Assessment of the risk of coronary heart disease in women with systemic lupus erythematosus

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ABSTRACT

Introduction: The risk of death from cardiovascular disease is nearly five times greater in patients with systemic lupus erythematosus (SLE) than in the general population. Traditional risk factors for cardiovascular disease do not explain this increase. An instrument for early identification of increased risk of cardiovascular disease in this population does not exist. **Objective:** The objective of the present study was to evaluate the usefulness of the Framingham risk score to determine the risk of cardiovascular disease in SLE patients compared to normal individuals. **Patients and Methods:** Eighty female patients with SLE and 60 women without rheumatic disorders participated in this study. The Framingham risk score was used to estimate the 10-year mortality secondary to cardiovascular disease. **Results:** Body mass index (BMI) (26.8 ± 6.2 vs. 24.9 ± 3.8), triglyceride levels (159.3 ± 103.7 vs. 113.8 ± 50.3), and diastolic blood pressure (84.3 ± 11.5 vs. 79.1 ± 12.0) were higher in SLE patients than in the control group ($P < 0.05$). Hypertension was observed in 56% of SLE patients and in 33% of the control group ($P < 0.05$). Despite the differences observed between both groups, the risk of cardiovascular disease according to the Framingham risk score was similar in both groups, i.e., 1%. Statistically significant differences were not observed when individuals whose risk was ≥10% were compared ($P > 0.05$). **Conclusions:** Although SLE patients have a higher cardiovascular mortality rate, the risk of myocardial infarction or mortality from coronary artery disease in 10 years in SLE patients is similar to that of patients without rheumatic diseases. The Framingham risk score cannot estimate the increased risk of cardiovascular disease in women with SLE.

Keywords: systemic lupus erythematosus, cardiovascular risk, Framingham risk score.

INTRODUCTION

Survival of patients with systemic lupus erythematosus (SLE) increased dramatically since the decade of 1950, when it was approximately 50% in five years, to more than 90% in 10 years in the last decade. Several factors have contributed for this increased in survival: early diagnosis, inclusion of less severe cases, high doses of prednisone, more aggressive schedules cytotoxic/immunosuppressive drugs, and advances in the treatment of hypertension, infections, and renal failure, including dialysis and kidney transplant.[1,2,3]

The reduction in mortality and longer survival are responsible for the chronicity of SLE and changes in the types of complications. Since the first report on the bimodal pattern of mortality in SLE, higher incidence of deaths in the first decades of the disease secondary to disease activity and infections, and atherosclerotic disease in the following decades, cardiovascular complications have been identified as one of the main causes of morbimortality in SLE patients.[4,5,6]

Despite considerable improvements in the treatment of SLE, the mortality of SLE patients is still elevated, with mortality rates ranging from 6.8% to 20.2%, 8 to 14 years after the diagnosis.[3,7] When compared to women in the general population, female SLE patients have a five- to eight-fold higher risk of death from cardiovascular disease, especially those younger than 55 years.

Coronary heart disease is responsible for 20-30% of the deaths in SLE patients, and the proportion is higher

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if we consider the duration of the disease. Jonsson *et al*. demonstrated that the incidence of acute myocardial infarction in Swiss SLE patients is nine times higher than in women without SLE.[8] Strokes affect more that 15% of SLE patients, and some of them have multiple ischemic events.[9,10] Thus, the risk of death from cardiovascular disease in SLE has been increasing progressively.[11]

Known risk factors for cardiovascular disease (hypertension, hyperlipidemia, smoking, diabetes mellitus, obesity, sedentary lifestyle, history of coronary heart disease) are very prevalent in SLE patients. Several studies have identified an increase in traditional risk factors for atherosclerosis in SLE patients. Roldan *et al*. observed three or more risk factors in 53% of 229 patients with SLE with a mean age of 38.3 years.[12]

Several studies have suggested that the development of atherosclerosis is accelerated in SLE.[13,14] The causes of this phenomenon are unknown, but the presence and/or increase of traditional risk factors cannot explain the accelerated atherosclerotic process seen in SLE.

