Lupus (2018) 0, 1–9
journals.sagepub.com/home/lup

PAPER

Incidence of cardiovascular risk factors in female patients with systemic lupus erythematosus: a 3-year follow-up cohort

CSA Monção, LN Martins, MPS Penteado, RCP Reis, FMM Santos, CCD Lanna, AL Ribeiro and RW Telles
Universidade Federal de Minas Gerais, Faculdade de Medicina Belo Horizonte, Minas Gerais, Brazil

Objectives: To evaluate the incidence and variability of traditional coronary artery disease (CAD) risk factors in a cohort of lupus patients and to investigate if prednisone use predicts an increase in the number of risk factors. **Methods:** A total of 151 women, 37.8 ± 11.1 (mean ± SD) years old at baseline, were reevaluated after a median period of 39 (interquartile range 36.5–42.0) months. The cumulative incidence of traditional risk factors, the incidence rate (with 95% confidence interval) of hypertension, diabetes, dyslipidemia and hypertriglyceridemia, and the frequency of the risk factors' disappearance were calculated. Metabolic syndrome (MetS) and Framingham risk score (FRS) were computed. Logistic regression was used to investigate if maximum or cumulative prednisone dose used during follow-up predicted an increase in the cardiometabolic risk factors' number. **Results:** The cumulative incidence of risk factors varied from 39.1% (abdominal obesity) to zero (smoking), and the incidence rate varied from 133.2 (87.8–178.6) per 1000 person-years (dyslipidemia) to 10.4 (1.3–19.5) per 1000 person-years (diabetes). The cumulative incidence for MetS was 18.8%, and 11.7% of 143 patients with low FRS at baseline (T_1) were classified in the high-risk category at the end of the study (T_2). Dyslipidemia was the most variable risk factor, with 43.5% disappearance at T_2. The maximum prednisone dose used during follow-up was borderline ($p = 0.050$) for prediction of an increase in the number of cardiometabolic risk factors in an adjusted model for antimalarial use, modified Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and age. **Conclusion:** The authors described high incidence and variability of CAD risk factors in female lupus patients, with higher prednisone dose being borderline for an increase in the number of cardiometabolic risk factors. *Lupus* (2018) **0,** 1–9.

Key words: Cardiovascular disease; risk factors; incidence; prednisone side effects

Introduction

Cardiovascular disease (CVD), especially coronary artery disease (CAD), is a leading cause of mortality in systemic lupus erythematosus (SLE) and affects 5–8% of patients in the first decade and up to 28% of patients after four decades of disease.[1] The increased prevalence and premature incidence of CAD in SLE patients have been widely recognized and are a major concern of the current clinical researches.[2,3] However, studies on the incidence of its risk factors are uncommon.[2,3]

The increased risk of CVD observed in SLE patients cannot be fully explained by the traditional risk factors for CAD.[4,5] Other risk factors for accelerated atherosclerosis in SLE include disease inflammation, mainly nephritis, circulating immune complexes and antiphospholipid antibodies, dysregulation of T and B cells, and increased circulating levels of inflammatory cytokines.[5]

The traditional proatherogenic lipid profile (low high-density lipoprotein (HDL)-cholesterol, high low-density lipoprotein (LDL)-cholesterol and high triglycerides), along with increased proinflammatory HDL and increased oxidized LDL-cholesterol antibody, had been more frequently identified in SLE patients, and is also associated with atherosclerosis in those patients.[5] In addition, Nikpour et al. observed that the blood pressure and the cholesterol level are dynamic in lupus patients, varying due to disease activity and treatment changes.[4]

Correspondence to: Rosa Weiss Telles, Avenida Alfredo Balena 190, Sala 246, Santa Efigênia, Belo Horizonte, Minas Gerais, Brazil, CEP 30130-100.
Email: rwtelles@uol.com.br
Received 7 March 2018; accepted 29 June 2018

10.1177/0961203318790676

The role of steroids and immunosuppressive drugs in the atherosclerosis development in SLE patients remains controversial, with conflicting data in the literature.[1,6–9] These drugs are either identified as factors associated with increasing odds of clinical and subclinical atherosclerosis or as protective factors, sometimes with a null effect.[6,10] However, the association between corticosteroids and immunosuppressive drugs with atherosclerosis in lupus was evaluated mostly in cross-sectional and retrospective studies.[6,8,11–16]

The present study describes the incidence, variability of prevalence and the treatment of traditional CAD risk factors in a prospective cohort of SLE patients. The hypothesis that prednisone used during follow-up could be associated with an increase in the number of CAD risk factors was tested in this prospective study.

Patients and methods

Patients

This prospective observational study was performed at the Rheumatology Unit of the Hospital das Clínicas of the Universidade Federal de Minas Gerais (UFMG), Brazil. This study complies with the Declaration of Helsinki and was approved by the Human Research Ethics Committee and by the Board of Education, Research and Extension of the Hospital das Clínicas/UFMG (ETIC 274/08).

