Carotid plaques in patients with long-term lupus nephritis

B. Gallelli[1], L. Burdick[2], S. Quaglini[3], G. Banfi[1], C. Novembrino[5], F. Bamonti[4], P. Messa[1], G. Moroni[1]

[1]Divisione di Nefrologia e Dialisi, and [2]Unità Operativa di Medicina 1b, Centro di Malattie Metaboliche del Fegato, Fondazione Ospedale Maggiore, Mangiagalli, Regina Elena, Milano; [3]Dipartimento di Informatica e Sistemistica, Universita' degli Studi di Pavia; [4]Dipartimento Scienze Mediche, Università degli Studi di Milano, Fondazione Ospedale Maggiore, Mangiagalli, Regina Elena, Milano; [5]Dipartimento Scienze Neurologiche, Universita' degli Studi di Milano, Fondazione Ospedale Maggiore, Mangiagalli, Regina Elena, Milano, Italy.

Abstract

Objective

To evaluate the prevalence of carotid plaques in patients with long-term lupus nephritis (LN).

Methods

Intima-media thickness (IMT) and carotid plaques were evaluated with ultrasound in 75 patients after a follow-up of LN of 158±106 months and in 75 sex -and age-matched controls. Traditional and non-traditional atherosclerotic risks factors were also tested.

Results

IMT was not different between LN patients and controls, but 18% of LN patients had carotid plaques in comparison to 2.6% of controls (p=0.004). The LN patients more frequently had hypertension (p=0.0001), hypercholesterolemia (p=0.0001), were overweight (p=0.009), in menopause (p=0.01) than controls.

More frequently, LN patients with carotid plaques had renal insufficiency (p=0.03), longer duration of lupus (p=0.05), anti-phospholipid antibodies (p=0.018), high C-reactive protein (p=0.03), high reactive oxygen species (p=0.001) than those without plaques. Patients with plaques were older (p=0.000001), in menopause (p=0.000001) and more frequently had cardio-vascular accidents during observation (p=0.02). The time of exposure to pathological values of systolic and diastolic blood pressure was longer (p=0.000001) and the percentage of pathological values of these variables during the follow-up was higher (p=0.000001) in patients with carotid plaques.

At multivariate analysis, older age (p=0.0025), longer time of exposure to pathological values of blood pressure (p=0.015) and of cholesterol (p=0.04) were independent predictors of carotid plaques.

Conclusions

Carotid plaques were more frequently found in LN patients than in controls.

Although inflammatory markers and lupus related factors may contribute to the development of atherosclerosis, only traditional risk factors such as age, hypertension and hypercholesterolemia were the independent predictors.

Key words

Lupus nephritis, carotid atherosclerosis, Doppler ultrasound

Beniamina Gallelli, MD
Larry Burdick, MD
Silvana Quaglini, PhD
Giovanni Banfi, MD
Cristina Novembrino, PhD
Fabrizia Bamonti, PhD
Piergiorgio Messa, PhD
Gabriella Moroni, MD

Please address correspondence and reprint requests to:
Gabriella Moroni, MD,
Divisione di Nefrologia e Dialisi,
Fondazione Ospedale Maggiore IRCCS,
Via della Commenda 15,
20122 Milano, Italy.
E-mail: gmoroni@policlinico.mi.it

Received on October 30, 2009; accepted in revised form on January 19, 2010.

Competing interests: none declared.

Introduction

Whilst the prognosis of systemic lupus erythematosus (SLE) has progressively improved during the last 5 decades, premature atherosclerosis has emerged as the most frequent cause of morbidity and mortality (1) in the long term outcome of SLE patients. Manzi *et al*. (2) reported that the rate of myocardial infarction is up to 50 fold higher in SLE women younger than 45 years than in healthy controls. Compared with healthy young women (between 18-44 years), those with SLE were 2.05 times more likely to be hospitalised because of cerebrovascular accidents (3). Traditional risk factors such as arterial hypertension, obesity and diabetes have also been implicated in the pathogenesis of premature atherosclerosis in SLE patients (4-7): all of them are probably enhanced by protracted corticosteroid therapy. In addition, Esdaile *et al*. (8) suggested that the chronic activation of the immune system in SLE represents *per se* one of the major causes of premature atherosclerosis in these patients.

