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Predictors of incident proteinuria among patients with SLE

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ABSTRACT

Objective: To identify fixed and time-varying predictors of incident proteinuria.

Methods: This analysis was based on patients who did not have a history of diabetes and who did not have a prior episode of renal involvement. We defined an incident case of proteinuria as two or more measures of urine protein to creatinine ratio (or 24-hour protein measure) greater than 0.5 in two visits separated by more than 30 days and less than 180 days. We estimated rates of incident proteinuria in subgroups of patients with lupus defined by time-invariant and time-varying predictors.

Results: Among 895 patients included in the analysis, 840 (94%) were female, and 518 (58%) were Caucasian, 304 (34%) African-American, with mean age of 42 years at the start of follow-up. We observed 57 incident cases of proteinuria over a span of 4669 person-years of cohort follow-up. The overall rate of incident proteinuria was 12.2 per 1000 person-years. The rate was significantly lower among those of older age, and higher among those who were not Caucasian. In those with a very low C3 measure in a previous cohort visit, the rate was increased by a factor of 16.1 and in those with a very low C4 by 16.3. The rate among those prescribed hydroxychloroquine or ACE inhibitors/ARB was similar to those not on them.

Conclusions: Older patients with SLE are at low risk for developing proteinuria. There was not strong evidence that hydroxychloroquine or angiotensin-converting-enzyme (ACE) inhibitor reduced the risk of proteinuria. The highest rates of incident proteinuria were among those with recent low complement.

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INTRODUCTION

Lupus nephritis is a common manifestation of SLE, occurring in 22%–41% of Caucasians,[1 2] up to 70% of African-Americans,[1 3] 20%–60% of Hispanics and 24%–67% of Asian-Americans.[3 4] Sociodemographic, clinical, histopathological, immunological and genetic features have all been associated with the occurrence of lupus nephritis.[5–7] African-Americans, Hispanics, those with greater disease activity and those with anti-dsDNA and anti-ribonuclear protein (RNP) were more likely to develop lupus nephritis in one study.[3]

Despite advances in immunosuppressive therapy, dialysis and transplantation, the morbidity and mortality of lupus nephritis remain high. Based on studies using the US Renal Data System the incidence of end-stage renal disease (ESRD) has been stable, however in some groups—African-Americans and patients younger than 40 years— the incidence has increased.[8–10] From the economic standpoint, the 4-year cumulative direct costs of lupus nephritis were reported to be close to $100 000 per patient.[11] Therefore, it is of vital importance to find factors that predict lupus nephritis and, if modifiable, target them to prevent lupus nephritis or delay ESRD.

Most previous studies of predictors have studied the factors that predict the development of ESRD.[12 13] Proteinuria is the clinical expression of lupus nephritis; few studies of incident proteinuria in SLE are prospective or incorporate time-varying predictors. Previously a study by Bastian *et al*[14] reported predictive factors of new or worsening proteinuria using the dipstick method which has several limitations compared with newer methods like protein to creatinine ratio.

The Hopkins Lupus Cohort prospective database has the advantage of systematic follow-up quarterly, inclusion of both Caucasian and African-American patients, and a large number of patients with proteinuria measured by protein to creatinine ratio. We leveraged this large clinical cohort to identify fixed and time-varying predictors of incident proteinuria.

PATIENTS AND METHODS

Hopkins Lupus Cohort

This study was based on patients in the Hopkins Lupus Cohort from 2006, when urine protein to creatinine ratio started to be measured routinely, through 2015. The Hopkins Lupus Cohort was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB# NA_00039294) on a yearly basis. All patients gave written informed consent. Patient inclusion in the cohort was based on the clinical

diagnosis of SLE by one rheumatologist (MP). Ninety-five per cent of the patients fulfilled at least four of the 1982 American College of Rheumatology revised criteria for the classification of SLE.[15 16] At cohort entry, a detailed clinical history of each patient was collected. Thereafter, patients in the cohort were seen quarterly, or more frequently if medically indicated. At each patient visit, a complete history, physical examination and routine laboratory testing were performed in a systematic and prospective fashion by protocol. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) revision of the SLE Disease Activity Index[17] and Physicians Global Assessment on a 0–3 visual analogue scale[18] were calculated at each visit.

