EXTENDED REPORT

African–American and Hispanic ethnicities, renal involvement and obesity predispose to hypertension in systemic lupus erythematosus: results from LUMINA, a multiethnic cohort (LUMINAXLV)

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Objective: To examine the predictors of the occurrence of hypertension in a large multiethnic US cohort.
Patients and methods: There were 614 patients with systemic lupus erythematoses (SLE; ⩾4 American College of Rheumatology revised criteria) with ⩽5 years of disease duration at entry into the cohort (T0) and of Hispanic (Texan or Puerto Rican), African–American or Caucasian ethnicity. T0 variables were compared between patients who did and did not develop hypertension (blood pressure ⩾140/90 mm Hg on at least two occasions and/or the use of antihypertensive drugs) after T0. Significant and clinically relevant variables were then examined by a stepwise logistic regression model.
Results: A total of 379 patients without hypertension at T0 were included (patients who developed hypertension prior to SLE diagnosis (n = 126) or before T0 (n = 109) were excluded). Predictors of hypertension were African–American and Texan–Hispanic ethnicities, renal involvement and a higher body mass index.
Conclusions: Traditional cardiovascular risk factors, disease-related factors and ethnicity play a role in the occurrence of hypertension in patients with SLE. Controlling renal involvement and optimising body weight may prevent the occurrence of hypertension.

It has been well established that systemic lupus erythematosus (SLE) is associated with an increased risk of cardiovascular disease; compared with the general population, women with SLE have a 5–6-fold increased risk of coronary heart disease and the risk in women aged 35–44 years is approximately 50 times higher.[1] As early as 1976, cardiovascular disease was recognised as a major cause of death, particularly late in the course of SLE.[2 3] Both traditional (age, hypertension, hypercholesterolaemia, obesity, tobacco use and diabetes mellitus) and SLE-related (disease duration, increased C reactive protein levels, the presence of antiphospholipid (aPL) antibodies and glucocorticoid use) factors have been identified as contributors to the occurrence of premature atherosclerosis in SLE.[1 4–6]

According to data from the National Health and Nutrition Examination Survey IV, the prevalence of hypertension in the general US population was 15% in 1999–2000.[7] However, hypertension occurs more frequently in patients with SLE than in the general population as evidenced by data from the Hopkins Lupus Cohort (41% and 46% in 1992 and 2000, respectively),[4 8] the Toronto Risk Factor Study (33% vs 13% in age-matched controls)[9] and a study from Vanderbilt University (48% vs 25% in age, gender and ethnic-matched controls).[10]

Hypertension is a well-established risk factor for cardiovascular mortality[11] and it has been shown to be a continuous, consistent risk for cardiovascular disease, independent of other risk factors.[12] The association between hypertension and cardiovascular disease, both clinically and subclinically, in SLE had also been confirmed by several studies.[4 5 8 9 13–16]

Given the importance of hypertension as a risk factor for cardiovascular morbidity, and possibly mortality, in patients with SLE[17] and its frequent occurrence in these patients, we used the large and comprehensive LUMINA (Lupus in Minorities: Nature vs Nurture) database to study the factors predictive of the occurrence of hypertension in SLE. We hypothesised that, in addition to known risk factors for hypertension, disease-related risk factors and possibly ethnicity play a role in the occurrence of hypertension in these patients.

PATIENTS AND METHODS

LUMINA is a multiethnic (Hispanic, Caucasian and African–American) longitudinal study of lupus outcome being conducted in three medical centres in the US (the University of Alabama, the University of Texas; Houston and the University of Puerto Rico) and their affiliated practices. Patients with SLE as per the revised and updated American College of Rheumatology (ACR) criteria[18] with ⩽5 years of disease duration at entry into the cohort (T0) and of well-defined ethnicity are eligible to participate in LUMINA. Visits are conducted every 6 months during the first year and yearly thereafter. The other time points that are referred to in this article are the time patients meet four ACR criteria for SLE (TD) and the time of last visit (TL). For those patients who did not develop hypertension, total disease duration was defined as the interval between TD and TL whereas follow-up time was defined as the interval between T0 and TL. For patients who developed hypertension, the end point was not TL but the visit in which hypertension first occurred.

