High Risk of Ischemic Heart Disease in Patients with Lupus Nephritis

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ABSTRACT. ***Objective.*** To investigate the occurrence of ischemic heart disease (IHD) in a cohort of 104 Danish patients with biopsy-proven lupus nephritis (LN).

Methods. Information on all hospitalizations in Denmark for IHD between 1977 and 2006 was obtained from the Danish National Hospital Register. Occurrence of IHD after date of first renal biopsy in the LN cohort was compared to the occurrence of IHD in the general population by calculation of standardized ratios of observed to expected events (O:E ratios) for different manifestations of IHD registered during inpatient and outpatient hospital visits.

Results. The median duration of followup was 14.7 (range 0.1–30.0) years. Thirty-one first-time hospitalizations for IHD occurred in the cohort, yielding an overall O:E ratio for IHD of 6.8 (95% CI 4.6–9.7). Increased risks were found for angina pectoris (O:E ratio 6.0, 95% CI 3.0–11), myocardial infarction (O:E ratio 7.9, 95% CI 3.8–15), and other IHD-related diagnoses combined (O:E ratio 6.9, 95% CI 3.3–13). A high IHD risk was observed for patients aged < 31 years at time of first renal biopsy (O:E ratio 17.1, 95% CI 9.1–29) and for patients aged 30–39 years during followup (O:E ratio 42.3, 95% CI 21–76). Patients undergoing chronic renal replacement therapy also had a pronounced risk of IHD (O:E ratio 19.4, 95% CI 7.8–40).

Conclusion. LN is associated with markedly increased morbidity from IHD. Our findings indicate that patients with early-onset LN have a disturbingly high risk of IHD compared to the general population. (First Release Sept 1 2011; J Rheumatol 2011;38:2400–5; doi:10.3899/jrheum.110329)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS ISCHEMIC HEART DISEASE
ENDSTAGE RENAL DISEASE CARDIOVASCULAR DISEASE

Systemic lupus erythematosus (SLE) is an inflammatory disorder characterized by multiorgan involvement, the presence of antinuclear autoantibodies, and a chronic relapsing clinical course. Despite therapeutic advances, patients with SLE have increased mortality compared to the general population[1]. Ischemic heart disease (IHD) is a major cause of life-threatening comorbidity in SLE[2,3]. A high occurrence of IHD-related events has been demonstrated in numerous investigations of patients with SLE, and the magnitude of the IHD risk has been analyzed in a range of population-based studies[4,5,6,7,8,9]. Compared to the background population, some investigators have reported a 2.2 to 2.6 times increased risk of IHD-related events for patients with SLE[4,5,6]. Other groups have reported higher risk estimates, especially for young patients[7,8,9].

Lupus nephritis (LN) is a serious manifestation of SLE, which affects about 50% of patients during their course of illness. Only 25%–50% of patients with LN treated with immunosuppressive agents will achieve complete renal remission within 2 years, renal disease flares are common, and 5%–20% of patients progress to endstage renal disease (ESRD) within 10 years following the diagnosis of nephritis[10,11]. Studies have demonstrated that SLE patients with reduced glomerular filtration rate at the time of SLE diagnosis[12] and patients with LN[13,14,15] experience excess morbidity from cardiovascular disease compared to other patients with SLE. These findings indicate that the combined IHD-promoting effects of SLE and chronic kidney disease[16,17] lead to a high cardiovascular risk in LN. To our knowledge, however, the IHD risk of patients with LN has not been compared with that of the general population.

We compared the occurrence of IHD in a cohort of

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Danish LN patients with the occurrence of IHD in the general population of Denmark by calculation of standardized risk estimates for specific cardiovascular events. The IHD risk of the LN patients was also examined in analyses stratified according to age, duration of followup, calendar-year period of first renal biopsy, and renal status.

MATERIALS AND METHODS

Patients. Patients with biopsy-proven LN were selected from a Danish SLE cohort established in 1995 as described[18,19]. The 513 patients of the SLE cohort were recruited from 8 clinical centers by means of hospital contact lists covering the period 1975–1995. Some of the participating centers had access to valid patient registrations beginning only in 1976, 1980, and 1983, respectively. In each center, all patients registered with an SLE diagnosis were identified, and patients who met the 1982 diagnostic criteria for SLE defined by the American College of Rheumatology[20] were included in the cohort. First-time renal biopsy specimens were available from 128 patients with LN. In 1996, these biopsy specimens were reassessed by an experienced pathologist (HS), who classified the histological findings according to the 1982 World Health Organization (WHO) criteria for LN[21]. In addition, the biopsies were scored for active and chronic histological lesions using the scoring systems developed at the US National Institutes of Health[22]. Twenty-three of the 128 patients with LN were not included in our study because of lack of clinical information and 1 patient died the day of the first renal biopsy, leaving 104 patients diagnosed with LN between 1971 and 1995 for further analyses. Included and excluded patients did not differ significantly in risk of ESRD or death during followup (Kaplan-Meier analyses with log-rank testing), or with respect to available baseline clinical findings. Among the included patients, 5 had been diagnosed with LN before first patient registration in the hospital contact lists.