The number of clinical events probably underestimates the prevalence of atherosclerosis in SLE. A test to assess the presence of silent atherosclerotic lesions is the B-mode carotid ultrasound which makes a careful evaluation of the intima-media thickness (IMT) possible and also identifies the presence of carotid plaques (9-12). Studies employing this technique have documented higher rates of carotid plaques in SLE patients than in healthy controls (13). However, no data are available about the prevalence of carotid plaques in patients with lupus nephritis (LN), a subset of SLE patients at high risk of accelerated atherosclerosis.

The aims of this study are: i) to compare the prevalence of carotid plaques in patients with LN followed in a single Renal Unit with that of matched controls; ii) to assess the role of the traditional and non traditional risk factors associated with the atherosclerotic plaques and with IMT in this cohort of patients.

Materials and methods

Between January 2007 and June 2008, all patients followed in our Unit for LN were submitted to carotid ultrasonography with assessment of the IMT and the presence of atherosclerotic plaques.

The results were compared to those of a cohort (hospital personnel) matched for age and gender. Every year hospital personnel are submitted to a complete medical check-up, including blood and urine tests.

This study was conducted according to the guidelines of the Declaration of Helsinki for Research on Human Subjects and was approved by the Human Ethics Committee at the Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Fondazione IRCCS, Milano, Italy. Each subject signed informed consent.

Patients and biochemical methods

The diagnosis of SLE had to match the American College of Rheumatology (ACR) criteria (14). The diagnosis of LN was based on clinical and biochemical criteria as well as on renal biopsy evaluated following the ISN/RNP classification (15). At the time of carotid ultrasonography patients were submitted to clinical evaluation; history of cardiovascular accidents, changes in drug treatment were recorded, and routine laboratory tests and serological markers of SLE activity were determined. Serum Reactive Oxygen Species (ROS) concentrations were determined by spectrophotometric method using the commercial kit (d-ROMs test, Diacron, Grosseto, Italy) on FREE analyser (Diacron). The test evaluates, in the presence of transition metals acting as catalyzers, the capacity of hydroperoxides to generate free radicals reacting with a chromogenic substance and developing a colored complex whose concentration is proportional to hydroperoxides levels (16). The following SLE-related disease factors were recorded: duration and cumulative dose of prednisone (mg/kg of body weight), use of hydroxychloroquine and immunosuppressive agents, the occurrence and the duration of nephrotic syndrome (proteinuria >3.5g/day, albumin <3.5g/dl), the presence of renal insufficiency (creatinine clearance <60 ml/min according to Cockcroft and Gault) and the presence of antiphospholipid antibodies (aPL). According to the Sapporo criteria (17) we con-

sidered patients to be positive for aPL when they had at least two positive tests for anticardiolipin antibodies IgG and IgM at moderate or high titer (>20U/ml GPL) and/or Lupus Anticoagulant confirmed on two separate occasions 6 weeks apart.

The LN patients were also evaluated for the presence of traditional cardiovascular risk factors: arterial hypertension (systolic blood pressure >140mm/Hg, diastolic blood pressure >90mm/hg or the use of anti-hypertensive agents), percent of pathological values of systolic and diastolic blood pressure, length of exposure to pathological values through the whole follow-up, body mass index (BMI) (overweight >25, obesity >30 kg/m^2), family history of cardiovascular disease (myocardial infarction before 55 years of age in first degree male relatives or before 65 years in female relatives), smoking habits (current = more than 5 cigarettes day), value of cholesterol, of trygliceride and of LDL as well as percent of pathological values and duration of pathological values through the whole follow-up, of cholesterol (>200mg/dl) and triglycerides (>170mg/dl), diabetes, menopausal status.

Before the present carotid ultrasound evaluation, the 75 LN patients had been followed for 13.2±8.8 years, during which time they had been submitted to 2572 clinical and biochemical evaluations (in mean, 34 evaluations for each patient).

The demographic and clinical characteristics of patients at the time of carotid ultrasonography are reported in Table I.

At the time of carotid ultrasound, 75 controls were evaluated for the presence of arterial hypertension, body mass index, family history of cardiovascular disease, smoking habits, diabetes, menopausal status, cholesterol.

Table I. Characteristics of patients with lupus nephritis at the time of the study.

