pressure measurements or when the patients were undergoing antihypertensive treatment[18]. Family history of premature coronary artery disease was considered positive when it had occurred in a first-degree male relative younger than 55 years or female relative younger than 65 years[19]. The analysis of the fasting lipid profile was considered a risk factor if the low-density lipoprotein (LDL-cholesterol) was ≥ 160 mg/dL, the high-density lipoprotein (HDL-cholesterol) was < 40 mg/dL and total cholesterol was ≥ 240 mg/dL[19].

At the end of the study, the number of SLE patients that presented CVE after two years of disease duration was analyzed and the traditional risk factors were correlated with the presence of CVE.

Statistical analysis - The percentages of individuals with SLE according to sex, age range, race, origin, presence or not of atherosclerosis, presence or not of diabetes, family history of atherosclerosis and drug use were determined.

The mean values and standard deviations of the variables concerning the lipid profile, as well as the associations between the risk factors and the presence of atherosclerosis were calculated using Chi-square test and logistic regression[20].

Significance level was set at 5%.

Results

Charts of seventy-one patients with SLE were analyzed, being 68 female and 3 male patients, with mean age = 34.2 ± 12.7 years. Most patients (81.6%) were Caucasian (n=58), followed by 8 patients of mixed ethnicity (11.2%), 4 Black patients (5.63%) and 1 Asian patient (1.4%), as shown in Table 1. Ten patients (14.08%) presented some cardiovascular event secondary to atherosclerosis: 5 presented angina pectoris (7.04%), three, myocardial infarction (4.22%) and two, stroke (2.81%).

The frequency of risk factors for the development of atherosclerosis is shown in Table 2 and are as follows: 26 patients were smokers (36.6%), 16 (22.53%) had a family history of CVE secondary to atherosclerosis, 2 (2.81%) had diabetes mellitus, 17 (23.94%) had hypertension, 6 (8.45%) presented nephropathy, 67 (94.36%) were chronic corticosteroid users, 27 (38.02%) used antimalarial drug therapy, 12 (16.9%) were treated with cyclophosphamide and BMI was 24.0 ± 1.3 kg/m^2. The lipid profile analysis of 51 patients showed that 22 (43.13%) had hypercholesterolemia and 20 (39.21%) presented hypertriglyceridemia. LDL-cholesterol measurement was registered in 39 patients and 16 of them (41.02%) presented elevated levels. None of these parameters showed a significant statistical difference when compared to patients that did not present vascular events secondary to atherosclerosis. It is noteworthy that the lipid profile was not documented in 28.1% of the charts analyzed.

Patients with cardiovascular events were older (42.7± 10.9 yrs, p=0.021) and had longer disease duration (10.8 ± 3.6 yrs. p=0.011) as shown in Table 3. Mean daily doses and annual cumulative doses of corticosteroids were 23.1 ± 7.4 mg (p>0.05) and 8,414.3 ± 2,702.9 mg (p>0.05), respectively. The mean daily dose of antimalarial drugs was 250.5 ± 176.2 mg (p>0.05) and the annual dose was 91,080.0 ± 64,040.5 mg (p>0.05). Immunosuppressive drugs were used at a mean daily dose of 23.6 ± 12.5 mg (p>0.05) and the annual dose was 8,678.5 ± 4,640.3 mg (p>0.05).

Table 1 - Distribution of patients' frequencies according to gender, ethnic background, and presence of atherosclerotic event

	Atherosclerotic event				
	Yes		No		Total
	n	%	n	%	n
Females	10	14.7	58	85.3	68
Males	-	-	3	100.0	3
Caucasians	6	10.3	52	89.7	58
Mixed ethnic background	2	25.0	6	75.0	8
Blacks	2	50.0	2	50.0	4
Asians	-	-	1	100.0	1
Total	10	14.1	61	85.9	71

None of the female patients were receiving hormonal replacement therapy.