The following clinical information was recorded at time of first renal biopsy for the majority of the patients included: systolic and diastolic blood pressure, 24-hour urinary protein excretion, and s-creatinine. Information on cyclophosphamide exposure (ever/never) was collected for all patients by medical records review. Valid data on cumulative drug doses, renal remission rates, and number of nephritis flares were not available. Dates of death or emigration were obtained from the Danish Central Population Register, which holds key information on all citizens of Denmark. Data on direct and contributory causes of death were obtained from the Danish Causes of Death Registry; the registry has collected medical information on all fatalities in Denmark since 1943[23].

Endstage renal disease. ESRD was defined as the need for at least 3 months of dialysis treatment or preemptive renal transplant. The occurrence of ESRD until 1995 was determined by review of patients' medical files. Cases of ESRD occurring during later calendar-year periods were identified through The Danish National Registry on Regular Dialysis and Transplantation, which has collected information on patients receiving chronic renal replacement therapy with almost complete coverage since 1990[24].

Ischemic heart disease. Information on IHD was obtained from the Danish National Hospital Register using a described search strategy[25]. The hospital register was established in 1977 and contains data on > 99% of all admissions to nonpsychiatric hospital departments in Denmark[26]. Inpatient registrations have been supplemented with information on outpatient contacts since 1994. Each hospital visit initiates a record, which includes the personal identification number of the patient, dates of admission and discharge, a primary discharge diagnosis, and supplementary diagnoses. The diagnoses were coded according to a Danish version of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and have been coded according to the ICD-10 thereafter.

The validity of the combined group of IHD diagnoses and of myocardial infarction (MI) as a separate diagnosis in the Danish National Hospital Register has been estimated to be at least 90%[27,28]. The LN cohort was linked to the files of the register, and a search was performed for diagnoses listed under the ICD-8/10 block of IHD (ICD-8: 410-414; ICD-10: I20-I25). For the search, IHD was divided into 3 categories: (1) MI (ICD-8: 410; ICD-10: I21); (2) angina pectoris (ICD-8: 413; ICD-10: I20); and (3) other diagnoses listed under the IHD block [ICD-8: 411 (other acute and subacute forms of IHD)]; 412 (chronic IHD); 414 (asymptomatic IHD); ICD-10: I22 (recurrence of MI); I23 (certain acute complications following MI); I24 (other acute IHD); I25 (chronic IHD). Followup for IHD started at the date of first renal biopsy or January 1, 1977, whichever came last, and continued until date of death or emigration or December 31, 2006, whichever came first. If a patient had attended a Danish hospital with a diagnosis listed under an IHD category before the diagnosis of LN, this event was not counted, but the patient was followed for diagnoses listed under the other predefined categories of IHD. In case of more than 1 diagnosis belonging to the same IHD category, only the first event in that category was counted. If several different IHD diagnoses belonging to more than 1 category had been recorded for a patient, these diagnoses were counted once in each of the appropriate categories.

Data on all in- and outpatients registered in the Danish National Hospital Register with a diagnosis of IHD from 1977 to 2006 were used to calculate IHD event rates for the background population using the same rules for selection of events as described above. The event rates were computed separately for men and women in 5-year age groups and calendar-periods of observation, by dividing the number of events in each specific group by the corresponding number of persons in the general Danish population.

Statistics. Multiplication of person-years under observation for the patients by the appropriate IHD event rates for men and women separately in 5-year age groups and 5-year calendar time periods yielded the expected number of first-time hospitalizations for IHD in the cohort. Ratios of observed to expected events (O:E ratios) for IHD with 95% CI were computed on the assumption that the observed numbers followed a Poisson distribution. Exact Poisson limits were used when the observed number was < 10; otherwise, Byar's approximation was used. Subanalyses were stratified according to age at time of first renal biopsy, age at IHD event, sex, cyclophosphamide exposure status, and duration of followup. Moreover, we analyzed the influence of ESRD on the IHD risk in the cohort. In this analysis, all patients contributed patient-years to the non-ESRD group from date of first renal biopsy. Patients who started renal replacement therapy contributed person-years to the ESRD group from the date of therapy start.