It is possible that a combination of factors seen in this population plays a role, such as: SLE itself, adverse effects of corticosteroids and/or conventional cardiovascular risk factors. This can be illustrated by a study with 263 patients whose risk of developing cardiovascular events was eight to 17 times higher than expected for traditional risk factors.[15]

The ultrasound identifies atheromatous plaques in the carotid arteries in 24-40% of SLE patients, which was confirmed in autopsies that showed a 41-53% prevalence of atheromatous plaques in carotid, renal, and cerebral arteries.[16,17]

Non-traditional risk factors for atherosclerotic disease might play an important role in this process. Patients with SLE have particularities that can accelerate atherosclerosis, behaving as non-traditional risk factors: use of glucocorticoids, chronic glomerulonephritis, low C3 levels, high titers of anti-DNA, antiphospholipid antibodies, and genetic factors.[15]

Assessment of the cardiovascular risk based on risk scores is widely used in the general population. The Framingham risk score for coronary artery disease considers gender, age, total cholesterol levels, HDL levels, systolic and diastolic blood pressure, diabetes, and smoking. This table estimates the risk of coronary events and stratifies patients in risk categories: low (< 10% of events in 10 years), intermediate (10-20%), and high (> 20%). This index estimates a prognosis and suggests the necessary clinical interventions.[18]

In the present study, we investigated the hypothesis that the Framingham risk score for coronary artery disease can identify an increased cardiovascular risk in SLE patients when compared to a control group composed of normal individuals.

PATIENTS AND METHODS

Patients

Eighty female patients with a diagnosis of SLE, according to the criteria of the American College of Rheumatology[19], were analyzed. Patients are followed-up at the Systemic Lupus Erythematosus Outpatient Clinic at PUC/SP and at Conjunto Hospitalar de Sorocaba.

The control group was composed of 60 patients who sought medical care for investigation of kidney stones. All patients were female, they did not have classification criteria for SLE or any other autoimmune disease, and were matched for race and age with the group of SLE patients.

Demographic and clinical data were collected during regular clinical appointments (last three appointments). Results of laboratorial exams were obtained from routine exams requested on clinical appointments.

This study was approved by the Ethics Committee of the Medical and Biological Sciences Center from PUC/SP. All participants were informed about the study and signed an informed consent.

Methods

Clinical evaluation

Patients with SLE and those in the control group underwent complete clinical examination and laboratorial testing (fasting glucose, total cholesterol, HDL-c, and triglycerides). Family history of cardiovascular disease was defined as the presence of acute myocardial infarction or ischemic stroke in first degree relatives. Weight and height were determined and body mass index (BMI) was calculated by dividing the weight, in kilograms, by the square of the height, in meters.

Blood pressure was measured with a mercury sphygmomanometer, considering the mean of two measurements obtained with the patient in the sitting position with a five-minute interval between measurements after a ten-minute rest period. The blood pressure used in the study was the mean of the levels recorded in the last three clinic appointments.

Lupus activity was determined by the mean of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of the last 12 months, and the mean accumulated damage index of the Systemic Lupus International Collaborative Clinics (SLICC) of the last 12 months.[20,21]

Laboratorial Tests

Blood samples were collected after a 12-hour fasting period to determine the levels of glucose, total cholesterol, HDL-c, and

triglycerides. The levels of LDL-c were calculated by using the Friedrich formula [LDL-C = TC – (HDL-C) – (Trigl/5)].

Determination of the Cardiovascular Risk by the Framingham Table

The following parameters were used: age, total cholesterol, HDL-c, blood pressure, diabetes, and smoking; the scores of the Framingham table were added and the percentage mortality risk from cardiovascular disease in ten years was calculated.[18]

Statistical analysis

The Chi-square test and Fisher's exact test were used to determine the dependency relationship among categorical parameters. Quantitative parameters are presented as means, medians, and standard-deviation. Means with normal distribution were compared with the Student *t* test. The Mann-Whitney test was used to compare two means of parameters without normal distribution. Spearmen's coefficient was used to determine the correlation among coronary heart disease scores and age, diastolic blood pressure, body mass index, and triglycerides. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Table 1 shows the characteristics of the 80 female patients and 60 females of the control group. Patients with SLE had median disease duration of 5.0 (1-29) years, and median follow-up of 3.0 (1-18) years; median SLEDAI scores of 3.0 (0-24), and median SLICC scores of 0.0 (0-3).