The profile of the group of patients who presented CVE consisted of 10 females: six Caucasians (60%), 2 of mixed ethnicity (20%) and 2 Blacks (20%). Minimum and maximum ages were 33 and 66 yrs, respectively. Three were smokers (30%), 2 had a family history of CVE secondary to atherosclerosis (20%), 2 had hypertension (20%), one presented nephropathy (10%), nine utilized corticosteroids (90%), 5 utilized anti-malarial drugs (50%) and 4 utilized immunosuppressive drugs (40%). Lipid measurements were carried out in 8 patients and 5 (62.5%) had hypercholesterolemia and 3 (37.5%) had hypertriglyceridemia. LDL-cholesterol was measured in 4 patients and 2 (50%) presented elevated levels. None of the patients were diabetic. BMI in this group was 23.97 ± 1.35 kg/m^2 (26 – 22.36), so none of them were obese.

Table 2 - Distribution of patients' frequencies according to qualitative variables and atherosclerotic event

	Atherosclerotic event				
	Yes		No		Total
	n	%	n	%	n
Variable					
Smokers	3	11.5	23	88.5	26
Non-smokers	7	15.6	38	84.4	45
Family history of CVD	1	6.2	15	93.8	16
No family history of CVD	9	16.4	46	83.6	54
Diabetes	-	-	2	100.0	2
No diabetes	10	14.5	59	85.5	69
Arterial hypertension	3	17.6	14	82.4	17
No arterial hypertension	7	13.0	47	87.0	54
Nephropathy	1	16.7	5	83.3	6
No nephropathy	9	13.8	56	86.2	65
CST use	9	13.4	58	86.6	67
No CST use	1	25.0	3	75.0	4
AM use	4	14.8	23	85.2	27
No AM use	6	13.6	38	86.4	44
IMN use	4	33.3	8	66.7	12
No IMN use	6	10.2	53	89.8	59
Hypercholesterolemia	6	27.3	16	72.7	22
No hypercholesterolemia	2	6.9	27	93.1	29
Hypertriglyceridemia	4	20.0	16	80.0	20
No hypertriglyceridemia	4	12.9	27	87.1	31
LDL increase	2	12.5	14	87.5	16
No LDL increase	2	8.7	21	91.3	23

CVD- cardiovascular disease; CST - corticosteroid; AM –antimalarial drug; IMN – immunosuppressive drug.

Table 3 - Frequency distribution according to quantitative variables and presence of atherosclerotic event

	Atherosclerotic event	
Variables	**Yes**	**No**
Age (yrs)	42.7 ± 10.9	32.8 ± 12.5*
BMI (kg/m^2)	24.0 ± 1.3	24.3 ± 3.4
Time of disease (yrs)	10.8 ± 3.6	7.2 ± 4.2*
Daily CST dose (mg)	23.1 ± 7.4	18.9 ± 8.8
Annual CST dose (mg)	8,414.3 ± 2,702.9	7,122.4 ± 3,294.4
Daily AM dose (mg)	250.5 ± 176.2	158.0 ± 82.8
Annual AM dose (mg)	91,080.0 ± 64,040.5	57,573.6 ± 30,153.8
Daily IMS dose (mg)	23.6 ± 12.5	26.5 ± 23.9
Annual IMS dose (mg)	8,678.5 ± 4,640.3	9,680.4 ± 8,744.0

*BMI: body mass index; CST - corticosteroid; AM – antimalarial drug; IMS – immunosuppressive drug. * p <0.05.*

Discussion

SLE is an inflammatory disease prototype that secondarily affects the vascular system. The vascular manifestations typically associated to SLE are varied and include vasculitis, vasospasm and thromboembolism. Disease survival has increased with the new and improved therapeutics, which allowed the appearance of new vascular complications such as the premature atherosclerotic vascular disease[21]. In this study, the prevalence of this type of vascular event was 14.08% in a population of SLE patients followed at a university hospital. Five patients (7.04%) had angina pectoris, 3 had acute myocardial infarction (4.22%) and 2 (2.81%) had a stroke. In literature, this number is variable according to the method utilized. In the retrospective studies in which only the coronary clinical manifestations were considered, i.e., angina pectoris and MI, the prevalence was 6%, however, in prospective and autopsy studies this number increases to 2-19.8% and 10-54%, respectively, for angina pectoris and MI[14].