Data collection took place between May 2005 and February 2006 (T_1), during the routine ambulatory care. The patients were consecutively included in a cohort study for prospective evaluation of atherosclerotic CVD according to the following criteria: female patients who fulfilled the American College of Rheumatology (ACR) classification criteria for SLE (ACR 1982/1997) and were aged 18 years or older.[17,18] The representativeness of the sample, including the sample calculation, has been previously published.[6] After a median period of 39 months (interquartile range 36.5–42.0) (T_2) the patients followed prospectively were reevaluated by one of the authors (RWT). Of the 174 patients initially included, 10 died before the second evaluation was performed, 2 moved from the city, 4 dropped out of the study, 5 interrupted treatment at the Rheumatology Unit, and 2 could not be contacted.

Methods

The included patients were assessed at baseline (T_1) and at the end of the study (T_2) for lupus characteristics and for CAD traditional risk factors according to previously published protocols, including treatment for the CAD risk factors in the definition (see Supplementary Material).[6,15] In addition to the T_1 and T_2 evaluation, the structured medical records were reviewed for CAD risk factors at each patient visit at the clinic during follow-up, defining the time when a risk factor was first seen. Due to the lack of consistent information regarding weight, waist circumference and family history of coronary event in the medical records, such factors were computed only at T_1 and T_2. Cumulative SLE clinical and laboratory characteristics and treatment of SLE and CAD risk factors, including maximum and cumulative prednisone dose used during follow-up, were also investigated through medical records.

The risk of a future coronary event was calculated using the Framingham risk score (FRS).[19] Patients under the age of 30 years were considered part of the 30–34-year age bracket.[20] Additionally, the total number of traditional CAD risk factors present in each patient was counted, including age ($\geq$55 years old), positive first-degree family history for an early coronary event, hypertension, smoking, diabetes, dyslipidemia and hypertriglyceridemia.[15,21] Metabolic syndrome (MetS) was defined according to the executive summary of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), including treatment for the variables.[16,22] The NCEP/ATPIII defines the MetS as being present if three or more of the following five criteria are met: central obesity (waist circumference >88 cm); hypertriglyceridemia (triglycerides $\geq$150 mg/dL); low HDL-cholesterol (<50 mg/dL); high blood pressure ($\geq$130/85 mmHg); and fasting glucose $\geq$110 mg/dL.[22]

The increase in the modifiable cardiometabolic risk factors' number between T_1 and T_2 was calculated considering the following traditional risk factors for CAD: hypertension, diabetes, dyslipidemia, hypertriglyceridemia and abdominal obesity.[22]

Renal function was estimated by calculating glomerular filtration rate (GFR), with chronic kidney disease defined as GFR <60 mL/min/1.73 m^2.[23,24] The lupus activity was measured using the modified Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (excluding the serologic items: anti-dsDNA and complement)[25,26] and the damage index was assessed according to Systemic Lupus International Collaborating Clinics (SLICC/ACR).[27]

Statistical analysis

Categorical variables were described as number and percentage (%) and the continuous variables as

median and interquartile range (IQR). The traditional CAD risk factors' cumulative incidence during follow-up and the cardiometabolic risk factors' incidence rate (1000 person-years) were calculated. The statistically significant increase (or decrease) in the prevalence of risk factors between T_1 and T_2 was analyzed by McNemar's test.

A multivariate analysis, using logistic regression, was performed to assess whether the maximum or cumulative dose of prednisone used during the follow-up (explanatory variables) predicted an increase in the number of cardiometabolic risk factors for CAD at T_2 (response variable: number of cardiometabolic risk factors at T_2 *minus* number of cardiometabolic risk factors at $T_1 \geq 1$), in a predefined model adjusted for age at T_1, higher modified SLEDAI-2K and antimalarial use during follow-up. These variables were chosen considering the association between them and the risk factors for CAD in lupus patients in the medical literature, independently of univariate levels of significance in the present analysis.[28,29] The multicollinearity between the model variables was tested by calculating the variance inflation factor (VIF), being considered present when VIF >5. Subsequently, the median of the prednisone maximum dose required that would result in a probability of an increase in the number of cardiometabolic risk factors for CAD was calculated and presented graphically.

Results

The median (IQR) age at baseline and at SLE diagnosis of 151 patients reevaluated after a median period of 39 (36.5–42) months was 38 (29–46) years and 27 (21.5–34.8) years, respectively. Thirty-seven (24.5%) patients considered themselves, through self-identification, to be white and 114 non-white (mixed) race/color: 35 (23.2%) black, 77 (51.0%) brown (''pardo'') and 2 (1.3%) ''other''. At baseline, the median (IQR) SLE duration was 7.9 (4.3–11.7) years, damage index according to SLICC/ACR was 1 (0–2) and modified SLEDAI-2K was 1 (0–4).