Abbreviations: ACR, American College of Rheumatology; aPL, antiphospholipid; BMI, body mass index; ds DNA, double stranded DNA; LDL, low-density lipoprotein; LUMINA, Lupus in Minorities: Nature vs Nurture; SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLAM-R, Systemic Lupus Activity Measure-Revised; SLE, systemic lupus erythematosus

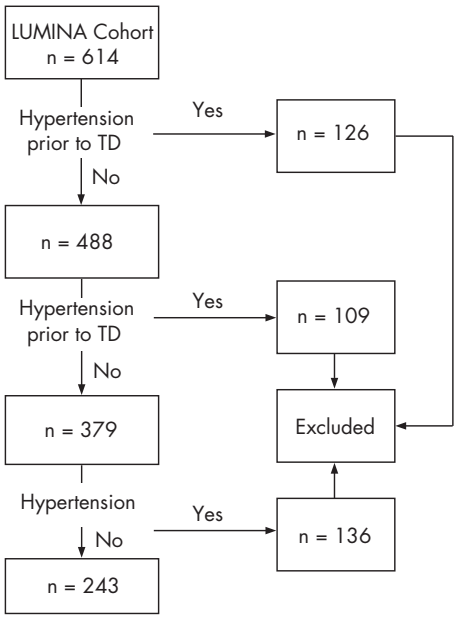

Figure 1 Flow diagram of Lupus in Minorities. Nature vs Nurture (LUMINA) cohort of patients studied. TD, time of systemic lupus erythematosus diagnosis.

The LUMINA study conforms to the guidelines of the Declaration of Helsinki for the use of human subjects in research and was approved at the three participating institutions; all patients gave written informed consent. Details relative to the constitution of this cohort and its main features have been described previously.[19–22]

Variables

The LUMINA database includes variables from the following domains: socioeconomic–demographic, clinical, immunological, genetic, behavioural and psychological. These variables were measured at T0 and at the follow-up visits. Only the variables included in these analyses will be described:

- Socioeconomic–demographic variables: age, gender, ethnicity, smoking, years of education, health insurance status and poverty (as defined by the US Federal Government, adjusted for the number of subjects in the household).[23]
- Clinical variables: disease activity ascertained using the Systemic Lupus Activity Measure Revised (SLAM-R),[24] damage accrual ascertained using the Systemic Lupus International Collaborating Clinics Damage Index (SDI),[25] disease onset type (defined as acute if time to the accrual of four ACR criteria is <4 weeks and insidious if otherwise), body mass index (BMI) calculated from the patients' height and weight, and diabetes mellitus (self-reported and/or physician-diagnosed and/or the use of oral hypoglycemic agents or insulin). Renal involvement was defined as nephritis by histopathology (World Health Organization class II or higher and/or >2+ proteinuria).
- Laboratory variables: levels of serum creatinine recorded at T0, non-fasting low-density lipoprotein (LDL) cholesterol (high if >130 mg/dl) and triglycerides (high if >205 mg/dl). Autoantibodies included are antinuclear antibodies (by immunofluorescence using HEp-2 cell line as a substrate), anti double-stranded-DNA (ds DNA; by immunofluorescence against *Crithidia luciliae*)[26] and aPL antibodies (IgG and/or IgM aPL antibodies by ELISA technique[27] and the lupus anticoagulant by Staclot test (Diagnostica Stago, Asnieres-sur-Seine, France)).[28]
- Medication use: from T0 to TL in patients who did not have hypertension and from T0 to the visit in which hypertension occurred in those who developed hypertension: non-steroidal anti-inflammatory drugs, hydroxychloroquine, low-dose aspirin and glucocorticoids. The use of glucocorticoids was recorded as current or past and also as the weighted average dose of prednisone equivalent used up to T0.
- Dependent variable: Hypertension (regardless of the cause) was defined as a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg on at least two occasions and/or patient's self-reported use antihypertensive drugs. Patients who were taking antihypertensive drugs for other indications such as proteinuria or Raynaud's symptoms were not included. As noted in fig 1, only patients who developed hypertension after T0 (n = 136) were included in these analyses; those who developed hypertension prior to TD (n = 126) or T0 (n = 109) were not included (n = 235).

