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Cardiovascular risk factors and the long-term outcome of lupus nephritis

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Summary

We evaluated cardiovascular risk factors, morbidity and mortality in patients with lupus nephritis (LN). We prospectively studied 70 consecutive patients with LN, and 70 age- and sex-matched controls with systemic lupus erythematosus (SLE) but no evidence of nephropathy, from 1988 to 1998. Patients were evaluated at entry for hypertension, diabetes, hyperlipidaemia, smoking, menopause and antiphospholipid syndrome. The LN patients (64 women, 6 men) had a mean age of 35 years (SE 1.7, range 11–67). During the 10 years, 15 (21%) LN patients and 18 (25%) of the controls were lost to follow-up. Compared with controls, LN patients had a higher prevalence of hyperlipidaemia (44% vs. 2%, $p<0.001$), hypertension (44% vs. 9%, $p<0.001$) and antiphospholipid antibodies (45% vs. 22%, $p=0.01$) at study onset. At the last visit, 37 (67%) LN patients had normal plasma creatinine, 13 (24%) had renal failure and only five (9%) end-stage renal failure. Hyperlipidaemia (78% vs. 27%, $p<0.001$) and hypertension (67% vs. 32%, $p=0.01$) at study onset were associated with development of renal failure. Nine LN patients and one control died (16% vs. 2%, $p=0.02$). These patients showed more antiphospholipid syndrome (56% vs. 17%, $p=0.03$) and hyperlipidaemia (78% vs. 37%, $p=0.03$) at study onset. The main causes of death in LN patients were vascular complications (cardiovascular or cerebrovascular events) in five patients (four of whom had antiphospholipid antibodies) and sepsis in three.

Introduction

Systemic lupus erythematosus (SLE) is the most clinically and serologically diverse of the autoimmune connective tissue diseases; it may affect any organ of the body and displays a broad spectrum of clinical and immunological manifestations. The diversity of its clinical manifestations, with very distinct forms of presentation, include articular and mucocutaneous involvement, renal disease, haematological abnormalities and central nervous system disease.[1]

Renal disease is a frequent complication of SLE that can greatly influence the prognosis. Many factors affect the prognosis of this highly pleomorphic disorder, and the diversity of predictors identified in various clinical studies has led to some controversy. Clearly, the mortality rate is higher for SLE patients with nephritis than in those without renal involvement,[2,3] and some 10%–60% of SLE patients with nephritis eventually develop end-stage renal failure that requires dialysis or

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transplantation.[4–8] Some series have reported a 10-year kidney survival rate of around 80%, even in patients with diffuse lupus nephritis (LN).[9,10] Several factors may have contributed to these encouraging results, but more appropriate use of corticosteroids and immunosuppressive agents has certainly played a major role. Unfortunately, the continuous use of these drugs, as well as the persistent disease activity, may expose patients with SLE to several late complications,[11–16] and in addition significant morbidity and mortality persist. In this study, we prospectively analysed the outcome and clinical features of 70 patients with LN followed in a single reference centre for over 10 years, focusing especially on the role of cardiovascular risk factors in the renal outcome and mortality of this subset of SLE patients.

Methods

Patients

Our total cohort included 431 consecutive patients with SLE (381 female and 50 male, mean age 32 years, SE 0.7, range 11–80) who had been registered in our Unit from 1970 to 1988. All patients fulfilled the 1982 revised criteria of the American College of Rheumatology for the classification of SLE.[17] The study began in 1988 with a consecutive and prospective design, and included 70 patients with LN and 70 age-sex-matched SLE patients without evidence of nephropathy. The groups had a similar prevalence of the major non-renal SLE features. At inclusion, information was obtained on age, race, smoking habit, menopausal status, diabetes and hypertension. Hypertension was defined as blood pressure $>140/90$ mmHg, respectively, in two consecutive determinations. We treated the hypertension of our LN patients with calcium-channel blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor antagonists (with careful supervision for development of hyperkalaemia and azotaemia) adding, if necessary, diuretics or β-blockers. Fasting total cholesterol and triglyceride levels were measured in blood samples using standardized laboratory tests. Normal renal function was defined as a plasma creatinine <124 μmol/l. Proteinuria was considered to be nephrotic when urinary protein excretion exceeded 3 g/day and non-nephrotic when 0.2–3 g/day. Altered urine sediment was considered when >3 red blood cells or 5 white blood cells or any casts (either red cell, hemoglobin, granular, tubular or mixed) were observed per high power field. Renal biopsies were reviewed by two pathologists and categorized according to the modified classification proposed by the WHO:[18] I, normal or minimal disease; II, mesangial nephritis; III, focal proliferative nephritis; IV, diffuse proliferative nephritis; and V, membranous nephritis. Patients with normal renal function, proteinuria <0.2 g/day and inactive urine sediment were considered to be patients without nephropathy. The outcomes studied were renal failure (creatinine >125 μmol/l), end-stage renal failure and death.