The cumulative SLE clinical and laboratory characteristics during the monitoring period, median 6.63 years (IQR 4.18–10.75), at the Rheumatology Unit and the manifestations of lupus activity at T_1 are presented in Table 1. Regarding SLE treatment at T_1, 119 patients (78.8%) were on prednisone, 76 (50.3%) on antimalarial and 68 (45.0%) on immunosuppressive drugs (azathioprine 22.5%, intravenous cyclophosphamide 11.3%, and methotrexate 8.6%).

Table 1 Clinical and laboratory characteristics of 151 SLE patients at baseline (T_1)

Characteristics[a]	*Cumulative*[b] n *(%)*	*At T_1* n *(%)*
Mucocutaneous manifestations	131 (86.8)	32 (21.2)
Serositis	45 (29.8)	1 (0.7)
Pleurisy	35 (23.2)	1 (0.7)
Pericarditis	21 (13.9)	0
Arthritis	106 (70.2)	10 (6.6)
Nephritis	95 (62.9)	30 (19.9)
Proteinuria >3.5 g/24 h	31 (20.5)	3 (2.0)
Neuropsychiatric disorders	17 (11.3)	0
Hematologic abnormalities	140 (92.7)	65 (43.0)
Hemolytic anemia	33 (21.9)	3 (2.0)
Thrombocytopenia	27 (17.9)	1 (0.7)
Lymphopenia	137 (90.7)	63 (41.7)
Leukopenia	72 (47.7)	24 (15.9)
Positive ANA	151 (100)	–
Immunological criteria	115 (76.2)	–
Anti-dsDNA ($n=150$)	73 (48.7)	–
Anti-Sm ($n=150$)	41 (27.3)	–
False positive VDRL	14 (9.3)	–
Positive aCL ($n=150$)	38 (25.3)	–
Positive LA	17 (11.3)	–
Chronic kidney disease	2 (1.3)	2 (1.3)

[a]According to the American College of Rheumatology classification criteria for SLE (1982/1997).
[b]Cumulative during the time of SLE treatment at Rheumatology Unit.
aCL: anticardiolipin; ANA: antinuclear antibody; LA: lupus anticoagulant; VDRL: venereal disease research laboratory.

At the end of follow-up, 102 (67.5%) patients were on prednisone, 99 (65.6%) on antimalarial drugs and 73 (48.3%) on immunosuppressive drugs (azathioprine 27.2%, intravenous cyclophosphamide 4.6%, and methotrexate 15.9%). The median (IQR) daily prednisone dose at T_1 and T_2 was 5.0 (2.5–10) mg/day and 5.0 (0–10.0) mg/day, respectively. Furthermore, the median (IQR) cumulative prednisone dose at T_1 was 27.8 (14.5–43.6) g and at T_2 was 37.2 (21.0–52.7) g, with median (IQR) follow-up prednisone cumulative dose of 7.4 (3.4–12.3) g and maximum prednisone dose of 20.0 (5.0–30.0) mg/day.

Cardiovascular events at T_1 were identified in five female patients (3.3%), with six different diagnoses. Three patients had previous histories of coronary events, one had ischemic cerebrovascular accidents and two had lower limb peripheral artery disease.[20] During follow-up, two new events were identified in two different patients: one patient had a stroke and one had a diagnosis of lower limb peripheral artery disease based on the ultrasound ankle-brachial index <0.9.[20]

Table 2 shows the cumulative incidence and the incidence rate with 95% confidence interval (CI) of

Table 2 Coronary artery disease risk factors: cumulative incidence and incidence rate at baseline (T_1)

Risk factor for CAD	*Patients without risk factor at T_1* n	*Cumulative incidence* n *(%)*	*Incidence rate (95% CI) (1000 person-years)*
Hypertension	79	18 (22.8)	72.1 (38.8–105.4)
Smoking	130	0	0
Diabetes mellitus	143	5 (3.5)	10.4 (1.3–19.5)
Dyslipidemia[a]	89	33 (37.1)	133.2 (87.8–178.6)
Total cholesterol ≥200 mg/dL	122	27 (22.1)	71.9 (44.8-99.0)
LDL-c ≥130 mg/dL	126	20 (15.9)	49.9 (28.1–71.8)
HDL-c <40 mg/dL	111	15 (13.5)	44.2 (21.8–66.5)
TGL ≥150 mg/dL	108	16 (14.8)	49.1 (25.0–73.1)

[a]Dyslipidemia: total cholesterol ≥200 mg/dL and/or LDL-c ≥130 mg/dL and/or HDL-c <40 mg/dL.
CAD: coronary artery disease; CI: confidence interval; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TGL: triglycerides.

CAD risk factors. The cumulative incidence during follow-up were 3.8% (5 out of 131 patients) for positive family history for premature CAD, 16.5% (20 out of 121 patients) for obesity and 39.1% (34 out of 87 patients) for abdominal obesity. From 143 women with <10% chance of having a cardiovascular event in the next 10 years according to FRS at T_1, 11 (7.7%) were classified in the high-risk category (≥10%) at T_2. The cumulative incidence of patients with multiple (+2) risk factors was 27.5% (22 out of 80 patients) and of MetS was 18.8% (19 out of 101 patients).