Statistical analysis

T0 variables (except for disease activity in which the average of all SLAM-R scores were used and damage accrual in which the first available SDI score for patients with disease duration ⩽6 months at T0 was used) were compared between patients with and without hypertension by using descriptive statistical tests, χ^2 test for categorical (and Fisher's exact test, if appropriate) and Student's t test for continuous variables. For both SLAM-R and SDI, the scores from the renal domain were excluded; for SLAM-R, hypertension was also excluded. The association between hypertension and those variables significant at a p value ⩽0.10 in the univariable analyses and those felt to be clinically relevant, regardless of their level of significance, were further examined by multivariable logistic regression; first, domain-specific regression: demographic (age, gender and ethnicity), socioeconomic (poverty, years of education, insurance status, smoking, drinking and using recreational drugs) and clinical (SLAM-R, renal involvement, BMI, diabetes mellitus and LDL cholesterol, anti-dsDNA and aPL antibodies and current or past use of glucocorticoids) was performed. Then, a combined regression in which variables significant in the domain-specific regressions was examined. All analyses were performed using SPSS V.14.0 or SAS V.8.1.

Table 1 Socioeconomic–demographic features of patients in the LUMINA cohort as a function of the occurrence of hypertension any time after enrollment into the LUMINA cohort

Variables	Hypertension		p Value
	Present, n = 136	Absent, n = 243	
Mean (SD) age, years	34.3 (11.5)	35.3 (12.0)	0.463
Gender, % women	90	92	0.412
Ethnicity (%)			
Hispanic Texan	24	15	
Puerto Rican Hispanic	9	26	<0.001
African–American	45	25	
Caucasian	22	35	
Mean (SD) education, years	12.7 (3.0)	13.5 (3.0)	0.006
Below poverty level (%)	40	26	0.006
Health insurance (%)	82	74	0.058
Smoking (%)	11	14	0.463
Drinking (%)	6	12	0.055

RESULTS

Out of a total of 614 patients, 488 patients were studied: of them, 90% were women; 99 (20%) were Texan Hispanics, 85 (17%) were Puerto Rican Hispanics, 169 (35%) were African–Americans and 135 (28%) were Caucasians. The patients' mean (SD) age at T0 was 34.9 (11.7) years, the mean (SD) total disease duration (TD–TL) was 5.4 (3.6) years and the mean (SD) total follow-up time (T0–TL) was 3.9 (3.2) years and the number of follow-up visits was 5.1 (3.0) years; the estimated rate of loss to follow-up in the LUMINA cohort is 29%.[29] Of the 243 (50%) patients who developed hypertension after TD, 136 (56%) patients developed it after T0 and are included in these analyses.

UNIVARIABLE ANALYSES

Table 1 depicts the main socioeconomic–demographic features for those patients who developed hypertension after T0 and those who did not. Patients who developed hypertension were more likely to be African–American and Hispanic Texan, below the poverty line and less educated; however, they were less likely to have health insurance or to drink alcoholic beverages as compared with those who did not develop hypertension; the proportion of smokers was comparable in both groups.

Table 2 depicts the clinical and laboratory features. Patients who developed hypertension were more likely to develop renal involvement more frequently, to experience higher disease activity over time and to have accrued more damage, a higher BMI and diabetes mellitus.

Anti-dsDNA antibodies and aPL antibodies were more frequently found in patients with hypertension whereas the baseline creatinine, LDL cholesterol and triglyceride levels were comparable in both patient groups. However, the proportion of patients who have high LDL was higher in those patients who developed hypertension than in those who did not, although the difference did not reach statistical significance.

The use of hydroxychloroquine, non-steroidal anti-inflammatory drugs and low-dose aspirin were comparable in both patient groups whereas the use of glucocorticoids was more frequent in those who developed hypertension; however, there was no difference in the average dose of prednisone equivalent used by patients in the two groups.