Laboratory studies

The immunological tests included determination of antinuclear antibodies (ANA) by indirect immunofluorescence using mouse liver as substrate, antibodies to double-stranded DNA by Farr's technique, precipitating antibodies to the extractable nuclear antigens (U1-RNP, Sm, Ro/SS-A and La/SS-B) by counterimmunoelectrophoresis and rheumatoid factor (RF) by latex fixation and Waaler-Rose tests. Complement factors (C3 and C4) were estimated by the nephelometry (Behring BNA nephelometer) and CH50 by Lachmann's haemolytic technique.

IgG and IgM anticardiolipin antibodies (aCL) were estimated by an ELISA technique as described by Gharavi *et al.*[19] with minor modifications.[20] The lupus anticoagulant (LA) was measured by coagulation assays (prothrombin time, activated partial TP time, kaolin clotting time, diluted Russell's viper venom time and tissue TP inhibition time) following the recommendations of the subcommittee on LA of the Scientific and Standardization Committe of the International Society of Thrombosis and Hemostasis.[21]

Statistical analysis

We used conventional χ^2 and Fisher's exact test to analyse qualitative differences, Student's test for the comparison of means in large samples of similar variance, and the non-parametric Mann-Whitney U test for small samples. A value of $p<0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis in order to rule out possible related variables. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable, with 95%CI. Results of the analysis of continuous variables are indicated as mean and standard error (SE) of the mean. This statistical analysis used the SPSS program.

Results

Characteristics of LN patients

Seventy patients (64 female, 6 male) with LN entered this prospective study. Their mean age at entry was 35 years (SE 1.7, range 11–67). The first manifestation of renal involvement was altered urine sediment in 28 (40%) patients, nephrotic syndrome in 24 (34%), renal failure in eight (12%), nephrotic syndrome in three (4%) and other features in the remaining 7 (10%) patients. Tissue for optic microscopy study was obtained from 63 (90%) patients. Renal biopsies showed diffuse proliferative nephritis (class IV) in 20 (32%) patients, focal proliferative nephritis (class III) in 16 (25%), mesangial nephritis (class II) in 15 (24%), membranous nephritis (class V) in eight (13%) and minimal disease (class I) in four (5%) patients.

After presentation with LN, 27 patients with the most severe disease received immunosuppressive agents plus corticosteroids: cyclophosphamide (1.5 mg/kg/day) was administered in 17 patients (intravenously in 14 patients and orally in 3) and azathioprine (2 mg/kg/day) in 12 (two patients received both agents). Intravenous cyclophosphamide was administered monthly during 6 months and every 3 months during the following 1.5 years, and azathioprine was prescribed for 2 years. Immunosuppressive drugs were recommended particularly for patients with marked subendothelial deposits. Furthermore, 32 patients received oral prednisone (>0.5 mg/kg/day) alone.

Comparison between patients with and without LN

Fifteen (21%) patients from the LN group and 18 (25%) from the control group were lost to follow-up. Additionally, seven patients from the control group developed nephropathy in the course of follow-up, and were also eliminated from the analysis. Thus, we compared 55 LN patients and 45 patients without LN. We analysed their clinical and immunological features, therapy, and cardiovascular risk factors at the onset of follow-up (Table 1). LN patients showed a higher prevalence of positive anti-dsDNA antibodies (84% vs. 49%, $p<0.001$, RR 2.41, CI 1.35–4.29) and a lower prevalence of RF (4% vs. 15%, $p=0.04$, RR 0.38, CI 0.11–1.31) in the univariate analysis at the onset of follow-up, although only positive anti-dsDNA antibodies ($p=0.03$) was an independent variable in the multivariate analysis.