As for the medication used by SLE patients, 92% were taking prednisone, 92% antimalarials, and 80% immunosuppressors. Hypertension was present in 56% (45/80) of SLE patients and 85% were taking antihypertensive drugs on a regular basis. Among the 11% (9/45) of patients aware of having dyslipidemia, 89% were treated with diet alone. In the control group, 33% (20/60) had hypertension, and 65% (13/20) were taking antihypertensive drugs on a regular basis. Sixteen per cent (10/60) of the individuals in the control group were aware of the diagnosis of dyslipidemia and 40% (4/10) were taking hypolipedemic drugs daily.

Hypertension was present in 56% of SLE patients and in 33% of the individuals in the control group ($P < 0.01$). Mean diastolic pressure of SLE patients (84.3 ± 11.5 mmHg) was statistically higher than in the control group (79.1 ± 12.0 mmHg, $P < 0.01$). Mean systolic blood pressure was similar in both groups. Body mass index was significantly higher in SLE patients (26.8 ± 6.2 kg/m^2) when compared to the control group (24.9 ± 3.8 kg/m^2, $P = 0.04$). In patients with BMI greater than or lower than 30 kg/m^2, statistically significant differences between SLE patients and the control group were not observed ($P = 0.59$). The percentage of smokers was higher among SLE patients (27%) than in the control group (18%, $P < 0.04$).

Dislipidemia was present in 11% of SLE patients and in 16% of the individuals in the control group, which was not statistically significant ($P = 0.22$). Triglyceride levels were statistically more elevated in SLE patients (159.3 ± 103.7 mg/dL) than in the control group (113.8 ± 50.3, $P < 0.01$). The levels of cholesterol and fractions were not statistically different between both groups.

Table I. Demographic, clinical, and laboratorial characteristics of SLE patients and control group

	SLE (n = 80)	CONTROL (n = 60)	P
Age (years)	38.3±12.0	39.0±12.7	0.75
Caucasian	76%	80%	0.27
BMI (kg/m^2)	26.8±6.2	24.9±3.8	0.04
BMI <29.9	81%	91%	0.59
BMI >30.0	19%	9%	0.59
Blood pressure			
High blood pressure	56%	33%	0.01
Systolic BP (mmHg)	130.7±19.9	124.5 ± 21.2	0.07
Diastolic BP (mmHg)	84.3±11.5	79.1 ± 12.0	0.01
Lipid profile			
Dislipidemia	11%	16%	0.22
Total cholesterol (mg/dL)	208.6±69.4	198.5 ± 46.7	0.33
LDL-cholesterol (mg/dL)	123.9±51.0	120.2 ± 39.8	0.64
HDL-cholesterol (mg/dL)	53.8±15.5	53.9 ± 13.5	0.97
VLDL-cholesterol (mg/dL)	33.5±22.2	28.2 ± 16.2	0.15
Triglycerides (mg/dL)	159.3±103.7	113.8 ± 50.3	0.01
Other CVR factors			
Fasting blood glucose (mg/dL)	82.9±12.6	87.5 ± 13.4	0.03
Smoking	27.5%	18.3%	0.04
History of CVD	49%	33%	0.06
Framingham score (median)	-3.0	-3.5	0.83
CVR in 10 years			
Percentage (median)	1.0%	1.0%	0.82
Risk ≤1%	60%	61%	0.82
Risk >10%	11.5%	8.3%	0.07

Mean ± SD; BP = blood pressure; BMI = body mass index in kg/m^2; CVD = cardiovascular disease; CVR = cardiovascular risk.

Mean fasting glucose in the control group (87.5 ± 13.4 mg/dL) was statistically higher than in SLE patients (82.9 ± 12.6 mg/dL). The body mass index of SLE patients (26.8 ± 6.2 kg/m^2) was significantly higher than in the control group (24.9 ± 3.8 kg/m^2, $P < 0.04$). The incidence of a family history of cardiovascular disease was similar in groups, 49% for SLE patients and 33% in the control group.

Statistically significant differences in the score and risk of coronary artery disease in ten years according to Framingham risk score were not observed between both groups (Figure 1A). Patients with SLE had a median score of -3.0 (-14.0 to 13), while in the control group it as -3.5 (-17 to 30). Both groups had a coronary risk of 1%, which ranged from 1% to 27% in LSE patients and 1% to 15% in the control group (Figure 1B).

Statistically significant differences in the risk factors considered in the calculation of Cardiovascular Risk by the Framingham Table were not observed when patients with cardiovascular risk greater than 10% were analyzed.