Age (years, mean±SD)	46 ± 13
Sex (M/F) (n. of patients)	4/71
Myocardial infarction before the present study (1 pt was aPL positive)	3 pts (4%)
Cerebral thrombosis before the present study (2 pts were aPL positive)	7 pts (9.3%)
Duration of SLE (months)	167 ± 106
Duration of Lupus Nephritis (months)	158 ± 106
ISN/RNP Histological classes II/III/IV/V	1/14/41/15
Creatinine clearance <60 ml/min	17 pts (22.6%)
Serum creatinine >1.1 mg/dl	11 (15%)
Proteinuria >500mg/24h >3.5 g/24h	17 pts (22.6%)/ 3(4%)
Mean proteinuria g/24h, of 17 pts	2.7 ± 3.4
Arterial hypertension	41 pts (55%)
Use of anti-hypertensive agents	40 pts (53.3%)
Hemoglobin <12 g/dl	18 (24%)
Low C3 / Low C4	29 (39%)/ 17 (23%)
Anti-DNA Ab positivity	32pts (43%)
Positive Lupus anticoagulant	10 (13%)
Anti-phospholipid Ab positivity	21 pts (28%)
Cholesterol >200mg/dl	34 pts (45%)
Tryglicerides >170 mg/dl	None
LDL cholesterol mg/dl >130mg/dl	19 pts (33%)
Diabetes mellitus	None
Statin therapy	11 pts (15%)
Current smokers	20 pts (27%)
Steroid therapy	58 pts (77%)
Cyclophosphamide/azathioprine /mycophenolate/cyclosporine	1/17/5/11
Cloroquine	22 pts (29%)
Aspirin	26 pts (35%)
Family history of cardiovascular disease	7 pts (9%)
Body Mass Index kg/m^2 >25 >30	31 pts (41%)/ 7 (9%)
Menopause	35 pts (49%)

aPL: anti-phospholipid antibodies; pts: patients. All SLE patients were Caucasian.

Carotid atherosclerosis and intima-media wall thickness evaluations

Carotid intima-media thickness (CIMT) was measured according to accepted protocols (18).

In brief, employing a state-of-the-art ultrasound system (Philips IU 22) with a linear array high frequency probe, longitudinal B-mode images of the distal 1 cm of both common carotid arteries were acquired with direct storage of digital images for analysis. Multiple measurements were taken employing the software of the machine to determine the mean value of CIMT. The carotid bifurcations were scanned to identify plaque. Plaque was defined as any focal protrusion >50% of the surrounding wall thickness according to general consensus. (19).

All the images were acquired by the same blind operator (Dr Larry Burdick) .

Statistical analysis

Mean and standard deviation, together with median and interquartile (IQ) range (25°-75° percentile) were used as descriptive statistics. For continuous variables, the non-parametric Mann-Whitney test was used for assessing any difference between the two groups of patients. Pearson's coefficient was used to test correlation between continuous variables. The percentage of pathological values of a parameter was calculated as 100*(number of measurements over the established threshold) divided by the total number of measurements. To calculate the length of time spent with pathological values of a parameter, we linearly interpolated each patient's measurements of that parameter and then we added all the periods resulting in interpolated values higher than the threshold. Multivariate logistic regression analysis has been used to find predictors of carotid plaques. First we checked in the entire study population whether SLE was an independent risk factor for carotid plaque development. Then a multivariate model was built for patients with Lupus nephritis, testing all the variables listed in Tables III and IV and the histological classes of lupus nephritis.

Statistical significance has been considered for p-values equal or less than 0.05, while p-values between 0.05 and

Table II. Multivariate logistic regression coefficients and their statistical significance for Systemic lupus erythematosus (SLE) and the traditional risk factors of atherosclerosis.

	Value	Std. error	*p*-value
Intercept	-48.2	16.7	0.004
Log(age)	11.5	4.1	0.006
Hypertension	3.0	1.3	0.02
Smoking	1.9	1.2	0.1
High cholesterol	0.7	0.8	0.4
SLE	1.9	1.2	0.1

0.1 were considered as a tendency. Odds ratios (and 95% confidence intervals) were calculated as the exponential of the regression coefficients (±1.96*standard error). To interpret the odds ratios, it should be taken into account that we used continuous variables, then the odds ratio has to be interpreted as an approximation of the increase of the relative risk for a unitary increment of the variables. The statistical package S-Plus (MathSoft Inc, 20) was used for all the analyses and plots.