Table 2 Clinical and laboratory features of patients in the LUMINA cohort as a function of the occurrence of hypertension any time after enrollment into the LUMINA cohort

Variables	Hypertension		p Value
	Present, (n = 136)	Absent, (n = 243)	
Acute onset type (%)	84	87	0.285
Mean (SD) follow-up time, (years)	2.6 (2.4)	3.0 (2.5)	0.112
Mean (SD), total disease duration, (years)	4.1 (2.9)	4.2 (3.0)	0.716
Mean (SD) disease activity*	8.0 (3.8)	7.1 (4.2)	0.046
Mean (SD) damage accrual†	0.6 (0.9)	0.5 (1.0)	0.337
Renal involvement (%)	62	30	<0.001
Diabetes mellitus (%)	6	2	0.032
Body mass index (kg/m^2)	26.4 (4.8)	25.3 (4.5)	0.026
Mean (SD) baseline serum creatinine, (mg/dl)	0.7 (0.4)	0.7 (0.3)	0.307
Mean (SD) LDL cholesterol, (mg/dl)	99 (38)	94 (39)	0.193
LDL cholesterol >130 mg/dl (%)	20	12	0.061
Mean (SD) triglyceride, (mg/dl)	133 (69)	122 (66)	0.152
Mean (SD) high sensitivity-C reactive protein	13.3 (21.9)	12.2 (30.3)	0.712
Anti-dsDNA antibodies (%)	57	47	0.070
Antiphospholipid antibodies (%)	34	22	0.014
Low-dose aspirin use (%)	11	17	0.102
Use of NSAID (%)	56	57	0.864
Hydroxychloroquine use (%)	85	86	0.762
Glucocorticoid use (%)	96	89	0.035
Weighted average glucocorticoid dose (in mg of prednisone/day)	7.1 (10.3)	6.7 (11.7)	0.738

LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drugs.
*As per the Systemic Lupus Activity Measure-Revised over time, scores from the renal domain and hypertension were excluded.
†As per the Systemic Lupus International Collaborating Clinics Damage Index, scores from the renal domain were excluded.

MULTIVARIABLE ANALYSES

Table 3 shows the multivariable logistic regression analyses data. African–American and Hispanic Texan ethnicities, renal involvement and a higher BMI were found to be independently associated with the occurrence of hypertension.

DISCUSSION

We carried out this study in the LUMINA cohort to assess the risk factors associated with the occurrence of hypertension after patients entered the cohort, hence ''incident hypertension''. The strength of our study rests in that LUMINA is a longitudinal cohort with a large number of patients. Our study confirms previous reports from North American SLE cohorts that hypertension occurs frequently in SLE; the overall frequency of hypertension in our cohort was 60%. The prevalence of hypertension in other lupus cohorts with different ethnic composition from New York City (African–Americans), Toronto (Caucasians), Baltimore (African–Americans and Caucasians) and Pittsburgh (Caucasians) were 75%, 50%, 46% and 37%, respectively.[8 13 15 17] The longer follow-up time in the Toronto lupus cohort might explain the higher prevalence rate in this cohort than in the Pittsburgh cohort, despite the fact that both are constituted primarily of Caucasians. Given the ethnic composition of the LUMINA cohort and the total disease duration, our rate is consistent with the data from these cohorts. However, the prevalence of hypertension in SLE in other parts of the world including Europe (Eurolupus, Spain and Greece) and Latin America (GLADEL, for Grupo Latinoamericano de Estudio del Lupus or Latin American Group for the Study of Lupus) are much lower (17%, 21%, 14% and 27%, respectively).[2 30–32] This is paradoxical given that the reported prevalence of hypertension in the general population of selected European and Latin American countries is higher than in North America.[33 34]

The risk factors for hypertension have been examined previously in two smaller studies: one in 112 Spanish patients and the other in 150 patients from the Toronto lupus cohort. In the first study, use of glucocorticoids, disease duration and age were found to be predictive of hypertension[30] whereas in the second study hypercholesterolaemia was found to be the best predictor of hypertension.[13] In our study, we failed to identify any of these previously reported factors as independently contributing to hypertension. However, we have identified factors that were not previously by other investigators such as renal involvement, higher BMI and African–American and Hispanic Texan ethnicities.

Hypertension has been described to be associated with worse renal outcomes in patients with lupus nephritis.[17 35] We have now found renal involvement to be a strong predictor of hypertension even after adjusting for possible confounding variables; although this finding seems quite logical, such association has not been reported previously.

