Prevalence and Risk Factors for Liver Biochemical Abnormalities in Canadian Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the prevalence of abnormal liver enzymes in patients with systemic lupus erythematosus (SLE) and whether further investigations were done, and the differences in SLE-related and/or metabolic factors in patients with and without liver biochemical abnormalities.

Method. Patients from the University of Toronto Lupus Clinic who met at least 4 of the American College of Rheumatology classification criteria for SLE and had 1.5 times the upper limit for aspartate transaminase or alanine transaminase on 2 consecutive visits within a 2-year period were matched with controls for age, sex, and SLE duration. Demographic, clinical, and laboratory data were extracted at the time of the first appearance of liver enzyme abnormality for the cases and at the reference point for the controls.

Results. From the 1533 patients reviewed, 134 (8.7%) met the inclusion criteria. Thirty of these patients were evaluated by a hepatologist, 75 had imaging studies (41 were done specifically for liver investigation), and 13 had liver biopsies. Results based on these investigations showed 31 fatty livers, 35 cases of drug-induced hepatotoxicity, 10 autoimmune etiologies, and 3 cases of viral hepatitis. Compared to controls, cases were higher in body mass index, anti-dsDNA antibody, prevalence of hypertension, antiphospholipid syndrome, and use of immunosuppressive medication, especially azathioprine and methotrexate; they were lower in IgM.

Conclusion. Metabolic abnormalities such as obesity and hypertension and hepatotoxic effects of medication used to treat SLE may contribute more than SLE-related factors to liver biochemical abnormalities in patients with SLE. (J Rheumatol First Release Dec 15 2011; doi:10.3899/jrheum.110310)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LIVER DISEASE LIVER ENZYMES
ASPARTATE TRANSAMINASE ALANINE TRANSAMINASE

Systemic lupus erythematosus (SLE) is a systemic illness of autoimmune etiology. The prevalence of SLE in North America is between 30 and 100 per 100,000 people[1,2]. In Canada, Bernatsky, *et al*[1] estimated the prevalence rate of SLE at 51 cases per 100,000 individuals, with a 7:1 to 10:1 female sex bias depending on the age category. SLE is characterized by multisystem organ involvement. The American College of Rheumatology (ACR) lists 11 SLE classification criteria, at least 4 of which are required to meet the definition of SLE. These involve the kidneys, the joints, and the central nervous system[3]. The liver has not been considered a major target organ for SLE.

Although overt liver disease is uncommon in patients with SLE, the prevalence of subclinical liver abnormalities, espe-

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cially in the form of abnormal liver biochemical tests, is recognized and not infrequent. A retrospective study[4] of 206 patients with SLE found that 60% developed elevated liver enzymes. Clinical findings in these patients included hepatomegaly (39%), splenomegaly (6%), and jaundice (24%). Significant liver disease developed in 21% of patients. Another retrospective study of 141 Korean patients with SLE found that 33% had liver enzyme abnormalities[5]. A 12-month prospective study on 260 patients with SLE reported ongoing liver enzyme elevation in 23% of the cases[6].

The nature of the liver abnormalities detected in persons with SLE is not clearly understood and it remains to be determined whether the cause is the lupus itself or the presence of other pathological processes. Metabolic abnormalities associated with the metabolic syndrome, such as high body mass index (BMI), hyperlipidemia, insulin resistance, and hypertension, are highly prevalent in patients with SLE[7] and are risk factors for nonalcoholic fatty liver disease (NAFLD). In addition, SLE symptoms are often managed by an array of potentially hepatotoxic drugs. In a prospective study, Seaman and colleagues[8] demonstrated a dose-dependent hepatotoxicity to aspirin in 28 of 260 patients with SLE. Azathioprine (AZA) and methotrexate (MTX) are immunosuppressive drugs frequently used in the management of SLE; they carry a risk of hepatotoxicity[9,10,11]. Corticosteroid use itself has also been implicated as contributing to the risk of hepatic steatosis[12].