Cohort members not included in this analysis

This analysis was based on cohort follow-up that occurred after 1 January 2006 when the cohort began to measure urine protein to creatinine ratio routinely at every cohort visit. Only patients with three or more measures of urine protein were included. Patients with diabetes mellitus were excluded from the study. We also excluded patients with a history of renal disease prior to 2006. This was defined as a history of high urine protein (500 mg over 24 hours), renal insufficiency (serum creatinine >1.5 mg/dL or 75% decline in kidney function) or a clinical diagnosis of ESRD.

Definition of incident proteinuria

Patients were defined as having incident proteinuria if they had two or more measures of elevated urine protein (either a protein to creatinine ratio of >0.5 or a 24-hour urine collection of >500 mg) at least 30 days apart and within 180 days. Once an episode of incident proteinuria was established based on the above definition, we defined that episode as the start date of the proteinuria.

Statistical analyses

For each month of follow-up for each patient, we determined the patient's current and past clinical history up until that month, and also whether the patient developed incident proteinuria that month. Based on this information we calculated rates of proteinuria per person-month given various patient characteristics and clinical histories. Pooled logistic regression was then applied to the person-month data to estimate rate ratios and to adjust for confounding.

RESULTS

There were 1306 unique patients in the cohort database as in May 2015 who had at least three proteinuria assessments after 1 January 2006. Two hundred and thirty-five were excluded because they had a history of significant proteinuria (>500 mg over 24 hours) or a history of nephritis or ESRD. In addition, 86 were excluded because they had high urine protein at their first assessment (protein to creatinine ration of >0.5), and 90 more were excluded due to having diabetes.

Included in this study were 895 patients with SLE, of whom 840 (94%) were women. The mean age was 42 years at the start of follow-up. Ethnic make-up was 518 (58%) Caucasian, 304 (34%) African-American and 68 (7.6%) others. There was a total of 4669 person-years of cohort follow-up (mean=5.2 years per patient) in which 57 cases met the definition of incident proteinuria. The overall rate of incident proteinuria was 12.2 per 1000 person-years.

The relationship between demographic variables and the incident proteinuria is shown in table 1. The incidence rate was significantly higher in patients younger than 40 years compared with those 40–49 years (RR=0.4, p≤0.01), 50–59 years (RR=0.2, p=p≤0.01) and those 60 years or older (RR=0.01, p≤0.01).

The incidence rate was significantly higher in African-Americans (RR 2.9, p≤0.01) and other non-Caucasian patients had higher rates than Caucasians (RR=3.7, p≤0.01). There was no difference in the incidence of proteinuria between men and women.

Table 2 summarises the associations of incident proteinuria with autoantibodies and complement. History of low complement for both C3 and C4, anti-dsDNA, anti-Sm, anti-RNP and anti-Ro were associated with incident proteinuria. Lupus anticoagulant, anti-La and anticardiolipin antibodies were not associated with incident proteinuria.

Table 3 summarises the associations between past and current medication use and incident proteinuria. Those who used hydroxychloroquine in the past but who were not current hydroxychloroquine users (RR=4.8, p<0.05) as well as those using it for less than 6 months (RR=4.8, p<0.05) had a higher incidence of proteinuria than those patients that never used it. Among patients on medications for hypertension, those on ACE inhibitors/angiotensin receptor blocker (ARB) did not have a lower rate of incident proteinuria.

Some of the risk factors explored were highly correlated, so observed associations between incident proteinuria and one risk factor could be confounded by associations with other factors. To tease out the independent risk factors we fit multivariable models.

Table 4 shows the results of a single multivariable model including C3, C4, anti ds-DNA, age and race.

Although C3, C4 and anti-dsDNA are highly correlated with each other, a low C3 in the previous visit below 69 (RR=3.1, p<0.01), C4 below 9 (RR=4.3, p<0.01) and anti-dsDNA (RR4.2, RR p<0.01) provided independent predictive information for the development of proteinuria.