LN patients showed a higher prevalence of previous treatment with corticosteroids higher than 0.5 mg/kg/day (58% vs. 4%, $p<0.001$, RR 2.70, CI 1.92–3.80), azathioprine (22% vs. 4%, $p=0.01$, RR 1.71, CI 1.27–2.32) and cyclophosphamide (31% vs. 0%, $p<0.001$, RR 2.18, CI 1.73–2.76) in the univariate analysis, although only treatment with corticosteroids ($p=0.001$) was an independent variable in the multivariate analysis.

LN patients had a higher prevalence of hypertension (44% vs. 9%, $p<0.001$, RR 2.00, CI 1.47–2.70), hyperlipidaemia (44% vs. 2%, $p<0.001$, RR 2.32, CI 1.75–3.08) and antiphospholipid antibodies (45% vs. 22%, $p=0.01$, RR 1.55, CI 1.11–2.17) in the univariate analysis, although only hyperlipidaemia ($p=0.04$) was an independent variable in the multivariate analysis.

Finally, patients with LN had more infections (47% vs. 18%, $p=0.001$, RR 1.74, CI 1.25–2.42) and higher mortality (16% vs. 2%, $p=0.02$, RR 1.76, CI 1.32–2.35) during follow-up than those without LN.

Renal outcome

At the last visit, 37 LN patients (67%) had normal plasma creatinine, 13 (24%) had renal failure and five (9%) had entered end-stage renal failure (of these patients, four received a renal transplant, but one had acute rejection of the graft and currently requires dialysis).

We analysed the presence of several features at the onset of follow-up to see if they might predict progression to renal failure (Table 2). Patients with normal renal function showed a higher prevalence of altered urine sediment as a first manifestation of their LN (51% vs. 17%, $p=0.01$, RR 1.58, CI 1.11–2.25) and WHO class II at renal biopsy (35% vs. 6%, $p=0.02$, RR 1.59, CI 1.18–2.13), while those who developed renal failure showed a higher prevalence of WHO class IV at renal biopsy (50% vs. 19%, $p=0.02$, RR 2.44, 1.19–5.00). Only altered urine sediment ($p=0.03$) was an independent variable in the multivariate analysis. Patients treated with azathioprine were more likely to develop renal failure (50% vs. 8%, $p<0.001$, RR 3.58, CI 1.84–6.98).

We analysed the presence of some cardiovascular risk factors at the onset of follow-up to see if they might predict progression to renal failure, and found that hyperlipidaemia (78% vs. 27%, $p<0.001$, RR 4.52, CI 1.71–11.99) and hypertension (67% vs. 32%, $p<0.01$, RR 2.58, CI 1.14–5.88) were associated with development of renal failure in the univariate analysis, although only hyperlipidaemia ($p=0.04$) was an independent variable in the multivariate analysis.

Finally, patients who developed renal failure presented more infections (72% vs. 35%, $p=0.009$, RR 2.90, CI 1.20–7.03) and mortality (33% vs. 8%,

Table 1 Differences in the clinical and immunological features, therapy received and cardiovascular risk factors in patients with lupus nephritis, compared with controls

	No nephritis ($n = 45$)	Nephritis ($n = 55$)	Univariate analysis	Multivariate analysis
Sex (female)	43 (96%)	47 (92%)	–	–
Age (years)	35.9 ± 2.0	35.1 ± 2.1	–	–
Previous SLE evolution (months)	89.2 ± 13.7	67.6 ± 10.0	–	–
Anti-dsDNA antibodies (>10 UI/l)	22 (49%)	46 (84%)	<0.001	0.028
Rheumatoid factor	7 (15%)	2 (4%)	0.04	–
Anti-Ro/SS-A antibodies	7 (16%)	15 (27%)	–	–
Anti-La/SS-B antibodies	3 (7%)	4 (7%)	–	–
Anti-nRNP antibodies	8 (18%)	5 (9%)	–	–
Anti-Sm antibodies	4 (9%)	4 (7%)	–	–
Low C_3	17 (38%)	30 (55%)	–	–
Low C_4	22 (49%)	30 (54%)	–	–
Corticosteroids >0.5 mg/kg/day	2 (4%)	32 (58%)	<0.001	0.001
Azathioprine	2 (4%)	12 (22%)	0.01	–
Cyclophosphamide	0 (0%)	17 (31%)	<0.001	–
Hypertension	4 (9%)	24 (44%)	<0.001	–
Diabetes mellitus	0 (0%)	2 (4%)	–	–
Hyperlipidaemia	1 (2%)	24 (44%)	<0.001	0.045
Menopause	7 (16%)	8 (15%)	–	–
Smoking	1 (2%)	3 (6%)	–	–
Antiphospholipid antibodies	10 (22%)	25 (45%)	0.01	–
Antiphospholipid syndrome	5 (11%)	13 (24%)	–	–