We wished to establish in a carefully managed cohort of patients with SLE the frequency of liver biochemical changes, and their associations with lupus disease activity, damage, and metabolic measures. This was done in adult patients with SLE followed at the University of Toronto Lupus Clinic.

MATERIALS AND METHODS

Study subjects. The University of Toronto Lupus Database has prospectively evaluated patients with SLE since 1970 according to a standard protocol that includes demographic, clinical, and laboratory data and contains all the information necessary to calculate disease activity and damage. Ethics review and approval from the University Health Network Research Ethics Board were obtained for this database and written informed consent was collected from each patient. Subjects fulfilled at least 4 of the ACR classification criteria for SLE or had 3 of the criteria and a biopsy (skin or kidney) demonstrating SLE features[3]. Liver enzymes are measured at every protocol visit for all patients regardless of the patient's clinical and medication profile. Patients were included who had documented elevated transaminases ≥ 1.5 times the upper limit [defined as aspartate transaminase (AST) > 52 IU/l and/or alanine transaminase (ALT) > 60 IU/l] on 2 consecutive visits within a 2-year span. These cutoffs for ALT and AST were chosen because they were close to the clinicians' routine cutoffs for concern over liver disease. Among the 1533 patients in the database, 134 met our inclusion criteria.

Control subjects were selected from the same database and included patients with SLE matched to those with elevated liver enzymes by sex, age (± 5 years), and SLE duration, defined as the time between the diagnosis date and the first appearance of the abnormal liver enzyme (within 1.5 years) for the cases and the duration between the diagnosis date and a visit date of equivalent duration for controls. For the case-control study, both cases and controls were limited to those who had at least 2 years of followup. Data for cases were collected at the time of first appearance of the abnormal liver enzyme(s), and for the controls at a reference point defined as the time between SLE diagnosis and matched duration. Among the 1533 subjects in the database, we were able to find 104 controls to match the 104 cases with available followup data of 2 years or more.

Data collection. Demographic data were extracted on sex, age at diagnosis of SLE, SLE duration, and social history, including smoking and alcohol intake. Exposures to antiinflammatory and immunomodulatory agents such as prednisone, antimalarial drugs, and immunosuppressive medications were determined within the 2 years prior to the abnormal liver enzyme tests for the cases and at the reference timepoint for the controls.

Disease activity was determined using the SLE Disease Activity Index 2000 (SLEDAI-2K)[13]. SLEDAI encompasses central nervous system and musculoskeletal symptoms; urinary abnormal findings such as casts, hematuria, proteinuria and pyuria; skin changes; mucous membrane involvement; serositis such as pleurisy and pericarditis; low complement levels; increased DNA binding; hematologic involvement; and fever. All the items necessary to calculate the SLEDAI-2K are prospectively collected in the standard protocol. SLEDAI serves as a monitoring tool for assessment of activity of SLE and efficacy of its treatment[14]. We calculated the Adjusted Mean SLEDAI (AMS), a validated measure of the average SLEDAI over the 2 years prior to the abnormal liver enzyme tests for the cases and at the reference timepoint for the controls[15]. The Lupus Activity-Steroid Index (LASI) was then calculated using the methodology described by Akhavan, *et al*[16]. AMS and cumulative steroid dose are categorized into 4 quartiles with scores of 1, 2, 3, and 4, respectively, and the summation of the 2-year AMS and cumulative steroid dose constitutes the LASI score (range from 0 to 8).

The Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) was used to assess cumulative and irreversible damage due to SLE[17], its treatment, or other illnesses in 12 organ systems (ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, gonadal failure, diabetes, and malignancies). All the items necessary to calculate the SLICC/ACR damage index are prospectively collected in the standard protocol.

Laboratory data included blood levels of AST, ALT, alkaline phosphatase (ALP), albumin, and blood lipid profile, all collected prospectively in the standard protocol. Other data collected were anti-dsDNA by Farr assay, C3, and C4.