DISCUSSION

In this project we attempted to find the fixed and time-varying predictors of incident proteinuria in the Hopkins Lupus Cohort. Within the variables explored,

Table 1 Rates of incident proteinuria by demographic and metabolic risk factors

Subgroup	Observed number of new cases of proteinuria	Person-years of follow-up	Rate of events per 1000 person-years	Rate ratios	p Value
Everyone	57	4669	12.2		
Age (years)					
18–39	38	1515	25.1	1.0 (Ref)	
40–49	11	1171	9.4	0.4 (0.2 to 0.7)	0.0041
50–59	5	1183	4.2	0.2 (0.1 to 0.4)	0.0002
60+	2	780	2.5	0.1 (0.0 to 0.4)	0.0015
Sex					
Female	53	4376	12.1	1.0 (Ref)	
Male	4	293	13.7	1.1 (0.4 to 3.1)	0.81
Ethnicity					
White	19	2802	6.8	1.0 (Ref)	
Black	30	1548	19.4	2.9 (1.6 to 5.1)	0.0003
Other	8	319	25.1	3.7 (1.6 to 8.5)	0.0019
Calendar year					
2006–2009	26	1842	14.1	1.0 (Ref)	
2010–2013	19	1716	11.1	0.8 (0.4 to 1.4)	0.42
2013–2015	12	1110	10.8	0.8 (0.4 to 1.5)	0.44
Mean past systolic blood pressure (mm Hg)					
<120	20	1660	12.0	1.0 (Ref)	
120–129	13	1205	10.8	0.9 (0.4 to 1.8)	0.76
130–139	8	793	10.1	0.8 (0.4 to 1.9)	0.67
140+	7	413	16.9	1.4 (0.6 to 3.3)	0.44
Most recent systolic BP (mm Hg)					
<120	20	2065	9.7	1.0 (Ref)	
120–129	10	945	10.6	1.1 (0.5 to 2.3)	0.82
130–139	12	745	16.1	1.7 (0.8 to 3.4)	0.16
140+	15	726	20.7	2.1 (1.1 to 4.2)	0.026
Mean past diastolic BP (mm Hg)					
<70	18	1873	9.6	1.0 (Ref)	
70–79	20	1510	13.2	1.4 (0.7 to 2.6)	0.32
80+	10	588	14.5	1.5 (0.7 to 3.3)	0.29
Most recent diastolic BP (mm Hg)					
<70	21	2127	9.9	1.0 (Ref)	
70–79	18	1448	12.4	1.3 (0.7 to 2.4)	0.47
80+	18	905	19.9	2.0 (1.1 to 3.8)	0.029
Mean past total cholesterol*					
<150	12	782	15.3	1.0 (Ref)	
150–199	24	2228	10.8	0.7 (0.4 to 1.4)	0.32
200+	9	927	9.7	0.6 (0.3 to 1.5)	0.30
Body mass index					
<20	7	347	20.2	1.0 (Ref)	
20–25	17	1467	11.6	0.6 (0.2 to 1.4)	0.22
25–30	14	1212	11.6	0.6 (0.2 to 1.4)	0.23
30+	19	1435	13.2	0.7 (0.3 to 1.6)	0.34

we found that non-Caucasian ethnicity, young age, a low C3 and low C4 at the previous visit as well as an elevated anti-dsDNA were risks factors for developing proteinuria. There was no evidence that the use of ACE inhibitors or the use of hydroxychloroquine reduced the risk of proteinuria. Among the strengths of our study were the use of urine protein to creatinine ratio, frequent visits every 3 months by protocol, predictors measured every 3 months, and inclusion of both Caucasian and African-American ethnicities.

African-American and other non-Caucasian ethnicities were found to have higher rates of incident proteinuria. In a previous report in the Lupus in Minorities: Nature versus Nurture (LUMINA) cohort, African-Americans were at higher risk of developing lupus nephritis,[3] but in the same cohort, African-American ethnicity was not a risk factor for development of proteinuria in their multivariable model.[14] Ethnicity can be taken as a surrogate marker for environmental factors such as socioeconomic status and access to healthcare. A recent epidemiological