Results

Comparison between patients with lupus nephritis and controls

There were no significant differences between patients and controls in sex (female 96% *vs*. 92%; *p*=ns) mean age (46±13 *vs*. 43±11 years; *p*=ns), frequency of current smokers (26.6% *vs*. 22.6% *p*=ns), family history of cardiovascular disease (9.3% *vs*. 16%; *p*=ns). In comparison to controls, SLE patients more frequently had arterial hypertension (54.6% *vs*. 13% *p*=0.0001), overweight (43% *vs*. 21%, *p*=0.009), menopausal status (49% *vs*. 26% *p*=0.01), and hypercholesterolemia (45% *vs*. 17%, *p*=0.0001).

Carotid plaques were more frequently documented in SLE patients than in controls (14 out of 75, 18.6% *vs*. 2 out of 75, 2.6% *p*=0.004) while mean values of IMT were not different between the two groups (0.639±0.134mm *vs*. 0.623±0.108mm; *p*=ns). However, multivariate logistic regression on carotid plaques on the entire study population showed no statistical significance for SLE when the other classical risk factors are considered for adjustment (see Table II).

Carotid plaque (Tables III, IV)

Fourteen out of the 75 LN patients evaluated (18.6%) had evidence of focal carotid plaque. Before the present study, 3 patients had myocardial infarction. Of them 2 have carotid plaques (one aPL positive) and the third, aPL positive, has no carotid plaque (p=ns). Three patients with carotid plaque had had a cerebral thrombosis (one aPL positive) in comparison to 4 (one aPL positive) among patients with no carotid plaque (p=ns). Altogether, 36% of the patients with carotid plaques had had a cardiovascular accident in comparison to 8% of the patients with no carotid plaque (*p*=0.02).

Patients with atherosclerotic plaques had significantly higher IMT than patients without carotid plaque (*p*=0.000001). In comparison to patients with no plaques those with plaques were significantly older (*p*=0.000001) and in menopausal status (*p*=0.000001), were significantly more frequently hypertensive (*p*=0.02) and had a significantly longer exposure to pathological values of systolic (*p*=0.000001), diastolic (*p*=0.0018), systolic and/or diastolic blood pressure (*p*=0.000001) as well as a significantly higher percentage of pathological values of systolic blood

Table III. Comparison of traditional and non traditional risk factors of atherosclerosis in patients with and without carotid plaques.

Variables	Plaque (14 pts)	No Plaque (61 pts)	*p*-value
Intima-media thickness, mm	0.78 (0.75-0.88	0.59 (0.53-0.65)	0.000001
History of cardiovascular accident %	36%	8%	0.02
Age years	60.5 (57.3-65.3)	41.7 (33.9-48.3)	0.000001
Current Smokers %	28.5	26.2	Ns
Postmenopausal %	92.8	62.8	0.000001
Body Mass Index kg/m^2	25.6 (22.5-26.9)	23.9 (21.2-26.6)	Ns
Familial history of CV thrombosis %	21.4	6.5	Ns
Hypertension %	12 pts (41%)	2 pts (6%)	0.022
Percentage SBP >140 mmHg	58.3 (31.8-80.8)	16.7 (5.3-30)	0.000001
Percentage DBP >90 mmHg	43.2 (25.5-56.7)	18.7 (7.1-30)	0.0018
Percentage of follow-up with SBP >140 mmHg	32.3 (17.7-69.7)	2.7 (0-6.9)	0.000001
Percentage of follow-up with DBP >90 mmHg	12.3 (4.6-35)	0 (0-8.8)	0.001
Percentage of follow-up with high SPB or DBP	37.2 (19.5-71.5)	3.3 (0-11.4)	0.000001
Cholesterol at time of carotid evaluation mg/dl	207 (181-253)	207 (175-236)	Ns
LDL Cholesterol at time of carotid evaluation mg/dl	99.5 (92.8-139.5)	111.6 (88-137.1)	Ns
Percentage Cholesterol >200mg/dl	89.6 (80.2-100)	75.4 (50-100)	0.1
Percentage of follow-up with cholesterol > 200 mg/dl	95.2 (76.7-100)	74.4 (31-100)	Ns
Percentage Tryglicerides > 170mg/dl	7.6 (1.9-16.5)	5.9 (0-16.7)	Ns
Percentage of follow-up with Tryglicerides > 170 mg/dl	13.2 (1.3-31.7)	7.7 (0-31.1)	Ns
CRP > 0.5 mg/dl	5 pts (38%)	5 pts (9%)	0.02
Plasma homocystein μM	12.06 (8.9-17.8)	11.26 (8.9 -15.6)	Ns
Reactive Oxygen Species U. Carr	407 (367-488)	356 (319-396)	0.001

pts: patients; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein. If not specified, values are expressed as Median (25°,75° percentile).