Once those with abnormal liver enzymes were identified, a retrospective chart review was performed to determine whether data on further investigations were available in the hospital record or in the paper charts. Data, when available, were retrieved on liver imaging by ultrasound, computed tomography (CT) scan, and/or histological findings on liver biopsy within a 5-year period following the first appearance of abnormal liver enzyme test for cases and within the last 5 years of clinic followup for controls. Chart review was conducted on all cases and controls.

Statistical analysis. Descriptive statistics were used to report on the prevalence of liver abnormalities and to describe the demographic variables. Cases and controls were matched 1:1 and compared using conditional logistical regression analyses, and $p < 0.05$ was considered a statistically significant difference. Risk factors for fatty liver disease and drug-induced hepatotoxicity in cases were evaluated using univariate logistic regression. OR were generated to estimate the risk factors of fatty liver and drug-induced hepatitis in the group of people with liver abnormalities. We then used a cutoff of $p < 0.05$ for fatty liver and $p < 0.1$ for drug-induced hepatotoxicity to select the variables to be included in the multivariate analysis. SAS (version 9.1; SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Among the 1533 patients, 134 (8.7%) met the inclusion criteria of having at least 2 consecutive elevated liver enzyme tests, defined as AST > 52 IU/l and ALT > 60 IU/l over a 2-year period. On average, these subjects had 4 (range 0–10) measurements of ALT and AST over a 2-year period. Further investigations were done only in a small subset of these patients,

including referral to a hepatologist in 30/134 (22%), imaging by ultrasound, CT scan or MRI in 75/134 (55%), and liver biopsy at the request of hepatologists in 13/134 (9.7%). Only 41 of the abdominal imaging studies were done specifically for liver investigation. The findings on imaging are summarized in Table 1. Among those who underwent further investigation or were referred to a hepatologist along with serologic findings and chart review, 31 were found to have fatty liver, 35 were suspected for drug-induced hepatotoxicity (32 of which resolved after withholding the drug), 10 were found to have an autoimmune etiology (either SLE-related or autoimmune hepatitis), and 3 had viral hepatitis (hepatitis C). The results of the liver biopsy showed 4 cases of fibrosis (one with grade 1, 2 with grade 2, and 1 with grade 3 fibrosis) and 2 cases of cirrhosis.

In the nested case-control study, 104 of the cases with abnormal liver enzymes had more than 2 years of followup and were matched (by age, sex, and disease duration) to 104 controls. Among the 104 control subjects, 23 had abdominal imaging, and no abnormality was reported in the liver.

Demographic characteristics of the cases and their matched controls are reported in Table 2. Cases and the controls were matched by age, SLE duration, and sex. This cohort of cases and controls was 85.6% female and had a mean age of 40.4 (SD 13.5) years and SLE duration of 13.0 (SD 9.3) years. The 2 groups were predominantly white. Lifestyle behaviors such as smoking and patterns of alcohol consumption were also similar. SLE disease-related variables were comparable between the cases and the controls, including age at diagnosis, ACR criteria, SLEDAI-2K, LASI, and the SDI. However, some components of the metabolic syndrome, including body weight and BMI, were significantly higher in the cases, with a higher prevalence of obesity [BMI > 30; cases: n = 20 (23.8%); controls: n = 7 (12.1%); p = 0.027] and hypertension [cases: n = 68 (65.4%); controls: n = 54 (51.9%)]. Cases and controls were compared across the BMI ranges (27–30) and the difference between cases and controls for developing fatty liver appeared only when BMI > 29 was used as a cutoff. Waist circumference and waist-to-hip ratio were similar between the 2 groups.