Although not completely understood, the atherogenesis in SLE might be related to inherent characteristics of the disease and its therapeutics.

The analysis of the traditional risk factors and cardiovascular events did not show a positive correlation. Thus, in this group of patients, the presence of factors such as smoking, hypertension, diabetes or dyslipidemia contribute to, but are not likely to be the major factors in this disease[22].

In this study, renal involvement did not show an association with the presence of cardiovascular events. However, the nephritic syndrome, common in lupus nephritis, can also cause lipid disturbances and increased homocysteine levels, as well as other complications[23]. Homocysteine is considered a "new" independent risk factor in the development of atherosclerosis in SLE patients, it has a toxic effect that acts directly on the endothelium, it is pre-thrombotic, increases the production of collagen and decreases the availability of nitric oxide[24]. Increased plasma homocysteine levels can be found in 15% of patients with SLE associated to the male gender, presence of renal failure, prednisone use, and low levels of vitamin B, folic acid and pyridoxine[25]. Unfortunately, homocysteine measurement is not performed as part of the routine laboratory assessment in our country.

The measurement of the lipid levels of patients enrolled in this study was not performed in 20 (28.16%) of the 71 individuals and LDL-cholesterol measurement was not performed in 32 (45%) of them. Only 4 patients from the CVE group had LDL-cholesterol levels measured, which suggests the low level of concern by the clinicians in this regard, probably due to the fact that they are deeply involved in the underlying disease treatment. Thus, due to the large number of patients with no measurement of lipid levels, this parameter must be considered with reservations. Hypercholesterolemia was found in 22 patients (43.13%), hypertriglyceridemia in 20 (39.21%) and elevated LDL-cholesterol levels in 16 (41.02%). This lipid profile did not show statistical significance when associated to the occurrence of CVE. Nevertheless, considering the group that presented some CVE, 5 of the 10 patients (50%) presented hypercholesterolemia, 3 presented hypertriglyceridemia and 2 had increased LDL-cholesterol levels.

The treatment of SLE, especially steroid therapy, can also influence the atherosclerotic process. It is believed that this treatment is atherogenic, partially due to the effects on plasma lipoproteins. The elevation of circulating lipid levels in SLE can be explained by several mechanisms. The long-term use of corticosteroids is known to be responsible for the elevation of total cholesterol, triglycerides and apolipoprotein B levels and for promoting an abnormal distribution of high-density lipoprotein subclasses[26]. On the other hand, inflammation is associated with the atherosclerosis, and therefore, steroid therapy could have a protective effect. Studies published in literature about this matter are contradictory.

In this study, however, there was no correlation between steroid use and cardiovascular events. Time of use as well as the cumulative dose of these drugs were not significant. It is believed that prednisone use cannot be considered an isolated risk factor in the development of atherosclerosis. Time of use can also represent longer disease duration and a subgroup of patients with a more severe disease. However, prednisone can indirectly accelerate the process by augmenting other traditional risk factors: hypercholesterolemia, hypertension and obesity[14]. This hypothesis is supported by the fact that, in this study, patients who presented cardiovascular events were older (42.7 vs. 32.8 yrs p=0.0021) and longer disease duration (10.8 vs. 7.2 yrs p=0.011).

Jimenez et al[27] and Roman et al[28] found a negative correlation between the presence of carotid plaque and high mean daily doses of prednisone. Nevertheless, other studies found a positive correlation between steroid use, CVE and increased thickness of the intima-media space of the common carotid artery by ultrasonography[15,29]. Clearly, the role of treatment with steroids in the evolution of CVE in SLE needs to be further investigated.