The disappearance of modifiable CAD risk factors at T_2 among patients with the risk factor at T_1 is presented in Table 3. Dyslipidemia and hypertriglyceridemia are the two most variable risk factors. Furthermore, despite the high incidence rate of dyslipidemia (Table 2), and because of this high variability (Table 3), there was no significant prevalence difference for dyslipidemia between T_1 and T_2, except for the statistically significant isolated increase of total cholesterol prevalence (Table 4).

The cumulative incidence of LDL ≥100 mg/dL was 44.8% (39 out of 87 patients). Among patients with LDL ≥100 mg/dL at T_1, 16 (25%) out of 64 evolved with LDL <100 mg/dL at T_2, even though they were not on statins. Despite this high variability, there was an increase in prevalence of LDL ≥100 mg/dL during follow-up (T_1: 64 (42.4%) versus T_2: 87 (57.6%), $p = 0.003$).

In addition to the low frequency of hypertension, obesity and abdominal obesity disappearance at T_2 among patients with these risk factors at T_1 (Table 3), there was a statistically significant prevalence increase of those risk factors comparing T_2 and T_1 (Table 4). During follow-up, there was a significant increase in the number of female lupus patients with high risk for cardiovascular event according to the FRS, although the number of patients with multiple (+2) risk factors for CAD and the prevalence of MetS remained stable (Table 4).

Table 3 Disappearance of coronary artery disease risk factors among patients with the risk factor at baseline (T_1) and at the end of the study (T_2)

Risk factor for CAD	*Patients with risk factor at T_1* n	*Disappearance of risk factor at T_2* n *(%)*
Hypertension	72	6 (8.3)
Smoking	21	3 (14.3)
Diabetes mellitus	8	0
Dyslipidemia[a]	62	27 (43.5)
Total cholesterol ≥200 mg/dL	29	11 (37.9)
LDL-c ≥130 mg/dL	25	9 (36.0)
HDL-c <40 mg/dL	40	27 (43.5)
TGL ≥150 mg/dL	30	18 (41.9)
Obesity	30	5 (16.7)
Abdominal obesity	64	4 (6.3)
FRS ≥10	8	1 (12.5)
Multiple (+2) CAD risk factors[b]	70	13 (18.6)
Metabolic syndrome	50	13 (26.0)

[a]Dyslipidemia: total cholesterol ≥200 mg/dL and/or LDL-c ≥130 mg/dL and/or HDL-c <40 mg/dL.
[b]Namely: age (≥ 55 years old), positive first-degree family history for an early coronary event, hypertension, smoking, diabetes, dyslipidemia, and hypertriglyceridemia.
CAD: coronary artery disease; FRS: Framingham risk score; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TGL: triglycerides.

Among hypertensive patients, there was no modification of the frequency of antihypertensive medication use during follow-up (T_1: 66 (91.7%) versus T_2: 73 (86.9%), $p = 0.096$), with most hypertensive patients being on medication. Nonetheless, the use of anti-proteinuric drugs was increased: angiotensin-converting-enzyme (ACE) inhibitors at T_1: 36

(54.5%) versus at T_2: 45 (61.6%), $p = 0.023$; angiotensin receptor blockers (ARBs) at T_1: 2 (3.0%) versus at T_2: 9 (12.3%), $p = 0.039$. Likewise, there was an increased use of statins in patients with dyslipidemia (T_1: 2 (3.2%) versus T_2: 17 (25.0%), $p < 0.001$) and of acetylsalicylic acid in all patients (T_1: 6 (4.0%) versus T_2: 19 (12.6%), $p < 0.001$).

Considering the modifiable cardiometabolic risk factors, namely hypertension, diabetes, dyslipidemia, hypertriglyceridemia and abdominal obesity, there was a significant increase in their number between T_1 and T_2 (T_1: 2 (0–3) versus T_2: 2 (1–3), $p < 0.001$), with an increase of at least one cardiometabolic risk factor in 60 (39.7%) lupus women.

In multiple regression analysis, the prednisone cumulative dose during follow-up was not significantly associated with an increase in the number of cardiometabolic risk factors ($p = 0.518$). However, the maximum prednisone dose used between T_1 and T_2 showed borderline significance ($p = 0.050$), whereas none of the adjusted variables were significantly associated with the increased number of cardiometabolic risk factors for CAD (Table 5). This borderline p value is in accordance with the borderline 95% CI limits. Figure 1 shows the maximum prednisone dose distribution and the graphically represented probability of an increase in the number of cardiometabolic risk factors according to the median maximum prednisone dose. A sensitivity analysis showed that prednisone dose >40 mg/day predicted that increase ($p = 0.009$).