Table 2 Rates of incident proteinuria by compliment and autoantibodies

Subgroup	Observed number of new cases of proteinuria	Person-years of follow-up	Rate of events per 1000 person-years	Rate ratios	p Value
C3 (mg/dL) at previous cohort visit					
117+	10	1996	5.0	1.0 (Ref)	
79–116	14	2007	7.0	1.5 (0.7 to 3.5)	0.34
70–78	5	268	18.7	3.5 (1.2 to 10.4)	0.026
≤69	27	277	97.4	16.1 (7.5 to 34.6)	<0.0001
Ever low C3 during cohort					
No	13	2763	4.7	1.0 (Ref)	
Yes	44	1906	23.1	5.6 (2.9 to 10.6)	<0.0001
C4 (mg/dL) at previous cohort visit					
22+	11	2024	5.4	1.0 (Ref)	
12–21	14	2038	6.9	1.4 (0.6 to 3.1)	0.46
10–11	8	223	35.8	5.9 (2.3 to 15.1)	0.0002
≤9	23	261	88.0	16.3 (7.7 to 34.6)	<0.0001
Ever low C4 during cohort					
No	18	3086	5.8	1.0 (Ref)	
Yes	39	1583	24.6	4.8 (2.7 to 8.5)	<0.0001
Anti-dsDNA (titer) at previous visit					
0	17	3707	4.6	1.0 (Ref)	
1–80	13	476	27.3	4.9 (2.4 to 10.2)	<0.0001
81+	26	363	71.6	10.8 (5.7 to 20.3)	<0.0001
Ever positive for anti-dsDNA					
No	7	1034	6.8	1.0 (Ref)	
Yes	50	3635	13.8	2.8 (1.2 to 6.1)	0.013
Previous lupus anticoagulant					
No	41	3337	12.3	1.0 (Ref)	
Yes	16	1332	12.0	1.0 (0.5 to 1.7)	0.94
Recent lupus anticoagulant (RVVT<45)					
No	6	398	15.1	1.0 (Ref)	
Yes	51	4271	11.9	0.8 (0.3 to 1.8)	0.59
Anti-Sm					
No	35	3846	9.1	1.0 (Ref)	
Yes	22	806	27.3	3.0 (1.8 to 5.1)	<0.0001
Anti-Ro					
No	29	3188	9.1	1.0 (Ref)	
Yes	27	1466	18.4	2.0 (1.2 to 3.4)	0.0083
Anti-La					
No	43	3983	10.8	1.0 (Ref)	
Yes	13	669	19.4	1.8 (1.0 to 3.4)	0.063
Anti-RNP					
No	34	3580	9.5	1.0 (Ref)	
Yes	22	1079	20.4	2.2 (1.3 to 3.7)	0.0052
Anticardiolipin					
No	17	1756	9.7	1.0 (Ref)	
Yes	40	2910	13.7	1.45 (0.8 to 2.6)	0.22

RVVT, Russell viper venom time.

study in the US Medicaid population (high poverty group) showed a higher incidence and prevalence of lupus nephritis in African-Americans.[19]

In the Hopkins Lupus Cohort, having an elevated anti-dsDNA, and low C3 and C4, were found to be predictors of incident proteinuria, both in the univariable and multivariable analyses. Bastian *et al*[3 14] described anti ds-DNA as a predictor of lupus nephritis and incident proteinuria, and our observations confirm this association.

Previous studies identified that a decrease in complement levels occurred in some patients with SLE having a flare.[20 21] Previous reports based on the Hopkins Lupus Cohort showed that the decrease in complement levels was predominantly associated with renal and haematological flares.[22] Although reductions in complement are a recognised risk factor for renal flares, our data show that while having low complement is predictive, the degree to which the complement is low has a major impact.

Table 3 Rates of incident proteinuria by past and current medications

Subgroup	Observed number of new cases of proteinuria	Person-years of follow-up	Rate of events per 1000 person-years	Rate ratios	p Value
Currently on Plaquenil					
No	11	699	15.7	1.0 (Ref)	
Yes	46	3783	12.2	0.8(0.4 to 1.5)	0.44
Plaquenil, current and past					
Never	2	328	6.1	1.0 (Ref)	
Past, but not current	9	309	29.1	4.8 (1.0 to 22.2	0.045
Current, <6 months	14	476	29.4	4.8 (1.1 to 21.3)	0.037
Current 6+ consecutive months	32	3236	9.9	1.6 (0.4 to 6.8)	0.51
Proportion of cohort follow-up on plaquenil					
<20%	8	413	19.4	1.0 (Ref)	
20–79%	5	374	13.4	0.7 (0.2 to 2.1)	0.51
80%+	35	3119	6.1	0.6 (0.3 to 1.2)	0.16
Currently on ACE inhibitors/ARB*					
No	10	628	15.9	1.0 (Ref)	
Yes	24	1592	15.1	0.9 (0.5 to 2.0)	0.89
Proportion of cohort follow-up on ACE inhibitors/ARB*					
<20%	10	509	19.7	1.0 (Ref)	
20–79%	5	485	10.3	0.5 (0.2 to 1.5)	0.24
80%+	13	956	13.6	0.7 (0.3 to 1.6)	0.38

*These analyses only include patients on antihypertension medications to control for hypertension.