The medical history and medication profile of cases and controls are reported in Table 3. Compared to controls, cases had higher prevalence of antiphospholipid syndrome (APS) and hypertension. Although infrequent in both groups, the number of patients with APS was 3 times higher in cases (9 patients) than in controls (3 patients; p = 0.09). The prevalence of other autoimmune conditions, cardiovascular disease, and malignancies was similar between the 2 groups. The use of immunosuppressive medications such as MTX and AZA was significantly more prevalent in the cases than in the controls. Although the use of prednisone and statins was also more prevalent and the cumulative dosage of prednisone was higher in cases than in controls, those differences did not reach statistical significance. Among the 104 cases and their matched controls, 30 never received prednisone and 39 never received immunosuppressive medications. The demographic characteristics including ACR criteria, age at diagnosis, SDI score, and SLE duration were similar between these 2 subsets of patients (cases and controls not exposed to steroids or immunosuppressor; data not shown). The median SLEDAI-2K scores revealed low disease activity in both groups, but it was higher in the cases (4, range 2–6) compared to the controls (2, range 0–4; p = 0.063). There were deaths in 7 out of 104 (6.7%) cases and 17 out of 104 (16.3%) controls.

Comparison of serological variables is shown in Table 4. Cases had significantly lower total IgM levels compared to controls. As expected, liver enzymes AST, ALT, and ALP were significantly higher in cases compared to controls. There was also a trend toward higher serum triglycerides in cases compared to controls. There were no differences between cases and the controls in international normalized ratio (INR) and albumin levels. For INR, 13 (28.9%) out of 45 cases and 5 (21.8%) out of 23 controls had abnormal INR (> 1), while 27 cases and 30 controls had albumin levels below normal (40 mg/dl).

Table 1. Imaging and histological findings.

Method	No. Cases
Imaging, n = 75	
Ultrasound, n = 69	
No abnormalities	29
Hemangioma	5
Hepatomegaly	8
Fatty liver	31
Cirrhosis	2
Ascites	2
Calcification	1
Acute hepatitis	1
CT scan, n = 12	
No abnormalities	4
Hemangioma	2
Hepatomegaly	2
Fatty liver	3
Ascites	1
Cirrhosis	2
Portal hypertension	1
Autoimmune Hepatitis	3
MRI, n = 2	
Iron overload	1
Hepatomegaly	1
Liver biopsy, n = 13	
No abnormalities	3
Active hepatitis	6
Ascites	2
Steatohepatitis	2
Fibrosis	4
Cirrhosis	1
Epithelioid granulomata	1
Vascular changes	1
Hemophagocytic syndrome	1

CT: computed tomography; MRI: magnetic resonance imaging.

Table 2. Demographic characteristics of the cases and the controls. Comparison between the 2 groups using conditional logistic regression; $p < 0.05$ considered a statistically significant difference.

Characteristics	Cases, n = 104	Controls, n = 104	p
White, n (%)	72 (70.6)	71 (68.9)	0.873
Smoker, n (%)	27 (26.0)	26 (25.0)	0.873
Alcohol, n (%)	27 (26.0)	27 (26.0)	1.000
Age at diagnosis, yrs, mean ± SD	28.0 ± 11.0	26.8 ± 9.5	0.176
SLEDAI-2K score, median (IQR)	4.0 (2.0, 8.0)	4.0 (1.0, 8.0)	0.924
LASI, mean ± SD	5.1 ± 1.8	4.6 ± 1.9	0.122
SDI, median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	0.822
ACR SLE criteria, mean ± SD	6.7 ± 1.5	6.5 ± 1.6	0.355
BMI, kg/m^2, mean ± SD	27.3 ± 6.5	25.0 ± 5.2	0.049
> 30, n (%)	20 (23.8)	7 (12.1)	0.027
> 29, n (%)	26 (30.9)	9 (15.5)	0.031
> 28, n (%)	32 (38.1)	13 (22.4)	0.117
> 27, n (%)	39 (46.4)	19 (32.8)	0.301
Waist:hip ratio, mean ± SD	0.9 ± 0.1	0.8 ± 0.1	0.824

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; LASI: Lupus Activity and Steroid Index; SDI: Systemic Lupus International Collaborating Clinics damage index; ACR: American College of Rheumatology; BMI: body mass index; IQR: interquartile range.