Table 4 Coronary artery disease risk factors' prevalence in 151 SLE women at baseline (T_1) and at the end of the study (T_2)

Risk factor for CAD	*T_1* n *(%)*	*T_2* n *(%)*	p
Family history for premature CAD	19 (12.6)	24 (15.9)	0.063
Hypertension	72 (47.7)	84 (55.6)	0.023
Smoking	21 (13.9)	18 (11.9)	0.250
Diabetes mellitus	8 (5.3)	13 (18.6)	0.063
Dyslipidemia[a]	62 (41.1)	68 (45.0)	0.519
Total cholesterol ≥200 mg/dL	29 (19.2)	45 (29.8)	0.014
LDL-c ≥130 mg/dL	25 (16.6)	36 (23.8)	0.061
HDL-c <40 mg/dL	40 (26.5)	31 (20.5)	0.200
TGL ≥150 mg/dL	43 (28.5)	45 (29.8)	0.856
Obesity	30 (19.9)	45 (29.8)	0.004
Abdominal obesity	64 (42.4)	94 (62.3)	<0.001
FRS ≥10	8 (5.3)	18 (11.9)	0.006
Multiple (+2) CAD risk factors[b]	70 (46.4)	79 (52.3)	0.175
Metabolic syndrome	50 (33.1)	56 (37.1)	0.377

[a]Dyslipidemia: total cholesterol ≥200 mg/dL and/or LDL-c ≥130 mg/dL and/or HDL-c <40 mg/dL.
[b]Namely: age (≥55 years old), positive first-degree family history for an early coronary event, hypertension, smoking, diabetes, dyslipidemia and hypertriglyceridemia.
CAD: coronary artery disease; FRS: Framingham risk score; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TGL: triglycerides.

Discussion

This study presents the incidence and variability of the traditional risk factors for CAD in female SLE patients followed for approximately three years. Altogether, the cumulative incidence and the incidence rate were high. Some risk factors were highly variable, especially those related to cholesterol. In addition, the maximum prednisone dose used during follow-up predicted the increase in the number of cardiometabolic risk factors for CAD with a borderline significance ($p = 0.050$).

The cardiovascular risk factors' incidence varies considerably among different populations, probably due to ethnic and socioeconomic diversity, and a similar variability is observed in lupus patients.[30–36] The incidence rate of cardiovascular

Table 5 Association between maximum prednisone dose used during follow-up and chance of increased number of modifiable cardiometabolic risk factors for coronary artery disease at end of study

	Univariate analysis		*Multivariate analysis*	
Variable (during follow-up)	*OR (95% CI)*	p	*OR (95% CI)*	p
Age	0.996 (0.966–1.025)	0.782	1.004 (0.972–1.036)	0.800
Maximum prednisone dose	1.017 (0.999–1.035)	0.071	1.020 (1.000–1.039)	0.050
Antimalarial use	1.085 (0.300–1.869)	0.840	1.061 (0.243–1.880)	0.887
SLEDAI-2K (modified)[a]	0.985 (0.956–1.014)	0.297	0.980 (0.944–1.016)	0.270

Coronary artery disease namely: hypertension, diabetes, dyslipidemia, hypertriglyceridemia and abdominal obesity.
[a]Without complement and dsDNA. Variance inflation factor <5 for all variables.
The interaction term constructed as a product of SLEDAI-2K and Maximum prednisone dose was not significant and did not modify the final model.
CI: confidence interval; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