Table 4 Estimated association between incident proteinuria and low complement and anti-dsDNA controlling each other as well as race and sex, based on a multivariable model

Predictor	Rate ratio (95% CI)	p Value
Age (per 5-year increase)	0.8 (0.7 to 0.9)	<0.0001
Non-Caucasian (vs Caucasian)	2.4 (1.3 to 4.3)	0.0035
C3 (mg/dL) at previous cohort visit		
79+	1.0 (Ref. Group)	
70–78	1.3 (0.5 to 3.6)	0.65
≤69	3.1 (1.4 to 6.7)	0.0053
C4 (mg/dL) at previous cohort visit		
12+	1.0 (Ref. Group)	
10–11	2.2 (0.9 to 5.4)	0.090
≤9	4.3 (2.0 to 9.3)	0.0002
Anti-dsDNA (titer) at previous visit		
0	1.0 (Ref. Group)	
1–80	3.6 (1.6 to 7.9)	0.0017
81+	4.2 (2.0 to 8.6)	<0.0001

C3, C4 and anti-dsDNA are highly correlated with each other, and previously they have been reported to have the strongest serological association with renal involvement.[23] Our multivariable model showed that each of these markers (low C3, C4 and elevated anti-dsDNA) provide independent predictive information. For example, if a patient has a C3 below 9, C4 below 4 and an anti-dsDNA higher than 80, their risk of proteinuria at the next visit is increased by an estimated factor of 60 (3.1×4.4×4.2); these observations can have direct clinical applicability.

Hydroxychloroquine generally is used to treat constitutional and cutaneous manifestations of SLE, along with arthritis and pleurisy, but it now has a major role as a protective agent. The use of hydroxychloroquine is associated with improved survival,[24 25] decreased frequency of lupus flares,[26] reduced risk of damage accrual,[27] increased probability of remission if used in patients with membranous lupus nephritis treated with mycophenolate mofetil,[28] and decreased probability of renal failure if used prior to the onset of lupus nephritis.[29] In the univariate model having used hydroxychloroquine in the past but not currently was a risk factor for the development of incident proteinuria. It is possible that quitting hydroxychloroquine results in a risk for incident proteinuria. This could be an interpretation given previous data that showed the benefits of hydroxychloroquine as a protective medication.[30]

We did not observe a lower incident proteinuria among those using ACE inhibitors/ARB treatment, even when we confined the analysis to those taking some medications for hypertension. This finding must be viewed cautiously, however, because those with higher risk for nephritis, or those who had low level proteinuria might have been more likely to be prescribed ACE inhibitors/ARB creating confounding by indication. Our results contrast with those reported by Durán-Barragán *et al*[31] who reported a 73% reduction in incident renal involvement among users of ACE inhibitors. However,

we believe that estimate is biased towards a protective effect due to the way that they defined ACE inhibitor use. They defined ACE inhibitors as any use during the follow-up period. Since the follow-up period ends at the time of renal involvement, those who do not develop renal involvement are followed for a longer period. This makes it more likely that they will use ACE inhibitors at some point, inducing a possible false negative association between ACE inhibitors and renal involvement.

One limitation of this work is that we relied on a random urine protein to creatinine ratio to identify incident cases of proteinuria rather than a more accurate measure of proteinuria such as a 24-hour quantitative measure of urine protein. However, spot urine protein to creatinine ratio reliably predicts 24-hour total protein equivalents.[32]

Another limitation is that proteinuria can develop slowly and it is difficult to define the exact time of incident proteinuria. This difficulty could affect our results with respect to variables that might be altered (such as medication use) during the slow development of proteinuria. As noted above, this could result in confounding by indication in our effort to assess the association between ACE inhibitors/ARB use and incident proteinuria in SLE.

Finally, due to the small number of incident events (57), the statistical power was limited to conclusively show evidence for clinically important but moderate associations between predictors and incident proteinuria.

CONCLUSIONS

In summary, we found that a number of immunological markers and demographic factors were strongly predictive of future renal involvement. Anti-dsDNA, low C3 and low C4 were independent predictive markers. Our data do not indicate that ACE inhibitors/ARB or hydroxychloroquine reduced the risk of proteinuria.

Contributors AD-G, EB, LSM and MP contributed to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work and drafting or revising the work critically for intellectual content.

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