Table 3. Medical history and medication profile of cases and controls. Comparison between the 2 groups using conditional logistic regression; $p < 0.05$ considered a statistically significant difference.

	Cases, n = 104	Controls, n = 104	p
Medical history			
Autoimmune disease, n (%)	73 (70.2)	73 (70.2)	—
Hashimoto thyroiditis	4 (3.8)	4 (3.8)	—
Sjögren's syndrome	0 (0.0)	0 (0.0)	—
Arthritis	64 (61.5)	69 (66.4)	0.425
Inflammatory bowel disease	23 (22.1)	28 (26.9)	0.413
Antiphospholipid syndrome	9 (8.6)	3 (2.9)	0.099
Cardiovascular, n (%)	5 (4.8)	7 (6.7)	0.484
Hypertension, n (%)	68 (65.4)	54 (51.9)	0.034
Malignancy, n (%)	6 (5.8)	3 (2.9)	0.273
Chronic kidney disease, n (%)	37 (35.6)	36 (34.6)	0.847
Dialysis, n (%)	2 (1.9)	3 (2.9)	0.657
Diabetes mellitus, n (%)	14 (13.5)	10 (9.6)	0.349
Medication profile			
Prednisone, n (%)	67 (64.4)	57 (54.8)	0.191
Cumulative dose, g, median (IQR)	7.2 (0.0, 26.0)	4.2 (0.0, 24.7)	0.216
Average dose, mg/day, median (IQR)	7.5 (0.0, 14.9)	2.9 (0.0, 10.1)	0.133
Antimalarial, n (%)	72 (69.2)	61 (58.6)	0.097
Immunosuppressors, n (%)	63 (60.8)	39 (37.35)	0.001
Azathioprine	40 (38.5)	24 (23.1)	0.010
Methotrexate	24 (23.1)	12 (11.5)	0.050
Aspirin, n (%)	12 (11.5)	11 (10.6)	0.828
NSAID, n (%)	15 (14.4)	13 (12.5)	0.696
Statins, n (%)	17 (16.4)	9 (8.6)	0.096
Oral contraceptives, n (%)	23 (22.2)	24 (23.1)	0.869
Hormone replacement therapy, n (%)	15 (14.4)	13 (12.5)	0.670
Anticoagulants, n (%)	14 (13.5)	14 (13.5)	—

IQR: interquartile range; NSAID: nonsteroidal antiinflammatory drug.

The univariate logistic regression analyses for determining the associations between the demographic, metabolic risk, and SLE-related factors with fatty liver disease as an outcome (n = 30) and drug-induced hepatotoxicity as another outcome (n = 34) are reported in Table 5. High BMI, hypertension, and elevated triglycerides as well as the use of antimalarial drugs, aspirin, and nonsteroidal antiinflammatory drugs was associated with increased risk of fatty liver disease. However, in the multivariate analysis, only BMI (OR 1.26, 95% CI 1.10–1.44) was associated with fatty liver disease.

Table 4. Laboratory measures of cases and controls. Results are mean ± SD or median (interquartile range). Comparison between the 2 groups using conditional logistic regression; $p < 0.05$ considered a statistically significant difference.