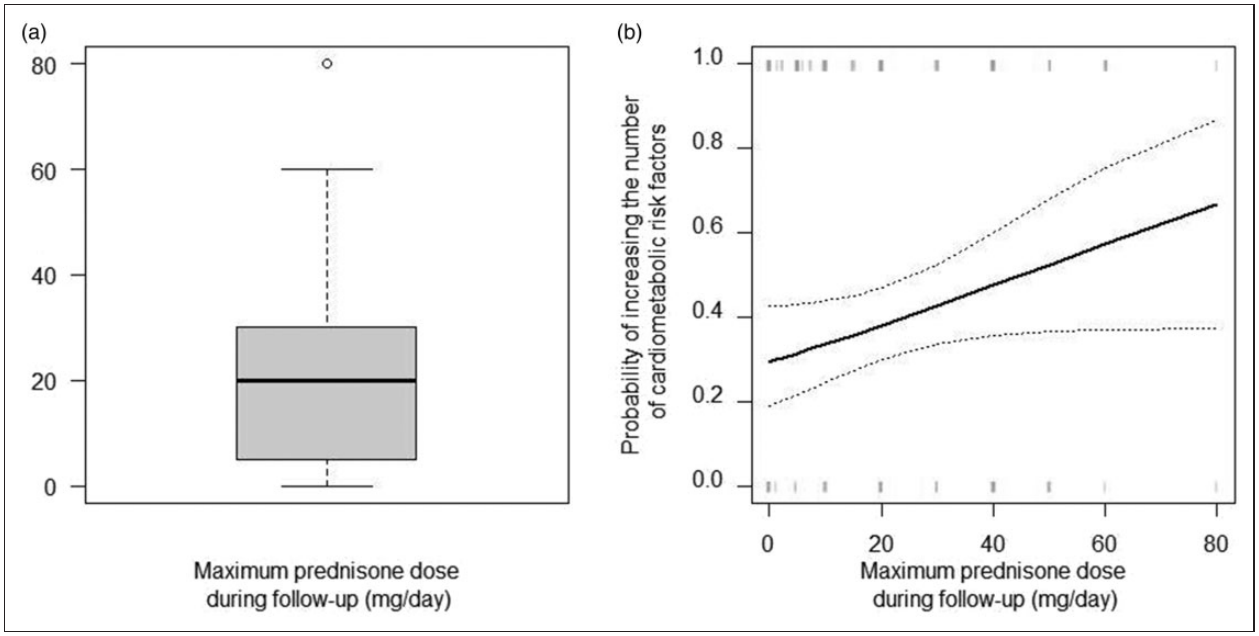

Figure 1 (a) Boxplot of maximum prednisone dose during follow-up. (b) Relationship between the median maximum prednisone dose and the probability of increasing the cardiometabolic risk factors' number for coronary artery disease during follow-up. The solid line represents the probability of an increase in the number of cardiometabolic risk factors; the dotted lines represent the 95% confidence interval for the predicted probability; the small bars on the graph represents the patients observed with no increasing (0) and increasing (1.0) in the number or cardiometabolic risk factors.

risk factors in lupus patients presented here was higher than observed in the general population of similar age.[30,31,34–36] For instance, the incidence rate of hypertension in the present study (72 per 1000 person-years) was higher when compared to the general population in Porto Alegre, Brazil, in women aged 36–45 years (40 per 1000 person-years).[36] This data corroborates with the knowledge of early and accelerated atherosclerosis in SLE women.[37,38]

A considerable number of patients with dyslipidemia at T_1 (62 patients) had normal lipid profile at T_2 (43.5%) even without statin use, confirming that a significant number of patients have non-sustainable dyslipidemia. This is in accordance with Bruce et al. who have shown that 24.6% of 134 patients had normal cholesterol, 40.3% had sustained hypercholesterolemia and 35.1% had variable hypercholesterolemia within three years of follow-up.[39] This dynamic course of dyslipidemia, beyond the natural variability of cholesterol, occurs because of changes in lupus disease activity and treatment. Borba et al. described that the inflammatory lipid profile in lupus patients is characterized by high levels of very LDL (VLDL)-cholesterol and triglycerides and low levels of HDL-cholesterol.[40] Nikpour et al. have suggested that two predictors of sustained hypercholesterolemia are cumulative dose of steroids and no antimalarial therapy.[4] On the other hand, once present, hypertension and abdominal obesity were much more sustained in the present study, resulting in a significant increase in prevalence of both CAD risk factors. This is in agreement with data from the general population, where the frequency of hypertension usually increases over time.[41,42]

There was a statistically significant increase in the frequency of anti-proteinuric antihypertensive medication (ACE inhibitors and ARBs), acetylsalicylic acid and statin use during the follow-up. The purpose of increasing the use of these medications was to achieve a nephroprotection effect, as well as better control of the cardiovascular events secondary to atherosclerosis, in accordance with the evidence reported in the literature. Despite this, the statins were used in a small percentage of patients with dyslipidemia in our cohort (3.2% at T_1 and 25.0% at T_2), which can be partially explained by the difficulty in the public free access to this medication in Brazil during the first year of the study. Nevertheless, our data is in accordance with the limited use of drugs to treat dyslipidemia in lupus patients described by other authors.[39]

The data regarding incidence of CAD risk factors in lupus patients are scarce and it is not well known

which variables are implicated in these risk factors' incidence. Corticosteroids are known to elevate levels of atherogenic lipids such as triglycerides and LDL-cholesterol, as well as blood pressure and serum glucose.[9,38,39,43–46] However, it is often difficult to dissociate the effect of corticosteroids from the lupus activity regarding CVD.[9,37] Even then, the present data suggest that a higher prednisone dose is a predictor of incident CAD risk factors, with a borderline *p* value, and that there is a linear dose-response association between the maximum prednisone dose and the probability of increasing the number of cardiometabolic risk factors for CAD.

In a prospective study with 229 SLE subjects, Petri et al. found that prednisone dose >10 mg/day was associated with higher incidence of hypercholesterolemia.[38] In the same direction, MacGregor et al. found, in a case-control study with 46 lupus patients, that the prednisone daily dose of >10 mg increased triglycerides and apolipoprotein B concentrations.[44] Furthermore, in the retrospective study of 310 SLE patients evaluated from 1971 to 2003, Karp et al. showed that a 10 mg increase in the average daily prednisone-equivalent dose in the preceding year was independently associated with a 16% increase in the estimated 2-year CAD risk, whereas a 6-point increase in SLEDAI score was associated with a 5% risk increase.[8] In the present study, there was no association of the modified SLEDAI-2K with the increase in the cardiometabolic risk factors' number, and the prednisone dose significantly associated with an increase in the cardiometabolic risk factors' number was higher than previously published.