Table 2 Clinical and histological features, therapy and cardiovascular risk factors of patients with lupus nephritis who finally developed renal failure, compared with those with normal renal function at the last visit

	Normal renal function ($n = 37$)	Renal failure ($n = 18$)	Univariate analysis	Multivariate analysis
Sex (female)	32 (87%)	18 (100%)	–	–
Age (years)	35.5 ± 2.2	33.1 ± 3.8	–	–
Previous SLE duration (months)	75.3 ± 12.4	58.8 ± 15.2	–	–
Nephropathy duration (years)	14.1 ± 0.9	15.4 ± 1.8	–	–
Initial renal failure	3 (8%)	5 (28%)	–	–
Nephrotic syndrome	11 (30%)	10 (56%)	–	–
Altered urine sediment	19 (51%)	3 (17%)	0.010	0.031
WHO Class I	0 (0%)	1 (6%)*	–	–
WHO Class II	13 (35%)	1 (6%)*	0.016	–
WHO Class III	8 (22%)	4 (22%)	–	–
WHO Class IV	7 (19%)	9 (50%)	0.017	–
WHO Class V	4 (11%)	3 (17%)	–	–
Corticosteroids >0.5 mg/kg/day	19 (51%)	13 (72%)	–	–
Cyclophosphamide	9 (24%)	8 (44%)	–	–
Azathioprine	3 (8%)	9 (50%)	<0.000	0.019
Hypertension	12 (32%)	12 (67%)	0.01	–
Diabetes mellitus	1 (3%)	1 (6%)	–	–
Hyperlipidaemia	10 (27%)	14 (78%)	<0.000	0.039
Menopause	5 (14%)	3 (17%)	–	–
Smoking	1 (3%)	2 (11%)	–	–
Antiphospholipid antibodies	16 (43%)	9 (50%)	–	–
Antiphospholipid syndrome	6 (16%)	7 (39%)	–	–

*Later progressing to class IV.

$p = 0.02$, RR 2.56, CI 1.31–5.00) during the follow-up in the univariate analysis, although only infection ($p = 0.02$) remained as an independent variable on multivariate analysis.

Mortality

Nine (16%) of the 55 LN patients died during the follow-up, compared with only one (2%) patient without LN ($p = 0.02$, RR 1.76, CI 1.32–2.35). Actuarial analysis of survival in both groups is shown in Figure 1. The causes of mortality in the nine patients with LN were vascular complications (cardiovascular or cerebrovascular events) in five patients (four of whom had antiphospholipid antibodies), sepsis in three patients and lung cancer in the remaining patient. The patient from the control group died of a cardiovascular event. In LN patients, mortality correlated with renal function measured at the last visit: three (8%) of the 37 patients with normal renal function died, compared with six (33%) of the 18 who developed chronic renal failure ($p = 0.03$, RR 4.11, CI 1.16–14.59). We analysed several features at the onset of the study to see if they might predict mortality in these patients (Table 3). We found that patients treated with azathioprine showed a higher mortality (56% vs. 15%, $p = 0.02$, RR 4.48, CI 1.42–14.13).

We also analysed the presence of our cardiovascular risk factors at the onset of follow-up to see if they might predict mortality; hyperlipidaemia (78% vs. 37%, $p = 0.03$, RR 4.52, CI 1.03–19.83) and antiphospholipid syndrome (56% vs. 17%, $p = 0.03$, RR 4.04, CI 1.27–12.86) were associated with mortality. Finally, patients who died had progressed to renal failure more frequently than survival patients (67% vs. 26%, p = 0.03, RR 4.11, CI 1.16–14.59).

Discussion

The course of LN is difficult to predict for a number of reasons, including the extreme heterogeneity of clinical characteristics, different criteria for selection, the incidence of histological changes, and the different therapeutic schedules used. No single factor seems to be more important in estimating prognosis, and this indicates the use of a range of demographic, clinical, laboratory and histopathological parameters in estimating the course and prognosis of the disease and in deciding upon therapy.[22]

We analysed the outcome of 70 patients with LN followed prospectively for a period of ten years in a single centre. Eighteen (33%) of our 55 surviving patients progressed to renal failure, and only five (9%) of these progressed to end-stage renal failure. Similar results were obtained by Moroni *et al.*[23] and, more recently, by Bono *et al.*[24] These data show that in patients who retain kidney function after more than 10 years of LN, renal status may remain satisfactory. In fact, most of our patients (67%) had normal renal function at the last visit. Whether this reduced clinical activity reflects a spontaneous remission of the disease over time, or was induced by the therapy, is difficult to assess.