Although aPL antibodies were found to be associated with hypertension in the univariable analyses, this variable was not retained in the multivariable analyses. It should be noted,

Table 3 Predictors of hypertension in patients from the LUMINA cohort by multivariable logistic regression analyses (n = 382)

Features	OR (95% CI)	p Value
Hispanic Texan	3.143 (1.398 to 7.063)	0.006
African–American ethnicity	3.780 (1.797 to 7.952)	<0.001
Caucasian	1.845 (0.858 to 3.967)	0.117
Renal involvement	2.953 (1.835 to 4.752)	<0.001
Obesity, body mass index (kg/m^2)	1.060 (1.009 to 1.114)	0.020

In addition to the variables listed in the table, the following were adjusted for in these analyses: age, gender, disease activity over time (Systemic Lupus Activity Measure-Revised scores from the renal domain and hypertension were excluded), diabetes mellitus, glucocorticoid use, low-density lipoprotein cholesterol and the presence of antiphospholipid and anti-dsDNA antibodies.

however, that in patients with SLE without renal involvement, these antibodies may still be important predictors of hypertension. It is known, for example, that these antibodies may upregulate endothelin-1 mRNA in endothelial cells.[36] These antibodies have also been shown to contribute to atherogenesis; patients with SLE with IgG anticardiolipin antibodies have significantly lower high-density lipoprotein cholesterol and Apo A-1 concentrations compared with those without them;[37] anti-β_2-glycoprotein 1 antibodies form a complex that promotes the uptake of oxidised LDL by macrophages, thus facilitating the formation of foam cells.[38] Furthermore, aPL antibodies have been found to be associated with poor renal outcomes in patients with lupus nephritis, a strong predictor of the occurrence of hypertension in our study.[39]

The association of higher BMI with hypertension has been recognised previously in the general population;[40–43] nevertheless, our data reinforce the notion that body weight should be optimised in patients with SLE to prevent the occurrence of hypertension; in fact, the data from the Nurses' Health Study have shown that women who lost at least 5 kg of body weight had a significantly lower risk of developing hypertension than women who did not.[44]

Although LUMINA patients of African–American and Hispanic ethnicity residing in Texas (of Mexican ancestry, predominantly) are known to have renal involvement more frequently than Caucasians (and Hispanics from the Island of Puerto Rico),[45 46] it is interesting to note that the association with hypertension was more significant than renal involvement, suggesting that other ethnic-associated factors may be operative.

There have been many studies investigating the role of glucocorticoids in clinical and subclinical cardiovascular disease in SLE; however, the role of glucocorticoids in hypertension have not been examined as extensively. We examined the effects of glucocorticoids using two approaches: first by categorising patients into past or current users vs non-users, and second by examining the weighted average dose of glucocorticoids as prednisone dose equivalent used up to T0. In contrast with the results from the Hopkins Lupus cohort and the cohort from Spain in which after adjustment for age, weight and antihypertensive drug use, incremental doses of prednisone led to increased blood pressure,[30 47] we could not document any such association. However, disease activity was not adjusted for in the two aforementioned studies, which may explain the discrepant results observed between them and ours.

This study is not without limitations. First, visits were annual, thus records of the exact time at which hypertension first occurred are not totally accurate; therefore, we chose not to perform time-dependent analyses to confirm the findings from the logistic regression model. Second, lipid profiles were measured in stored non-fasting sera; this is less than ideal as per the recommendations from the National Cholesterol Education Program, which may cause an overestimation of LDL and triglyceride levels and a false-positive result. Nevertheless, unlike the Toronto lupus cohort in which hypercholesterolaemia was found to be a predictor of hypertension,[13] we could not show such an association. Third, medication in the LUMINA cohort is recorded as current or past use; thus use of drugs recorded at T0 might not necessarily explain hypertension that occurred a few years later. Finally, although these risk factors are associated with the occurrence of hypertension, a causal relationship cannot be concluded from this study.

In summary, our data have direct applicability to the management of patients with SLE. Traditional cardiovascular risk factors SLE-related factors and African–American and Hispanic ethnicities seem to play a predictive role in the occurrence of hypertension in patients with SLE. This is important because hypertension is a strong risk factor for cardiovascular disease, which is one of the major causes of death in SLE. Recognising this might prompt clinicians to closely monitor blood pressure in all patients with lupus, aiming for its tight control. Finally, body weight is also modifiable; optimising it may further prevent the occurrence of hypertension and its deleterious consequences in patients with SLE.

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