The prednisone cumulative dose during follow-up in this sample was not significantly associated with an increase in the cardiometabolic risk factors' number. Nonetheless, previous studies have shown that longer duration of steroid use is an independent risk factor for CAD in SLE.[9,37] In the Toronto lupus cohort with 991 patients, over a follow-up of 6.7 (standard deviation = 6.4) years, Nikpour et al. showed that patients with CAD events received a significantly greater corticosteroid cumulative dose during follow-up than did those who remained CAD free.[7] Although steroids help in the control of lupus disease activity, current evidence suggests that increased exposure to steroids is likely to adversely affect cardiovascular health.[8,12]

Hydroxychloroquine appears to have multiple beneficial effects, including reducing glucose levels, increasing HDL-cholesterol and reducing triglycerides levels, besides beneficial effects on vascular endothelium.[4,7,9,47–50] In the present study this protective role was not evident when we used a composite endpoint (increasing the number of cardiometabolic risk factors).

We are aware that the CAD risk factors are not completely independent of each other and the frequency of each T_1 risk factor in our sample is high, with the possibility that the cumulative incidence and the incidence rate are overestimated in our study compared to studies including patients or individuals with no baseline risk factor. Another limitation is the lack of information concerning a possible association of disease activity oscillations and the occurrence of CAD risk factors over the three years of follow-up. More frequent analyses, considering shorter intervals, could verify the relation between disease activity and the variability of the modifiable CAD risk factors. We also emphasize the relatively high frequency of prednisone use and low frequency of antimalarial drugs, which could impact on the cardiovascular risk factors' incidences found in the present study. One last important limitation is the source of some information, namely medical records. We considered this a minor limitation because the medical records in our Unit, since 2004, is structured to allow a standardization of the research data register.

Conclusion

In summary, this study showed a high incidence of CAD traditional risk factors in a relatively young group of female lupus patients, especially hypertension and MetS. The dyslipidemia frequency presented a very dynamic course. Higher prednisone dose was a predictor of incident cardiovascular risk factors with borderline significance.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