Risk factors for IHD among various baseline findings were identified by determining a proportional hazard model using conditional Cox regression analysis. In the analysis, the independent variables were included in dichotomized form, with the value 1 in case of the condition being present, and the value 0 if not. We included the following baseline findings as independent variables: s-creatinine ≥ 140 μmol/l (n = 29), urinary protein excretion ≥ 10 g/day (n = 26), grade 2–3 hypertension according to standard definitions[29] (n = 27), WHO class II LN (n = 18), WHO class III LN (n = 12), WHO class IV LN (n = 61), and WHO class V LN (n = 10). The model was adjusted for the linear effect of age at time of first renal biopsy and for male sex. The dependent variable was defined as time to the earliest occurring IHD-related event registered for a patient by means of the search strategy and censoring rules described above.

The conditional Cox regression analysis was performed using IBM SPSS Statistics, version 19.0 (IBM, New York, NY, USA). All other analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics and clinical findings at time of first renal biopsy are summarized in Table 1. Eleven patients (10.6%) were diagnosed with LN in the 1970s, 56 (53.8%) were diagnosed in the 1980s, and 37 (35.6%) had their diagnostic renal biopsy in the 1990s. Six patients were diag-

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Table 1. Characteristics at time of first renal biopsy for 104 patients diagnosed with lupus nephritis between 1971 and 1995.

Characteristic	No.	
Women, n (%)	104	83 (80)
Median age at time of biopsy, yrs (IQR)	104	31 (21–41)
Median duration of SLE prior to biopsy, yrs (IQR)	104	0.3 (0.0–3.8)
Median s-creatinine level, μmol/l (IQR)	104	98 (79–149)
Median 24-h urinary protein excretion, g (IQR)	101*	4.0 (1.5–11.3)
Median systolic blood pressure, mm Hg (IQR)	100*	130 (120–150)
Median diastolic blood pressure, mm Hg (IQR)	100*	90 (75–95)
WHO class lupus nephritis, n (%)	104	
I (normal glomeruli)		1 (1.0)
II (pure mesangial alterations)		18 (17.3)
III (focal segmental)		12 (11.5)
IV (diffuse proliferative)		61 (58.7)
V (diffuse membranous)		10 (9.6)
VI (advanced sclerosing)		2 (1.9)
Median NIH activity index score (IQR)	104	5 (2–9)
Median NIH chronicity index score (IQR)	104	2 (0–3)

* Reduced number of patients due to missing data. IQR: interquartile range; WHO: World Health Organization; NIH: US National Institutes of Health.

nosed with LN before registrations in the Danish National Hospital Register began on January 1, 1977. No patient died before this date. In total, 28 patients progressed to ESRD during followup and 36 patients died. Direct causes of death encompassed SLE disease activity (7 patients), cerebro- and cardiovascular events (14 patients), cancer (1 patient), myelodysplasia (1 patient), infections (6 patients), pulmonary fibrosis (2 patients), uremia (4 patients), and pancreatitis (1 patient). Detailed information on renal outcome and mortality was previously provided for the majority of patients[30].

The median duration of followup was 14.7 (range 0.1–30.0) years. Thirty-one first-time IHD events occurred in 22 patients during a total of 1528 patient-years, corresponding to a significantly increased overall O:E ratio for IHD of 6.8 (95% CI 4.6–9.7). As outlined in Table 2, the risk was significantly increased for MI as well as for angina pectoris and other IHD-related events combined. A high IHD risk was found for both male patients (O:E ratio for IHD 6.6, 95% CI 3.4–12) and female patients (O:E ratio for IHD 7.0, 95% CI 4.2–11).

Table 2. Ratios of observed to expected events (O:E ratios) for all ischemic heart disease (IHD) diagnoses combined, angina pectoris, myocardial infarction (MI), and other diagnoses listed under the ICD-8/10 block of IHD in a cohort of 104 patients diagnosed with lupus nephritis between 1971 and 1995 and followed throughout 2006.

Diagnosis (ICD-8/10 code)	Observed*	O:E Ratio (95% CI)
IHD (410-410/I20-25)	31	6.8 (4.6–9.7)
Angina pectoris (413/I20)	11	6.0 (3.0–11)
MI (410/I21)	10	7.9 (3.8–15)
Other†	10	6.9 (3.3–13)

* Observed number of first-time hospital discharge diagnoses. † ICD-8: 411, 412, 414; ICD-10: I22-I25. ICD: International Classification of Diseases.