Laboratory Measurements	Cases, n = 104	Controls, n = 104	p
Hemoglobin, g/l	128.8 ± 17.7	125.5 ± 16.5	0.109
WBC, 1000/μl	6.7 ± 3.1	6.6 ± 3.0	0.908
Platelet, 1000/μl	254.7 ± 77.1	249.4 ± 89.1	0.606
INR	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	0.429
C3, g/l	1.0 ± 0.3	0.9 ± 0.3	0.649
C4, g/l	0.2 ± 0.1	0.2 ± 0.1	0.210
IgG, g/l	14.9 ± 7.6	13.8 + 4.7	0.754
IgM, g/l	1.1 ± 0.7	1.6 ± 1.0	0.047
Anti-dsDNA*	198.7 ± 171.2	103.4 ± 118.8	0.353
Albumin, g/l	42.6 ± 5.8	41.3 ± 6.9	0.097
AST, IU/l Normal 5-34	54.5 (47.5, 68.0)	25.0 (21.0, 31.0)	0.018
ALT, IU/l Normal 7-40	68.0 (60.0, 92.0)	23.0 (17.0, 33.0)	0.001
ALP, U/l Normal 40-150	78.0 (62.0, 95.0)	67.0 (54.0, 86.0)	0.015
Cholesterol, mmol/l	4.9 ± 1.4	4.8 ± 1.1	0.828
Triglycerides, mmol/l	1.6 (1.0, 2.6)	1.4 (1.0, 2.2)	0.210
Glucose, mmol/l	4.6 (4.0, 5.2)	4.7 (4.3, 5.4)	0.696
Antinuclear antibody	58 (17.2)	21 (34.4)	0.099

* Antibody by Farr assay. WBC: white blood cell count; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; INR: international normalized ratio.

Table 5. Univariate analysis of risk factors associated with fatty liver and drug-induced hepatitis in cases with liver abnormalities. Univariate logistic regression analyses were done to determine associations. Variables with $p < 0.05$ for fatty liver and those with $p < 0.1$ for drug-induced hepatitis in these univariate analyses were included in multivariate analyses.

Risk Factors	OR (95% CI)	p
Fatty liver, n = 30/135		
BMI	1.170 (1.067, 1.283)	0.001
Hypertension	2.562 (1.011, 6.491)	0.047
Triglyceride	1.283 (1.042, 1.581)	0.019
Aspirin	6.000 (2.008, 17.924)	0.001
NSAID	5.333 (1.921, 14.810)	0.001
Antimalarial	2.885 (1.088, 7.649)	0.032
IgG	0.909 (0.841, 0.982)	0.015
AST	1.862 (0.509, 6.807)	0.347
ALT	4.833 (0.612, 38.190)	0.135
ALP	0.995 (0.986, 1.004)	0.251
Drug-induced hepatoxicity, n = 34/135		
Sex (female)	2.667 (0.741, 9.599)	0.133
SLE duration	0.944 (0.898, 0.992)	0.023
Arthritis	0.465 (0.213, 1.018)	0.055
Methotrexate	2.377 (1.001, 5.642)	0.050
Immunosuppressants	2.377 (1.001, 5.642)	0.050
SLICC damage index	0.742 (0.560, 0.984)	0.038

BMI: body mass index; NSAID: nonsteroidal antiinflammatory drug; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

Women had almost 3-fold greater increase in risk of developing drug-induced hepatotoxicity. In a univariate logistic regression analysis (Table 5), increased use of immunosuppressive drugs, including MTX and AZA, was also associated with drug-induced hepatotoxicity. Conversely, longer SLE duration, having arthritis, and higher SDI scores were associated with decreased risk of drug-induced hepatotoxicity. In a multivariate analysis, only the use of immunosuppressive drugs was associated with drug-induced hepatotoxicity (OR 3.16, 95% CI 1.11–8.98).

DISCUSSION

In our study, < 10% of the patients with SLE had abnormal liver enzymes on at least 2 occasions over a 2-year period. About half (55%) of those underwent further investigations such as abdominal imaging and liver biopsies; however, only 41 patients (31%) underwent these studies specifically to investigate liver abnormalities. This is also reflected in the low proportion of patients (22%) who were referred to a hepatologist. This may reflect the belief that liver abnormalities in SLE are not considered by clinicians to be major comorbid conditions and so are investigated sparingly. In addition, it is conceivable that the low prevalence of liver abnormalities in this cohort may reflect the fact that 60% of the patients in the cohort received immunosuppressive medications at some point during their followup, a treatment that could theoretically at least mask a presentation of autoimmune liver disease. However, there is little evidence suggesting that SLE is a risk factor for autoimmune hepatitis, and the old name for autoimmune hepatitis, lupoid hepatitis, arose because the young women initially described had arthralgias, hepatitis, and lupus erythematosus cells. In our study, 27% of the cases had never received any immunosuppressive medications or prednisone, making it possible that the liver can be a subtle target organ in a subset of patients with SLE.