Table IV. Comparison between SLE factors in patients with and without carotid plaques.

Variables	Plaque (14 pts)	No Plaque (61 pts)	*p*-value
Median SLE duration years	19.7 (8.6-25.7)	14.3 (10.4-18.2)	0.05
Median LN duration years	16.9 (8-25.4)	11.2 (6.1-16.4)	Ns
Number of pts with class III/IV/V	3/6/5	11/35/10	Ns
Median steroid duration years	8.5 (2.3-13.9)	6.6 (2.9-11.4)	Ns
Median prednisone dosage mg/kg body weight	497 (164-789)	350 (237-798)	0.1
MP pulses number	3 (3-6)	3 (3-9)	Ns
Pts with renal flares	4 pts (28%)	34 pts (56%)	0.1
Hydroxychloroquine use %	28	27.8	Ns
Cyclophosphamide use %	64	78.6	Ns
Aspirin	7 pts (50%)	19 pts (32%)	Ns
Lupus anticoagulant %	35.7	9.4	0.02
Anticardiolipin antibodies %	57	21.3	0.018
Creatinine clearance ml/min	59.05 (47.8-72.3)	85.4 (65-106)	0.03
History of NS %	64	73.7	Ns
Duration of NS months	1.5 (0-3.5)	4 (3.8-4.3)	Ns
C3 <90 mg/dl	4 pts (31%)	26 pts (44%)	0.1
C3 >120 mg/dl	4 pts (31%)	7 pts (12%)	Ns
C4 <10mg/dl	4 pts (31%)	13 pts (22%)	Ns
Anti-DNA Ab titres	12 (10-100)	52 (25-134)	0.08

SLE systemic lupus erythematosus; LN: lupus nephritis; MP: Methylprednisolone; Pts: patients; NS: nephritic syndrome; Ab: antibodies.
If not specified values are expressed as Median (25, 75° percentile).

pressure (p=0.000001), diastolic blood pressure (p=0.001) or both (p=0.00001) during the follow-up.

More LN patients with plaque were positive for lupus anticoagulant (p=0.02) and for aPL antibodies (p=0.018), had significantly higher C-reactive protein (CRP) (p=0.03), reactive oxygen species (p=0.001) and lower creatinine clearance (p=0.03) than LN patients without plaque.

At multivariate logistic regression analysis older age of the patients (p=0.002 OR 1.2 CI 1.06-1.32), percentage of the follow-up with systolic blood pressure higher than 140 mmHg (p=0.015 OR 1.04 CI 1.05-1.08) and percentage of the follow-up with cholesterol higher than 200 mg/dl (p=0.04 OR 1.04 CI 0.99-1.1) were independent predictors of presence of carotid plaque.

Intima media wall thickness

The median values of IMT of the cohort was 0.630mm (0.553–0.707mm). IMT was between 0.4–0.5mm in 12 patients, between 0.5–0.6mm in 22 patients, between 0.6–0.7mm in 22 patients, between 0.7–0.8mm in 10 patients, between 0.8–0.9mm in 6 patients and between 0.9–1.1mm in 3 patients.

Discussion

To the best of our knowledge this is the first study that has evaluated the prevalence of atherosclerotic carotid lesions in a cohort of patients with established LN that have been followed in a single Unit for more than 13 years. The prevalence of carotid plaques in our lupus nephritis patients was compared with that of a healthy control group, even though the most appropriate comparison would have been made with a cohort of SLE patients with no renal involvement, unfortunately in our Nephrological Unit only patients with lupus nephritis are followed. As documented in SLE patients with any type of organ involvement (13), there were no significant differences between LN patients and healthy controls in median values of IMT while LN patients had significantly more frequently carotid plaques (21-22). In comparison to healthy controls LN patients were more frequently hypertensive, obese and in menopause and had more frequently hypercholesterolemia, all well known predisposing factors to atherosclerosis. However, multivariate logistic regression on carotid plaques on the entire study population showed no statistical significance for SLE when the other classical risk factors are considered (age, arterial hypertension, hypercholesterolemia, current smoking).