We also evaluated the prognostic role of some clinical, immunological and histological characteristics of the LN patients. Demographic factors such as age, sex or race have emerged as important prognostic indicators in some[25–27] but

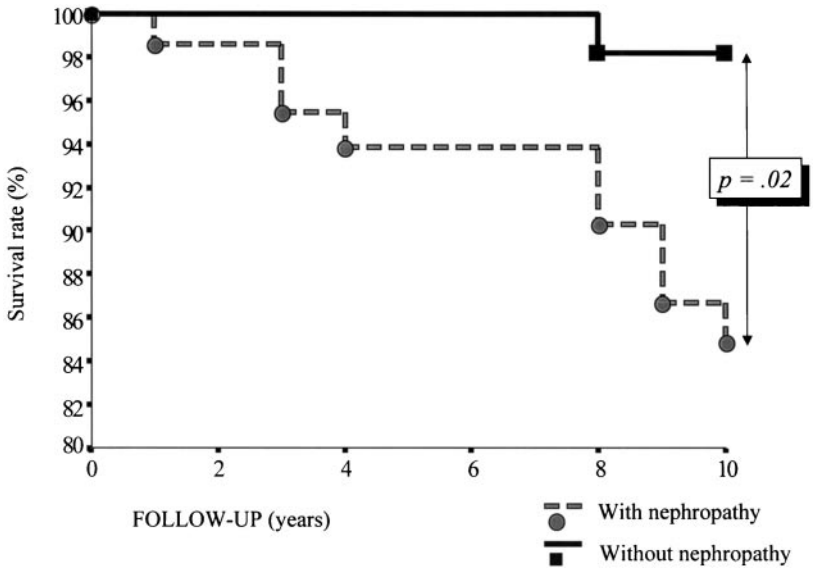

Figure 1. Survival curves for patients with and without nephropathy at the beginning of the prospective study.

Table 3. Clinical and histological features, therapy and cardiovascular risk factors of patients with lupus nephritis who died, compared with living patients

	No death ($n = 46$)	Death ($n = 9$)	Univariate analysis	Multivariate analysis
Sex (female)	43 (94%)	7 (78%)	–	–
Age (years)	35.0 ± 2.0	33.4 ± 5.8	–	–
Previous SLE duration (months)	69.3 ± 10.1	73.1 ± 30.7	–	–
Nephropathy duration (years)	17.3 ± 1.1	13.8 ± 2.9	–	–
Initial renal failure	8 (17%)	0 (0%)	–	–
Nephrotic syndrome	17 (37%)	4 (44%)	–	–
Altered urine sediment	18 (39%)	4 (44%)	–	–
WHO Class I	1 (2%)	0 (0%)	–	–
WHO Class II	10 (22%)	4 (44%)	–	–
WHO Class III	10 (22%)	2 (22%)	–	–
WHO Class IV	15 (33%)	1 (11%)	–	–
WHO Class V	5 (11%)	2 (22%)	–	–
Corticosteroids > 0.5 mg/kg/day	26 (56%)	6 (67%)	–	–
Cyclophosphamide	15 (33%)	2 (22%)	–	–
Azathioprine	7 (15%)	5 (56%)	0.02	0.03
Hypertension	19 (41%)	5 (55%)	–	–
Diabetes mellitus	2 (4%)	0 (0%)	–	–
Hyperlipidaemia	17 (37%)	7 (78%)	0.029	–
Menopause	6 (13%)	2 (22%)	–	–
Smoking	2 (4%)	1 (11%)	–	–
Antiphospholipid antibodies	19 (41%)	6 (67%)	–	–
Antiphospholipid syndrome	8 (17%)	5 (56%)	0.026	–

not all[28–34] previous studies. We did not find that these factors were predictors of renal function outcome in our study. On the other hand, almost a third of our patients with proliferative or membranous nephritis (class III, IV and V) finally developed renal failure, compared with only two (by posterior transformation into class IV) patients with class I or II. The present study confirms and extends previous observations regarding the prognostic importance of renal histological evaluation in patients with LN.[35] Some studies have suggested a protective effect of RF and anti-La/SS-B antibodies in the development of LN.[1,2,36–38] We confirmed that LN patients showed a lower prevalence of RF, but failed to demonstrate a protective effect of anti-La/SS-B.