When coronary risk scores were correlated with the age of SLE patients, a statistically significant positive correlation was observed both for SLE patients ($r = 0.67$, $P = 0.001$, with 95% confidence interval of 0.53-0.78) and the control group ($r = 0.67$, $P = 0.001$ with 95% confidence interval of 0.50-0.79). When coronary risk scores of SLE patients were correlated with DBP [diastolic blood pressure] and BMI, a statistically significant positive correlation was observed (DAP: $r = 0.30$, $P = 0.006$ with 95% confidence interval of 0.08-0.48; BMI: $r = 0.24$, $P = 0.02$, 95% confidence interval of 0.02-0.44). Although triglyceride levels in SLE patients were significantly higher than in the control group, we did not observe a positive correlation ($r = 0.70$, $P = 0.48$ with 95% confidence interval of -0.14-0.29). A correlation among DBP, BMI, and triglyceride levels and coronary risk was not observed in the control group.

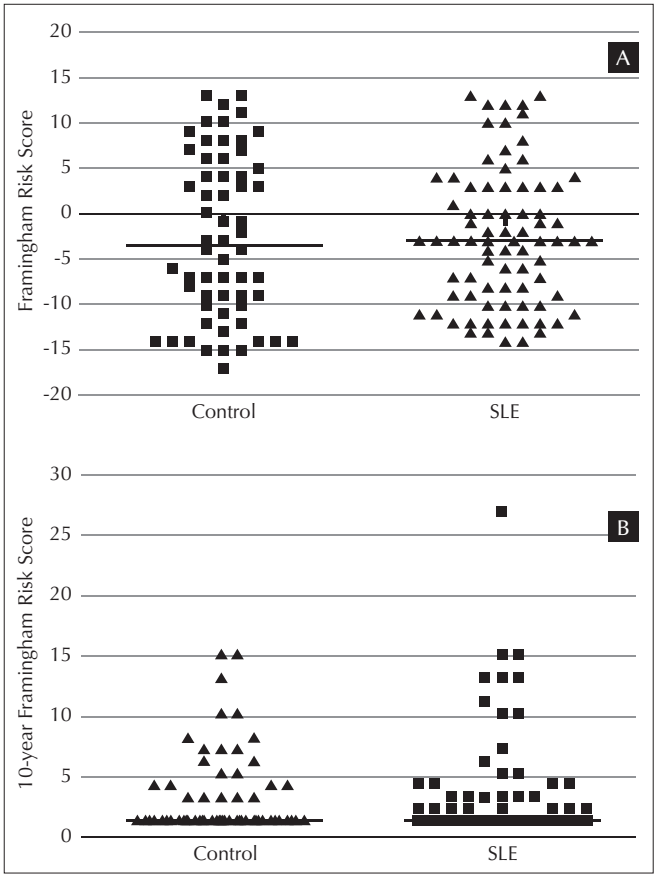

Figure 1. Individual Framingham risk score in SLE patients and control group. The abscissa represents the median.

DISCUSSION

In the present study, we observed that SLE patients had the same coronary artery disease risk as the control group according to the Framingham risk score, despite the elevated risk of cardiovascular events and the increase in the prevalence and severity of coronary atherosclerosis being documented as responsible for 20-30% of the deaths of lupus patients.[5,6,25] The estimated value for cardiovascular events in 10 years was lower than 1% in 60% of SLE patients and in 61% of the patients in the control group, demonstrating that the Framingham risk score was not able to identify the population of lupus patients at elevated risk of coronary artery disease.

Due to their modulating effects on the inflammatory process in rheumatic diseases, antimalarials are commonly used in SLE patients. They also reduce the levels of total cholesterol and LDL, and normalize HDL levels, which are relevant therapeutic effects due to the increase in the premature risk of atherosclerosis in lupus. Chloroquine diphosphate was used by 92% of lupus patients in the present study, which might partly justify the similar results in total cholesterol levels and its fractions in the control and study groups, therefore collaborating with the incapacity of the Framingham score to identify elevated risk of coronary events in this population.[22,23,24]

In the general population, the Framingham score is commonly used to identify and stratify patients at risk for coronary artery disease, therefore helping the orientation of interventions to control hypertension, dyslipidemia, and diabetes mellitus, to discontinue smoking, and lose weight. However, despite the usefulness of this score, when it is applied to SLE patients, it underestimates the risk of coronary artery disease in this population.