In all the previous studies in SLE patients, age was the most, or one of the most important predictors of carotid plaques. Also in this study LN patients with plaques were significantly older than those without plaques. As a matter of fact, among the 14 patients with a plaque, only one was aged 40, all the others were older than 55 years. As expected from the age of patients with carotid plaques, menopausal status was also significantly associated with plaques. Arterial hypertension was another traditional risk factor correlated with carotid plaques in our patients. To better evaluate its role we calculated the rate of pathological measures of systolic, diastolic blood pressure as well as the length of exposure to their pathological values, expressed in percentages of the follow-up period. All these measures appeared to be significantly correlated with carotid plaques, underlining that the constant control of blood pressure should be a priority in clinical practice.

Among the non traditional risk factors CRP has been associated with an increased risk of cardiovascular events in the general population and particularly in women (23). An association between cardiovascular events and CRP has also been reported in SLE patients (24). The potential atherogenic role of CRP is confirmed by the relationship between CRP and carotid plaques observed in this study. Recently oxidative stress, *i.e.* an excess of pro-oxidant

species not counterbalanced by an antioxidant defence system (25) has been proposed as a new player in accelerated atherosclerosis (26). In this study ROS concentration was significantly higher in patients with carotid plaques than in those without.

Chronic renal insufficiency is a well known cardiovascular risk factor independently from the presence of traditional risk factors (27). As an indirect confirmation, more than 50% of our patients with carotid plaques had a creatinine clearance lower than 60ml/min in comparison to less than 20% of those with no plaques.

Anti-phospholipid antibodies have been implicated in atherogenesis possibly as a result of their activation of endothelial cells (28). Some (29, 30) but not all studies (31) confirm this correlation. In this study, we found a significant association between anti-phospholipid antibodies and carotid plaques. A similar association was also observed with lupus anticoagulant. The median duration of SLE was significantly longer in patients with carotid plaques than in those without. The duration of LN, the length of prednisone treatment and its median dosage/kg body weight were higher in patients with carotid plaques but the difference was not significant.

A trend between the median prednisone dosage administered during the follow-up and the presence of carotid plaques has been documented in our cohort of LN patients. The association between corticosteroid use in lupus patients and atherosclerosis is controversial. Two studies have reported an independent association between the cumulative prednisone dosage and subclinical atherosclerosis (21, 31), while two other studies have demonstrated that the lower the average dosage of prednisone over the follow-up, the higher the prevalence and/or the progression of carotid plaques (32, 33). The apparent discrepancy may be partly accounted for by the dual influence of corticosteroids on atherogenesis. On the one hand, they can favour the development of conventional risk factors such as arterial hypertension, obesity, diabetes, dyslipidemia (34-36) and on the other they can contrast the atherogenic potential of SLE and its renal effects. Although the value of multivariate analysis could be questionable due to the low number of the events occurring in our patients, only traditional risk factors: older age, longer time of exposure to pathological values of blood pressure and of cholesterol, emerged as independent predictors of carotid plaques in our LN patients.

In spite of the fact that nephritis represents one of the most severe complications of SLE, an 18% prevalence of carotid plaques in our cohort is one of the lowest reported in SLE patients. Roman (37) and Manzi (21) reported the presence of plaques in around 40% of two large populations of SLE patients, while the prevalence of plaques was around 28-29% in three other studies (38-40). In another three studies, the prevalence of carotid plaques was comparable or lower than that of our study (ranging from between 9 to 17%) (31, 33, 41), but the patients evaluated were younger (31, 33) or with a shorter duration of the SLE (31, 33, 41) than those of our cohort. In two of those studies the presence of renal insufficiency (41) and of renal disease at baseline (31) showed a moderate association with the presence or the development of carotid plaque at univariate analysis, but in the majority of the studies devoted to SLE patients, the presence of LN was not predictive of the presence of carotid plaque (38, 32, 39). Rather, in the study of Telles *et al*. (33) the presence of nephritis was significantly associated with the absence of plaques. The low rate of plaques in our LN patients is difficult to explain. Atherosclerosis in SLE recognises a multifactorial pathogenesis that involves not only traditional but also non traditional risks factors such as immune complexes deposition, complement activation and anti-phospholipid antibodies, which can play a major role in under-treated patients. We can speculate that the aggressive therapies employed in the management of the acute phases of LN may have induced a stable quiescence of the disease. On the other hand, our policy of employing the lowest possible doses of prednisone as maintenance (42), or even to completely withdraw therapy in selected patients with stable remission (43) may have reduced the impact of traditional risk factors for atherosclerosis (34). In addition, in our cohort a high percentage of patients were taking aspirin, statins, and hydroxycloroquine and these therapies may have limited the impact of traditional risks factors.