We have shown that potentially modifiable risk factors (hypertension and hyperlipidaemia) and SLE-specific factors (antiphospholipid antibodies, corticosteroid therapy) are associated with renal outcome and mortality in patients with a long-term outcome of LN. Firstly, patients with LN showed a higher prevalence of hypertension, hyperlipidaemia, antiphospholipid antibodies and corticosteroid therapy (> 0.5 mg/kg/day) at the onset of follow-up, compared with an age- and sex-matched group of SLE patients who did not develop LN. Secondly, LN patients who developed renal failure had a higher presence of hypertension and hyperlipidaemia at the onset of follow-up. Lastly, LN patients who died had a higher prevalence of hyperlipidaemia and antiphospholipid syndrome at the onset of follow-up. However, hypertension and hyperlipidaemia may be the consequence of those types of LN that are most likely to progress to chronic renal failure, particularly type IV with nephrotic syndrome.

The true prevalence of vascular disease in women with SLE is unknown, but could certainly be higher than that defined by cardiovascular events alone.[39] With improved corticosteroid and immunosuppressive SLE therapy, there is a growing pool of women at increased risk of developing cardiovascular disease, which is now one of the leading causes of death. Hypertension and hyperlipidaemia have been identified as risk factors associated with atherosclerosis and coronary artery events in previous SLE studies.[11,40] While corticosteroids have been identified as a risk factor for cardiovascular disease by some investigators,[40–42] several other studies[11,43] have failed to detect an association. On the other hand, cardiovascular complications seem to be more likely in patients with a long duration of SLE. In a large series, Gladman and Urowitz[11] reported a 9% incidence of angina pectoris and/or myocardial infarction that occurred on average 89 months after the onset of SLE. Jonsson *et al.*[16] reported that patients with SLE

who developed myocardial infarction had significantly longer duration of the disease (19.5 years) than those who had no such complication (6.5 years). Recently, Bono *et al.*[24] found that 25% of LN patients with long-term disease died of cardiovascular events. We have confirmed that cardiovascular disease is one of the main causes of morbidity and mortality in young adults with long-term LN. Nevertheless, it is difficult to attribute the cause of death to a single factor or group of factors, as demonstrated by the lack of significance in the multivariate analysis.

In view of the high incidence of late cardiovascular complications, appropriate dietetic measures, the prohibition of smoking, and intensive antihypertensive and antihyperlipidaemic treatment should be strongly recommended in patients with SLE.[23] We recommend that SLE patients should be started on antihypertensive agents earlier in order to keep arterial pressure levels at a recommended level of $\leqslant$125/75 mm Hg. The marked increased mortality in LN from accelerated atherosclerosis mandates a higher state of vigilance in our SLE patients, and they must be monitored closely for symptoms and signs of cardiovascular disease. Primary prevention, by checking and treating hyperlipidaemia, hyperglycaemia and hypertension, counselling patients to stop smoking and exercise, and helping them lose weight, is of paramount importance. Additionally, we should use the lowest dose of corticosteroids, adding other drugs such as antimalarial agents. The maintenance of corticosteroid therapy at low doses in the quiescent phases might also help in reducing the risk of atherosclerotic lesions in the long term. Finally, our study shows that a new comorbid factor, the antiphospholipid syndrome, has been identified as an important prognostic marker of mortality in this subset of SLE patients with long-term evolution of LN. Frampton *et al.*[44] have reported that 44% of LN patients had antiphospholipid antibodies. The presence of an associated antiphospholipid syndrome in SLE patients may contribute to the development of nephropathy, and represent a new factor related to mortality in LN patients.

In conclusion, our study shows that although patients with long-term LN can maintain stable renal status, and there may be good kidney survival rates after more than 10 years of nephropathy, hypertension, hyperlipidaemia and antiphospholipid syndrome constitute risk factors associated with a higher mortality and the development of renal failure in this subset of SLE patients. Therefore, a more aggressive control of the cardiovascular risk factors (especially, hypertension and hyperlipidaemia) may be beneficial in the late prognosis of patients with long-term LN.

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