The prevalence of abnormal liver biochemistry tests in our cohort of patients with SLE was lower than the previously reported prevalence of 23%–60%[4,5,6]. This may be explained by differences in the criteria used to define abnormal liver enzyme tests. For example, both Runyon, *et al*[4] and Her, *et al*[5] defined abnormal liver enzymes as a 2-fold or greater increase at 1 timepoint in at least 2 of the following: total bilirubin, AST, ALT, lactate dehydrogenase, or ALP. Miller, *et al*[6] defined abnormal liver enzymes as an elevated AST, ALT, or ALP at 1 timepoint. In the Miller study, in 12 patients who did not have any other reason to have liver biochemical abnormalities, their values followed SLE disease activity. We also confirmed this, as a small subset of cases not exposed to steroids or immunosuppressors and with elevated liver enzymes had a higher SLEDAI-2K score when compared to the controls. Thus, there may be a small group of patients with SLE for whom the liver is indeed a target organ.

In our study, a small subset of patients had imaging or liver biopsy data available. The range of abnormalities observed

was similar to what is reported in the review by Schlenker, *et al*[18]. In a histologic review of 73 patients with SLE, Matsumoto and colleagues[19] identified the following coexisting primary liver disorders: fatty liver (72.6%), nodular regenerative hyperplasia (6.8%), viral hepatitis (4.1%), primary biliary cirrhosis (2.7%), and autoimmune hepatitis (2.7%). Case reports of additional liver diseases in patients with SLE include primary sclerosing cholangitis[20], autoimmune cholangiopathy[20], granulomatous hepatitis[21], and idiopathic portal hypertension[22]. Vascular disorders of the liver secondary to APS associated with SLE include Budd-Chiari syndrome[23], hepatic infarction[24], and hepatic rupture[25]. In our study, drug-induced hepatotoxicity and NAFLD were the most common attributed causes for liver biochemical abnormalities, at 23% and 26%, respectively, followed by autoimmune and viral etiologies in 7% and 2%. Our results were in agreement with the findings of Chowdhary, *et al*[26], who reported NAFLD in 9 of 40 American patients (23%) with SLE; however, their report on the prevalence of drug-induced hepatotoxicity (10%) was much lower and that of autoimmune (23%) and viral hepatitis (20%) were much higher than what we observed. As well, a retrospective study of 45 Italian patients with SLE who had liver enzyme abnormality[27] found that 31% of the patients had hepatitis, again a higher prevalence than in our findings.

In neonatal SLE, abnormal liver biochemistry is reported in 15%–25%[28,29]. The pathology of liver involvement tends to resemble idiopathic neonatal giant cell hepatitis, although more severe lesions associated with death have been described[30,31,32]. These discrepancies may be explained by differences in study populations and sample size in various studies. Our study investigated the prevalence of abnormal liver biochemistry tests in a cohort of 1533 patients that was much larger than the sample size for previous studies. Lifestyle habits may differ between our study populations and those of other studies and may explain some of the differences observed. Interestingly, however, one of the most common causes of liver enzyme abnormality is alcohol consumption, and this was found to be similar in our cases and controls. On the other hand, being female meant almost 3-fold increase in the risk of developing drug-induced hepatotoxicity. A female predominance of drug-induced hepatotoxicity is observed with several drugs[33,34,35,36]. Conforti, *et al*[35] showed increased susceptibility and severity of drug-induced hepatotoxicity in women compared to men, whereas Andrade and colleagues[33] found similar sex distributions of drug-induced hepatotoxicity, but that women had a higher risk for developing fulminant liver disease. In a French population-based study, the incidence rate of adverse hepatic reactions was similar in men and women until age 49 years, but it became twice as high in women as in men after that age[36]. However, chronic liver injury due to AZA seems to occur mostly in men[36].