RW Telles http://orcid.org/0000-0003-4027-2943

References

1 Nikpour M, Gladman DD, Urowitz MB. Premature coronary heart disease in systemic lupus erythematosus: what risk factors do we understand? *Lupus* 2013; 22: 1243–1250.
2 Roman MJ, Shanker BA, Davis A, *et al*. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2399–2406.
3 Asanuma Y, Oeser A, Shintani AK, *et al*. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2407–2415.
4 Nikpour M, Gladman DD, Ibanez D, Harvey PJ, Urowitz MB. Variability over time and correlates of cholesterol and blood pressure in systemic lupus erythematosus: a longitudinal cohort study. *Arthritis Res Ther* 2010; 12: R125.
5 Wilhelm AJ, Major AS. Accelerated atherosclerosis in SLE: mechanisms and prevention approaches. *Int J Clin Rheumtol* 2012; 7: 527–539.
6 Telles RW, Lanna CC, Ferreira GA, Souza AJ, Navarro TP, Ribeiro AL. Carotid atherosclerotic alterations in systemic lupus erythematosus patients treated at a Brazilian university setting. *Lupus* 2008; 17: 105–113.
7 Nikpour M, Urowitz MB, Ibanez D, Harvey PJ, Gladman DD. Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther* 2011; 13: R156.
8 Karp I, Abrahamowicz M, Fortin PR, *et al*. Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheum* 2008; 59: 169–175.
9 Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med* 1994; 96: 254–259.
10 Doria A, Shoenfeld Y, Wu R, *et al*. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003; 62: 1071–1077.
11 Sazliyana S, Mohd Shahrir MS, Kong CT, Tan HJ, Hamidon BB, Azmi MT. Implications of immunosuppressive agents in cardiovascular risks and carotid intima media thickness among lupus nephritis patients. *Lupus* 2011; 20: 1260–1266.
12 Bruce IN. "Not only…but also": factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. *Rheumatology (Oxford)* 2005; 44: 1492–1502.
13 Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine (Baltimore)* 1992; 71: 291–302.
14 Fangtham M, Petri M. 2013 update: Hopkins lupus cohort. *Curr Rheumatol Rep* 2013; 15: 360.
15 Telles RW, Lanna CCD, Ferreira GA, Carvalho MAP, Ribeiro AL. Frequência de doença cardiovascular aterosclerótica e de seus fatores de risco em pacientes com lúpus eritematoso sistêmico. *Rev Bras Reumatol* 2007; 47: 165–173.
16 Telles RW, Lanna CCD, Ferreira GA, Ribeiro AL. Metabolic syndrome in patients with systemic lupus erythematosus: association with traditional risk factors for coronary heart disease and lupus characteristics. *Lupus* 2010; 19: 803–809.
17 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). *Arthritis Rheum* 1997; 40: 1725.
18 Tam EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271–1277.
19 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837–1847.
20 Telles RW, Lanna CCD, Sousa AJ, *et al*. Progression of carotid atherosclerosis in patients with systemic lupus erythematosus. *Clin Rheumatol* 2013; 32: 1293–1300.
21 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001; 285: 2486–2497.
22 Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112: 2735–2752.
23 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
24 Levey AS, Eckardt KU, Tsukamoto Y, *et al*. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67: 2089–2100.
25 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288–291.
26 Uribe AG, Vilá LM, McGwin G Jr, Sanchez ML, Reveille JD, Alarcón GS. The Systemic Lupus Activity Measure-revised, the Mexican Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and a modified SLEDAI-2K are adequate instruments to measure disease activity in systemic lupus erythematosus. *J Rheumatol* 2004; 31: 1934–1940.
27 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363–369.
28 Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating*. USA: Springer, 2009, pp.174–189.
29 Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating*. USA: Springer, 2009, pp.191–211.
30 Pereira M, Lunet N, Paulo C, Severo M, Azevedo A, Barros H. Incidence of hypertension in a prospective cohort study of adults from Porto, Portugal. *BMC Cardiovasc Disord* 2012; 12: 114–121.
31 Jimenez-Corona A, Lopez-Ridaura R, Stern MP, Gonzalez-Villalpando C. Risk of progression to hypertension in a low-income Mexican population with prehypertension and normal blood pressure. *Am J Hypertens* 2007; 20: 929–936.
32 Longo-Mbenza B, On'kin JBKL, Okwe AN, Kabangu NK, Fuele SM. Metabolic syndrome, aging, physical inactivity, and incidence of type 2 diabetes in general African population. *Diab Vasc Dis Res* 2010; 7: 28–39.
33 Asghar S, Khan AKA, Ali SMK, *et al*. Incidence of diabetes in Asian-Indian subjects: a five year follow-up study from Bangladesh. *Prim Care Diabetes* 2011; 5: 117–124.
34 Joseph J, Svartberg J, Njølstad I, Schirmer H. Incidence of and risk factors for type-2 diabetes in a general population: the Tromsø Study. *Scand J of Public Health* 2010; 38: 768–775.
35 Hwang JH, Kam S, Shin J, *et al*. Incidence of metabolic syndrome and relative importance of five components as a predictor of metabolic syndrome: 5-year follow-up study in Korea. *J Korean Med Sci* 2013; 28: 1768–1773.
36 Moreira LB, Fuchs SC, Wiehe M, Gus M, Moraes RS, Fuchs FD. Incidence of hypertension in Porto Alegre, Brazil: a population-based study. *J Hum Hypertens* 2008; 22: 48–50.
37 Manzi S, Meilahn EN, Rairie JE, *et al*. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham study. *Am J Epidemiol* 1997; 145: 408–415.
38 Petri M, Perez-Gutthann S, Spence D, Hochberg M. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992; 93: 513–519.
39 Bruce IN, Urowitz MB, Gladman DD, Hallett DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 1999; 26: 2137–2143.
40 Borba EF, Bonfá E. Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. *Lupus* 1997; 6: 533–539.

41 Scala LC, Magalhães LB, Machado A. Epidemiologia da hipertensão arterial sistêmica. In: Moreira SM, Paola AV; Sociedade Brasileira de Cardiologia. *Livro Texto da Sociedade Brasileira de Cardiologia*. 2nd ed. São Paulo: Manole, 2015, pp.780–785..
42 Sociedade Brasileira de Cardiologia. Departamento de Hipertensão Arterial. VI Diretrizes brasileiras de hipertensão. *Rev Bras Hipertens* 2010; 17: 4–62.
43 Leong KH, Koh ET, Feng PH, Boey ML. Lipid profiles in patients with systemic lupus erythematosus. *J Rheumatol* 1994; 21: 1264–1267.
44 MacGregor AJ, Dhillon VB, Binder A, *et al*. Fasting lipids and anticardiolipin antibodies as risk factors for vascular disease in systemic lupus erythematosus. *Ann Rheum Dis* 1992; 51: 152–155.
45 Ettinger WH, Goldberg AP, Applebaum-Bowden D, Hazzard WR. Dyslipoproteinemia in systemic lupus erythematosus. Effect of corticosteroids. *Am J Med* 1987; 83: 503–508.
46 Bruce IN, Urowitz MB, Gladman DD, Ibañez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. *Arthritis Rheum* 2003; 48: 3159–3167.
47 Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. *Intern Med J* 2012; 42: 968–978.
48 Tam LS, Gladman DD, Hallett DC, Rahman P, Urowitz MB. Effect of antimalarial agents on the fasting lipid profile in systemic lupus erythematosus. *J Rheumatol* 2000; 27: 2142–2145.
49 Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. *Am J Med* 1990; 89: 322–326.
50 Sachet JC, Borba EF, Bonfá E, Vinagre CG, Silva VM, Maranhão RC. Chloroquine increases low-density lipoprotein removal from plasma in systemic lupus patients. *Lupus* 2007; 16: 273–278.