A 17.1 times increased occurrence of IHD was found among patients aged < 31 years at time of first renal biopsy (the median patient age at entry to the cohort; Table 3). Eleven of the 31 first-time registered IHD events (35.5%) occurred in patients aged 30–39 years at time of the cardiovascular episode, 8 IHD events (26%) occurred in patients aged 40–49 years, 7 IHD events (22.5%) occurred in patients aged 50–59 years, and 5 IHD events (16%) occurred among patients aged 60–73 years. Analyses stratified according to age at IHD event demonstrated a significantly increased IHD risk in most of these age groups, including a 42.3 times increased IHD risk for patients aged 30–39 years (Table 3).

During the first 10 years after the diagnostic renal biopsy, the IHD risk was more than 7 times higher in the LN cohort than in the background population. The cardiovascular risk decreased slightly during subsequent time intervals, but excess occurrence of IHD was observed after more than 15 years of followup (Table 3).

A 10-fold increased IHD risk was found for patients who had their first renal biopsy in the 1990s, while the risk of IHD was about 5 times higher than expected for patients biopsied during earlier calendar-year periods (Table 3). We

Table 3. Ratios of observed to expected events (O:E ratios) for all ischemic heart disease (IHD) diagnoses combined according to age at first renal biopsy, age at IHD event, time from first renal biopsy (latency), calendar-year period of first renal biopsy, and renal status, respectively, in a cohort of 104 patients diagnosed with lupus nephritis between 1971 and 1995 and followed throughout 2006.

Feature	Observed*	O:E Ratio (95% CI)
Age at first renal biopsy, yrs		
< 31	13	17.1 (9.1–29)
≥ 31	18	4.8 (2.8–7.5)
Age at IHD event, yrs		
< 30	0	0.0 (0.0–142)
30–39	11	42.3 (21–76)
40–49	8	8.5 (3.6–17)
50–59	7	6.0 (2.4–12)
60+	5	2.3 (0.8–5.5)
Latency, yrs		
0–4	7	7.4 (3.0–15)
5–9	10	9.5 (4.5–17)
10–14	7	6.2 (2.5–13)
15+	7	5.0 (2.0–10)
Calendar-year period of first renal biopsy		
1971–79	3	4.7 (0.9–14)
1980–89	16	5.7 (3.3–9.3)
1990–95	12	10.8 (5.6–19)
Renal status		
– ESRD	24	5.8 (3.7–8.6)
+ ESRD	7	19.4 (7.8-40)

* Observed number of first-time hospital discharge diagnoses. ESRD: Endstage renal disease (as defined in text).

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observed a pronounced risk of IHD for patients undergoing chronic renal replacement therapy based on 7 first-time cardiovascular events (Table 3). Moreover, an increased cardiovascular risk was found for both cyclophosphamide-exposed patients (O:E ratio for IHD 7.6, 95% CI 4.8–11; n = 79) and patients treated otherwise (O:E ratio for IHD 5.2, 95% CI 2.1–11; n = 25).

In the age- and sex-adjusted conditional Cox regression analysis, focal segmental (WHO class III) glomerulonephritis was the only baseline finding that emerged as a predictor of IHD (relative hazard ratio 7.0, 95% CI 1.8–28; p = 0.005). During followup, first-time IHD events affected 6 out of 12 patients presenting with this type of LN.

DISCUSSION

Our findings demonstrate that patients with LN have markedly increased cardiovascular comorbidity. The patients of our LN cohort experienced a 6.8 times higher occurrence of IHD than the general population, and subanalyses revealed high O:E ratios for MI, angina pectoris, and other IHD-related events combined. In analyses stratified according to time from first renal biopsy, excess occurrence of IHD was found during both short-term and longterm followup. Since a number of population-based studies have shown a 2 to 3-fold increased occurrence of cardiovascular disease in unselected SLE cohorts[4,5,6], these findings support that patients with LN constitute a subgroup of SLE patients with a particularly high cardiovascular risk[13,14,15].

A heavily increased risk of IHD was found for patients who were younger than 31 years of age at time of first renal biopsy. The increased cardiovascular risk observed for these patients did not simply reflect a low occurrence of IHD among age-matched persons of the general population, as the calculated O:E ratio for IHD was based on 13 IHD-related events within this group. To further examine the cardiovascular risk of young patients with LN, we performed risk analyses stratified according to age at IHD event. These analyses demonstrated a high occurrence of cardiovascular events and a 42.3-times increased IHD risk among patients aged 30–39 years, strongly suggesting that some of the cardiovascular complications in the cohort were caused by IHD-promoting factors other than atherosclerotic coronary vessel disease, for example, factors related to SLE and/or factors associated with chronic kidney disease. Thus, our observations show that young patients with LN have an extremely high risk of IHD, as previously observed for young SLE patients in general[8,9], and they add to the growing amount of data indicating that the increased IHD risk in SLE is caused by a complex interplay between traditional and SLE-related cardiovascular risk factors[31].