A limitation of the study is the low number of patients evaluated which may have limited the robustness of some of the statistical conclusions as well as the low number of the events which could have allowed the identification of the strongest predictors only.

In conclusion, these results, which need to be confirmed in larger prospective studies, suggest the need of an early, constant and effective control of traditional risk factors in LN to prevent the development of premature atherosclerosis. This goal could be obtained with a constant monitoring of the patients, with the use of antihypertensive and hypocholesterolemic drugs together with a treatment strategy whose aim is to use an aggressive therapy during the active phases of the disease to quench the activity of LN, while reducing the therapy to the lowest possible dosage during the quiescent phases of the disease to reduce its iatrogenicity.

References

1. IPPOLITO A, PETRI M: Un uptdate on mortality in systemic lupus erythematosus. *Clin Exp Rheumatol* 2008; 26: S72-9.
2. MANZI S, MEILAHN EN, RAIRE JE *et al*.: Age-specific incidence rates of myoacardial infarcion and angina in women with systemic lupus erythematosus: comparison with the Framingham study. *Am J Epidemiol* 1997; 145: 408-15.
3. WARD MM: Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthitis Rheum* 1999; 42: 338-46.
4. PETRI M, PEREZ-GUTTHANN S, SPENCE D, HOCHBERG MC: Risk factors for coronary artery disease in patients with systemic lupus erythematosus *Am J Med* 1992; 93: 513-19.
5. PETRI M, ROUBENOFF R, DALLAL GE, NADEAU MR, SELHUB J, ROSENBERG IH: Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet* 1996; 348: 1120-24.
6. 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* 1992; 71: 291-302.
7. AVALOS I, RHO YH, CHUNG CP, STEIN CM: Atherosclerosis in rheumatoid arthritis and