Cyclophosphamide was the other immunosuppressive agent utilized by patients in this study. The drug was administrated as pulse therapy, in which 1 g doses of the drug are administered endovenously each six weeks. No significant association between the use of cyclophosphamide and patients with or without CVE was observed. Other studies showed that treatment with immunosuppressive drugs could be related to the restoration of the endothelial function in patients with primary vasculitis[30]. In patients with SLE, the more aggressive therapy presented a negative correlation with atherosclerosis, which suggests that a more vigorous therapy can decrease the likelihood of atherosclerosis[28]. Thus, it is logical to conclude that patients who present cutaneous and/or systemic vasculitis, whose inflammatory process control was established early and aggressively performed, present better endothelial function and, in consequence, a lower chance of atherosclerosis.

This study showed that of the 71 patients studied, only 27 utilized antimalarial drugs (38.02%). These drugs, such as hydroxychloroquine and quinacrine, are used in the treatment of SLE for being corticosteroid sparing and photoprotective agents, and for being effective in improving the articular picture. Notably, they can reduce from 10 to 12% of total cholesterol levels and 12% of LDL cholesterol levels in SLE patients using steroids[31]. In addition to the antiatherogenic role, antimalarial drugs showed to be beneficial in hyperglycemia and have an anti-thrombotic role, thus helping in the control of other risk factors[14]. Therefore, being relatively safe drugs, they should be utilized more frequently in this kind of patient.

Other mechanisms might be involved in the development of early atherogenesis in SLE, which have not been evaluated in this study but are relevant.

The pathological production of auto-antibodies in SLE is characteristic. Several of these antibodies are directly involved either in the endothelial lesion or in the production and/or induction of the expression of inflammatory factors that result in endothelial lesion. It is noteworthy to mention the anti-phospholipid antibodies[32] and the oxidated anti-LDL antibodies, the latter also considered members of the anti-phospholipid family, and the anti-prothrombin antibodies[33,34]. These antibodies predispose patients with SLE to venous thrombosis and arterial disease and have been associated to atherogenesis in in vitro studies[35-40]. Its pathogenic role in atherosclerosis is yet to be clarified. Other antibodies, such as the antilipase antibody, have been detected in 47% of the sera of patients with SLE and can lead to the elevation of triglycerides due to the non-catabolism of kilomicrons, a lipase activity, which is blocked[41].

The pathological production of auto-antibodies in SLE involves binding of CD40 ligand (CD40L) present in T lymphocytes and CD40 in B cells[42]. These patients present an increased expression of CD40L and augmented number of cells that are positive for CD40L, which include endothelial cells. The binding can induce production and expression of the binding molecules, which will aid inflammation and vascular lesion in SLE as well as in atherosclerosis[43].

Vascular involvement is another characteristic of active SLE and can occur in different skin and/or systemic sites as vasculitis. The inflammatory lesion to the vascular wall can lead to endothelial injury and consequently to endothelial dysfunction, considered the first step for atherosclerosis. Endothelial dysfunction was demonstrated in an active disease study[44], but it was not found in quiescent patients (data not published). Possibly, similarly to the findings in patients with primary vasculitis, the endothelial function may be restored after SLE activity treatment.

It must also be considered that the highest incidence of cardiovascular events secondary to atherosclerosis in SLE may be associated to an increase in the levels of reactive C-protein, circulating immunocomplexes, complement proteins and homocysteine observed in this disease[45-48], but which were not the aim of this study.

Finally, the limitations of this study must be taken into account, as it is a retrospective analysis, and the fact that important data, such as the complete lipid profile of all patients, were not obtained. It is therefore of utmost importance that clinicians are careful not only of the treatment of the active disease but also of the early prevention and/or diagnosis and treatment of factors associated to early atherosclerosis.

Conclusions

The prevalence of CVE (cardiovascular events) secondary to atherosclerosis in SLE was similar to that found in literature, 14.08%.

The traditional risk factors except for the lipid profile, which could not be included in the study, did not shown an association with the occurrence or not of CVE in SLE.

The patients in whom the cardiovascular events were observed were of older age and presented longer disease duration.

It is a premature conclusion to state that SLE can be an independent risk factor in the development of atherosclerosis.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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