Other abnormalities such as epithelioid granulomas are reported to be the first sign of an ongoing systemic disease, although the mere presence of liver granulomas does not necessarily indicate an underlying systemic granulomatous process[37]. Epithelioid granulomas were seen in only 1 of the cases that led to further investigations in our study. As well, vascular disorders of the liver, often associated with antiphospholipid antibodies, have been documented in SLE. These include the Budd-Chiari syndrome[38] and hepatic infarction[24]. In our study, we observed 1 case with vascular changes on liver biopsy. Hemophagocytic syndrome was also reported to be present in 10% of patients with SLE in Yokohama, Japan, over a 10-year period[39]. In our study, we had only 1 patient with this abnormality, revealed by liver biopsy.

In our nested case-control study in which the control group was matched for age, sex, and duration of disease, we found higher prevalence of metabolic abnormalities, including high BMI and hypertension, in our cases compared to the controls. In general, high prevalence of metabolic syndrome is reported in patients with SLE[7,40]. These metabolic abnormalities included in the definition of the metabolic syndrome are strong risk factors for NAFLD[41]. Therefore, the higher prevalence of metabolic abnormalities among the cases may partially explain the relatively high prevalence of NAFLD in our study. The use of glucocorticoids in the management of SLE could also increase the risk of NAFLD. A study by Matsumoto and colleagues[42] found that exposure to glucocorticoids is a significant risk factor in the etiology of severe fatty liver disease. Our results showed a trend toward a higher use of prednisone in our cases compared to controls that may have also contributed to a relatively high prevalence of NAFLD in our study.

We also found a significantly higher use of immunosuppressive medications including AZA and MTX in our cases compared to controls. Both drugs have been shown to be associated with hepatotoxicity, either directly or indirectly[9,10,11], and the use of these drugs in treating SLE symptoms could cause drug-induced hepatotoxicity. Such treatment, however, does not rule out the contribution of the underlying disease itself in the predisposition to hepatotoxicity, since a small subset of cases who were naive to immunosuppressive medications and/or prednisone had abnormal liver enzymes. Interestingly, measures of disease activity and damage (SLEDAI-2K and SDI) and the serological marker of disease activity did not differ significantly among the 2 populations as a whole. However, in a subset of cases that were naive to immunosuppressive medications and/or prednisone, disease activity was higher than in the controls. This suggests that perhaps people with worse disease were treated with immunosuppressive medications and therefore it makes sense that disease activity would be the same when cases and controls were compared as a whole. That possibility does not rule out the contribution of SLE disease processes to liver abnormalities in a subset of patients.

In our study, in a univariate analysis, the use of antimalarial drugs was associated with an increased risk of fatty liver disease. This finding needs further investigation. Hepato-

toxicity from the use of antimalarial drugs has been reported in some cases, but not frequently[43]. Further, interest in hydroxychloroquine has evolved from its role as a disease modifier to its role as a prophylactic agent against some of the major morbidities of SLE and its treatment, such as hyperlipidemia, diabetes mellitus, and thrombosis, some of which are risk factors for developing fatty liver disease[44].

The strength of our study is that it was a real-world study with a large number of at-risk, actively managed patients with SLE, in whom liver biochemical changes are infrequent and rarely a major cause for concern. The first limitation was that because of our study's cross-sectional design, we could not examine the causation of liver enzyme abnormalities. Second, due to the retrospective design, and because not all tests were performed at every visit, several patients did not have the required test results in the timeframe we studied.

Our results suggest that the liver may indeed be a subtle target organ in a subset of patients with SLE, and that this may relate to the disease activity. Other comorbid factors associated with the metabolic syndrome, such as obesity and hypertension, as well as side effects of the drugs used in the treatment of SLE nevertheless likely contribute more to liver abnormalities in patients with SLE. Therefore it is important for the rheumatologists and family physicians treating patients with SLE to screen for liver disease and to manage risk factors at an early stage.

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