systemic lupus erythematosus. *Clin Exp Rheumatol* 2008; 26: S5-13.
8. ESDAILE JM, ABRAHAMOWICZ M, GRODZICKY T *et al*.: Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus.*Arthitis Rheum* 2001; 44: 2215-17.
9. ESPELAND MA, CRAVEN TE, RILEY WA, CORSON J, ROMONT A, FURBERG CD: Reliability of longitudinal ultrasonographic measurements of carotid intimal-medial thicknesses. Asymptomatic Carotid Artery Progression Study Research Group. *Stroke* 1996; 27: 480-85.
10. LI R, CAI J, TEGELER C, SORLIE P, METCALF PA, HEISS G: Reproducibility of extracranial carotid atherosclerotic lesions assessed by B-mode ultrasound: the Atherosclerosis Risk in Communities Study. *Ultrasound Med Biol* 1996; 22: 791-99.
11. PERSSON J, FORMGREN J, ISRAELSSON B, BERGLUND G: Ultrasound-determined intima-media thickness and atherosclerosis. Direct and indirect validation. *Arterioscler Thromb* 1994; 14: 261-64.
12. SUTTON-TYRRELL K, WOLFSON SK JR, THOMPSON T, KELSEY SF: Measurement variability in duplex scan assessment of carotid atherosclerosis. *Stroke* 1992; 23: 215-20.
13. ROMAN MJ, SHANKER BA, DAVIS A *et al*.: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2399-406.
14. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
15. WEENING JJ, D'AGATI VD, SCHWARTZ MM *et al*.: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241-50.
16. CAMPISE M, BAMONTI F, NOVEMBRINO C *et al*.: Oxidative stress in Kidney transplant patients. *Transplantation* 2003; 76: 1474-78.
17. WILSON WA, GHARAVI AE, KOIKE T *et al*.: International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999; 42: 1309-11.
18. O'LEARY DH, POLAK JF, KRONMAL RA, MANOLIO TA, BURKE GL, WOLFSON SK JR: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999; 340: 14-22.
19. TOUBOUL PJ, HENNERICI MG, MEAIRS S *et al*.: Mannheim intima-media thickness consensus. *Cerebrovasc Dis* 2004; 18: 346-9.
20. VENABLES WN, RIPLEY BD: Modern Applied Statistics with S-PLUS. *Springer* 1999. Third Edition.
21. MANZI S, SELZER F, SUTTON-TYRRELL K *et al*.: Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 51-60.
22. SELZER F, SUTTON-TYRRELL K, FITZGERALD SG *et al*.: Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis Rheum* 2004; 50: 151-9.
23. RIDKER PM, HENNEKENS CH, BURING JE, RIFAI N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836-43.
24. SVENUNGSSON E, JENSEN-URSTAD K, HEIMBÜRGER M *et al*.: Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation* 2001; 104: 1887-93.
25. HALLIWELL B, GUTTERIDGE JMC: Lipid peroxidation, oxygen radicals, cell damage, and antioxidant therapy. *Lancet* 1984; 1: 1396-97.
26. BONOMINI F, TENGATTINI S, FABIANO A, BIANCHI R, REZZANIN R: Atherosclerosis and oxidative stress. *Histol Histopathol* 2008; 23: 381-90.
27. BAIGENT C, BURBURY K, WHEELER D: Premature cardiovascular disease in chronic renal failure. *Lancet* 2000; 356: 147-52.
28. VAARALA O: Autoantibodies to modified LDLs and other phospholipid-protein complexes as markers of cardiovascular diseases. *J Intern Med* 2000; 247: 381-4.
29. VLACHOYIANNOPOULOS PG, KANELLOPOULOS PG, IOANNIDIS JP, TEKTONIDOU MG, MASTORAKOU I, MOUTSOPOULOS HM: Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: a controlled study. *Rheumatology* 2003; 42: 645-51.
30. FARZANEH-FAR A, ROMAN MJ, LOCKSHIN MD: Relationship of antiphospholipid antibodies to cardiovascular manifestations of systemic lupus erythematosus. *Arthitis Rheum* 2006; 54: 3918-25.
31. DORIA A, SHOENFELD Y, WU R *et al*.: Risk factors of sub clinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003; 62: 1071-7.
32 ROMAN MJ, CROW MK, LOCKSHIN MD *et al*.: Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. *Arthitis Rheum* 2007; 56: 3412-9.
33. 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: 105-13.
34. 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: 254-59.
35. BRUCE IN, UROWITZ MB, GLADMAN DD, HALLETT DC: Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 1999; 26: 2137-43.
36. 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? *Arthitis Rheum* 2008; 59: 169-75.
37. ROMAN MJ, SALMON JE, SOBEL R *et al*.: Prevalence and relation to risk factors of carotid atherosclerosis and left ventricular hypertrophy in systemic lupus erythematosus and antiphospholipid antibody syndrome. *Am J Cardiol* 2001; 87: 663-6.
38. AHMAD Y, SHELMERDINE J, BODILL H *et al*.: Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology* 2007; 46: 983-8.
39. JIMÉNEZ S, GARCÍA-CRIADO MA, TÀSSIES D *et al*.: Preclinical vascular disease in systemic lupus erythematosus and primary antiphospholipid syndrome. *Rheumatology* 2005; 44: 756-61.
40. WOLAK T, TODOSOUI E, SZENDRO G *et al*.: Duplex study of the carotid and femoral arteries of patients with systemic lupus erythematosus: a controlled study. *J Rheumatol* 2005; 31: 909:14.
41. MAKSIMOWICZ-MCKINNON K, MAGDER LS, PETRI M: Predictors of carotid atherosclerosis in systemic lupus erythematosus. *J Rheumatol* 2006; 33: 2458-53.
42. MORONI G, QUAGLINI S, GALLELLI B, BANFI G, MESSA P, PONTICELLI C: The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant* 2007; 22: 2531-9.
43. MORONI G, GALLELLI B, QUAGLINI S *et al*.: Withdrawal of therapy in patients with proliferative lupus nephritis: long-term follow-up. *Nephrol Dial Transplant* 2006; 21: 1541-8.