Analyses stratified according to calendar-year period of first renal biopsy revealed a somewhat higher IHD risk for patients biopsied in the 1990s than for patients biopsied in the 1980s and 1970s. As shown in Table 3, the 95% CI for these risk estimates are wide and partially overlap, and the limited statistical power of our analyses precludes a firm statement regarding the IHD risk of patients diagnosed with LN during different decades. Since the incidence of IHD-related hospitalizations in Denmark is declining[32], it is possible that a continuously high IHD risk among Danish patients with LN in the setting of a decreasing rate of IHD-related events in the general population contributed to the increase in relative cardiovascular risk observed across calendar-year periods.

Cardiovascular mortality rates among patients with ESRD are about 10 to 20 times those of the general population[33]. In agreement, we found a 19.4 times increased occurrence of IHD-related hospitalizations for patients undergoing chronic renal replacement therapy. Only 7 first-time cardiovascular events occurred in the ESRD group. Therefore, even though a high cardiovascular risk was observed for patients who started renal replacement therapy during followup, the overall increased IHD risk in our cohort was caused not only by the presence of these patients. In fact, the majority of hospitalizations due to IHD were experienced by patients not having ESRD, and as shown in Table 3, the O:E ratio for IHD was only slightly lower for patients without ESRD than that observed for the total cohort.

In previous studies, patients with SLE treated with cyclophosphamide had a lower occurrence of atherosclerotic plaques than patients treated otherwise, indicating that aggressive immunosuppressive therapy reduces the risk of atherosclerotic vascular changes in SLE[34,35]. We did not observe a lower risk of IHD-related events among cyclophosphamide-exposed LN patients than among other patients in our cohort. Thus, while cyclophosphamide therapy may reduce the risk of accelerated atherosclerosis in SLE, our observations do not suggest that treatment with cyclophosphamide reduces the risk of overt IHD among SLE patients with nephritis.

Most baseline clinical and histological findings did not emerge as risk factors for IHD in age- and sex-adjusted conditional Cox regression analysis, but focal segmental histopathology (WHO class III) was identified as a statistically significant predictor of cardiovascular morbidity. Interestingly, we previously identified focal segmental LN as a highly significant risk factor for mortality in a study based on the majority of patients included in the present investigation[30], and other groups have associated severe focal segmental LN (by these authors defined as segmental necrotizing glomerulonephritis involving > 50% of glomeruli, corresponding to class IV-S LN according to the International Society of Nephrology/Renal Pathology Society 2003 classification[36]) with an increased risk of a poor renal outcome[37,38]. These observations indicate that focal segmental histopathology may predict an aggressive disease course in LN. Further studies are clearly needed to test this hypothesis.

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Our investigation has methodological strengths and weaknesses. The completeness of the data in the Danish Central Population Register allowed prolonged tracking of subjects, and the high validity of the IHD diagnoses in The Danish National Hospital Register enabled us to calculate population-based standardized O:E ratios for specific IHD-related events. Moreover, cases of ESRD were effectively identified by medical records review and linkage with the Danish National Registry on Regular Dialysis and Transplantation. The lack of information regarding cumulative drug doses, antiphospholipid antibody profiles, and renal disease flares is an important weakness of our study, which prevented more detailed analyses of IHD risk factors. Our risk factor analyses were also weakened by the lack of data on traditional cardiovascular risk factors such as tobacco use, blood lipid levels, obesity, diabetes, and blood pressure control during followup. Further, we were unable to determine the chronic kidney disease stage of each patient according to established definitions[39], since we had access to only one measurement of s-creatinine per patient. Therefore, our data did not allow a comprehensive analysis of the extent to which the well known IHD-promoting effect of chronic kidney disease[16,17] influenced the cardiovascular risk of our patients. Only 5 patients (4.8%) were diagnosed with LN before first patient registration in the hospital contact lists, which formed the basis for the establishment of our cohort. A potential survival bias, in the direction of underestimating the risk of IHD, is therefore expected to have a minor influence on the cardiovascular risk estimates.

Our study demonstrates that LN is associated with excess morbidity from IHD and provides evidence that patients with early-onset LN have a disturbingly high cardiovascular risk compared to the general population. Routine care for patients with LN should include screening for symptoms suggestive of IHD and intervention against modifiable cardiovascular risk factors.

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