In the Framingham risk score, age has an important role in both genders. For females, its importance is even greater, with -9 points for the 30 to 34 age group, and up to +8 from 70 to 74 years. Since the mean age of lupus patients in the present study was 38 years, the scores of all other risk factors (total cholesterol, HDL, systolic blood pressure, diastolic blood pressure, diabetes, and smoking) that they might have presented were annulled by the negative score as a function of their age, which could also justify the incapacity of the Framingham risk score to identify the risk of coronary artery disease in this population.

Considering that SLE usually affects young female patients, Chung *et al*. compared tomographies of the coronary arteries with the Framingham scale and PDAY (Pathobiological Determinants of Atherosclerosis in Youth) scale, which allows predicting the development of atherosclerotic lesions in younger patients.[21] The authors concluded that, despite the identification of calcified plaques in the coronary arteries, neither the Framingham nor PDAY scales were capable of stratifying the risk of coronary artery events in women in SLE.[25,26]

Over the last several years, inflammatory activity has been gaining importance as a determinant of the progression of atherosclerosis and its complications. Atherosclerosis is an inflammatory process characterized by infiltration of the intima by activated monocytes/macrophages and T cells, with production of proinflammatory cytokines by those cells, and this is one of the possible common mechanisms of atherosclerosis and SLE.[27,28,29]

It is possible that traditional cardiovascular risk factors present in SLE women are not enough to explain this increased risk.[30] Through its inflammatory activity, SLE could contribute as a non-traditional risk factor for the development of atherosclerosis by activating of the endothelium, one of the initial steps in the development of atherosclerosis.[31,32] *In vivo* studies have demonstrated that endothelial activation is present in SLE, which was identified by the increased level of endothelial adhesion molecules (VCAM-1), thrombomodulin (TM), Von Willebrand factor (vWf), and increase in the expression of adhesion molecules.[33,34]

Dislipidemia is commonly seen in SLE patients, and it is considered an important factor in the development of atherosclerosis in this population. Drugs, especially corticosteroids, as well as nephrotic syndrome, and lupus activity are considered collaborators in the development of dyslipidemia in SLE patients.[35,36,37]

Kashef *et al*. have demonstrated that lupus activity is associated with dyslipidemia, with a pattern characterized by elevated levels of triglyceride and VLDL and reduced HDL levels. The exact mechanism of this relationship is unknown; however, it is possible that activation of lipoprotein lipase, the main enzyme in VLDL catabolism, is hindered, resulting in the accumulation of VLDL and LDL, and reduction in HDL levels.[8,39,40] The only change in lipid profile seen in our study was the significant elevated triglyceride levels in SLE patients.

Leeuw *et al*. demonstrated that SLE is associated with an increase in the prevalence of atherosclerosis when compared with the group of normal individuals, especially in SLE of longer duration and with greater damage index. All traditional risk factors have an important role in accelerating atherosclerosis, especially hypertension, contributing with this process and reflecting in the increase in cardiovascular events in lupus patients. It is possibly not enough to attack only traditional risk factors to prevent cardiovascular events in SLE patients, since non-traditional risk factors (endothelial activation, change in vascular remodeling, and SLE duration) also have a decisive role.[41] The knowledge that SLE patients are at an increased risk for cardiovascular events leads to the search for markers that allow identify and stratify those patients.

The institution of guidelines and measures for different comorbidities presented by SLE patients, such as diabetes mellitus, hypertension, and dyslipidemia, associated with smoke cessation and physical activity, can improve the prognosis of SLE. Considering the results of the present study, actions to deal with obesity, hypertension, smoking, and high triglyceride levels can increase survival of the lupus patients evaluated.

The primary focus of medical care in lupus patients usually focus the assessment of disease activity and the presence of infections, neglecting the risk of cardiovascular complications in this population. Studies in Baltimore and Toronto suggest that, in academic centers caring for SLE patients, measures to prevent those risk factors are not considered important.[42]

To conclude, our data demonstrate that the Framingham score was not capable to evaluate the risk of coronary artery disease in SLE patients and the need to identify other markers of coronary artery disease. This evaluation should include, besides traditional risk factors, non-traditional risk factors and reduction of the age factor, since most patients are young.

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