Prevalence and risk factors of liver biochemical abnormalities in patients with systemic lupus erythematosus

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Aim of the work
The aim of this work was to study the prevalence and risk factors of liver biochemical abnormalities in patients with systemic lupus erythematosus (SLE) and to investigate the cause of these abnormalities.

Patients and methods
A total of 200 SLE patients attending the Rheumatology and Rehabilitation Department, Cairo University, were subjected to full medical history, assessment of disease activity using SLE disease activity index, calculation of BMI, laboratory investigations including complete blood count (CBC), erythrocyte sedimentation rate, C3, C4, liver and kidney functions, lipid profile, antinuclear antibodies, and anti-dsDNA. Patients with alteration of liver functions had further laboratory tests including viral hepatitis markers, hepatitis C virus (HCV) antibodies, hepatitis B virus surface antigen and hepatitis A virus antibodies, PCR for patients who had HCV-positive tests, autoimmune hepatitis (AIH) profile (antimitochondrial antibodies, antismooth muscle antibodies, and anti-liver–kidney microsomal antibodies), antiphospholipid profile (anticardiolipin, lupus anticoagulant, and B_2 glycoproteins), creatine phoshokinase (CPK), and abdominal ultrasound.

Results
The prevalence of liver biochemical abnormalities was 6.5% two patients (15.4%) had HCV-positive antibodies, two patients (15.4%) had probable AIH, five patients (38.5%) had fatty liver, four patients (30.8%) had drug-induced hepatotoxicity, and two patients (15.4%) had no cause other than SLE itself. Hypertension, diabetes mellitus, and hyperlipidemia were more frequent in patients with elevated liver enzymes.

Conclusion
The prevalence of elevated liver enzymes among SLE patients attending the Rheumatology and Rehabilitation Department during the time of the study was 6.5%. The most common liver abnormality was found to be fatty liver, affecting 38.5% of the patients, followed by drug-induced hepatotoxicity (30.8%), and then HCV infection, AIH, and SLE (each 15.4%).

Keywords:
drugs, liver, prevalence, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease with a broad range of circulating autoantibodies, which, after forming immune complexes with antigens, are deposited in different organs and cause damage after activating the complement [1].

SLE may be associated with liver abnormalities secondary to the presence of a coexisting autoimmune liver disease [particularly primary biliary cirrhosis or autoimmune hepatitis (AIH)], the direct involvement of the liver parenchyma, or the impact of medical treatments on the liver [2].

Liver histology is not peculiar in systemic rheumatic diseases with hepatic involvement, and different patterns can be observed in patients with liver enzyme abnormalities undergoing liver biopsy or in autoptical studies. Chronic active hepatitis, chronic persistent hepatitis, cirrhosis, nodular regenerative hyperplasia, fibrosis, steatosis, and granulomas are the major findings reported in rheumatic diseases, along with less specific findings such as mild chronic inflammatory cell infiltrate of the portal space [3].

Vascular involvement is not uncommon and has been described as intrahepatic small vessel arteritis, the Budd–Chiari syndrome, or isolated portal hypertension. Drug-induced liver injury is significantly more frequent than primary disease-related liver involvement, and concurrent viral hepatitis or opportunistic infections have to be ruled out in rheumatic patients. Finally, amyloidosis is a rare cause of liver involvement in chronic systemic rheumatic diseases [4].

Numerous histopathological patterns can be found in liver biopsies of SLE patients, including small-

artery vasculitis reported in up to 21% of the patients, nonalcoholic fatty liver diseases in 20–73%, nodular regenerative hyperplasia in 5.7%, chronic persistent or active hepatitis in 2.4%, and cirrhosis in 1.1% or fibrosis in 0.8% [5]. Moreover, cases of giant cell hepatitis, granulomatous hepatitis, massive hepatic necrosis, cholangitis, isolated portal hypertension, the Budd–Chiari syndrome, and liver infarction have also been described. End-stage liver disease is a very infrequent finding, whereas cases of Budd–Chiari syndrome have been reported in association with the antiphospholipid syndrome. Moreover, antiphospholipid antibodies have been shown to be involved in small-artery intrahepatic damage and in the pathogenesis of nodular regenerative hyperplasia [3].

Abnormal liver function tests are common in patients with SLE — being reported in 3–29% of the patients [3], often during disease exacerbations, and 4.4% of patients with SLE may have serious chronic liver diseases, including chronic active hepatitis and liver cirrhosis. The most common liver histologic manifestation of SLE is steatosis, which may not be associated with corticosteroid therapy.

The aim of this work was to study the prevalence and risk factors of elevated liver enzymes in patients with SLE and to investigate patients with elevated liver enzymes to determine the cause of liver affection.

Patients and methods

A total of 200 SLE patients attending the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals, were involved in this study. All patients were previously diagnosed according to the Systemic Lupus International Collaborating Clinic (SLICC) SLE criteria [6].

All patients gave informed consent to participate in the study, which was approved by the Kasr Al Aini medical ethics committee.

Patients were subjected to full medical history, assessment of disease activity using the SLE disease activity index (SLEDAI), and calculation of BMI [7].

All patients were subjected to routine laboratory investigations including CBC, erythrocyte sedimentation rate, C3, C4, liver and kidney functions, lipid profile, antinuclear antibodies (ANAs), and anti-dsDNA antibodies.

Further investigations were carried out for patients with elevated liver enzymes:

(1) Viral hepatitis markers [hepatitis C virus (HCV) antibodies, hepatitis B virus surface antigen, and hepatitis A virus antibodies].
(2) PCR for those with chronic viral hepatitis.
(3) AIH profile was performed (antismooth muscle antibodies and anti-liver–kidney microsomal antibodies), and the score of AIH was calculated using the simplified criteria for AIH [8].
(4) Antimitochondrial antibodies to exclude primary biliary cirrhosis.
(5) Antiphospholipid profile (anticardiolipin, lupus anticoagulant, and anti-B_2 glycoproteins).
(6) CPK.
(7) Abdominal ultrasound (U/S).

Statistical methods

Data were statistically described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was performed using the Mann–Whitney *U*-test for independent samples, and for comparing categorical data, the χ^2-test was performed. The exact test was used instead when the expected frequency was less than 5; *P* values less than 0.05 were considered statistically significant. All statistical calculations were performed using the computer program SPSS version 15 for Microsoft Windows (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA).

Results

The study included 200 SLE patients: 183 female (91.5%) and 17 male (8.5%). Demographic, clinical, and laboratory characteristics of the SLE patients are demonstrated in Tables 1 and 2.

Steroids were used by all patients (100%): 113 patients (56.5%) were receiving azathioprine (AZA), 33 patients were receiving cyclophosphamide (CYC), and 21 patients (10.5%) were receiving mycophenolate mofetil (MMF) (totally, more than 80% of our patients were receiving immunosuppression). Antimalarials

Table 1 Demographic data of systemic lupus erythematosus patients (*n* = 200)

	Range	Mean ± SD
Age (years)	16–54	29.89 ± 8.6
BMI (kg/m^2)	16.3–44.8	27.36 ± 5.47
Age of onset of disease (years)	12–54	26.92 ± 11.98
Duration of disease (years)	1–36	12 ± 4.91
Sex [*n* (%)]		
Male	17 (8.5)	
Female	183 (91.5)	

Table 2 Clinical characteristics of systemic lupus erythematosus patients (*n* = 200)

Clinical manifestations	*n* (%)
Fever	194 (97)
Weight loss	45 (22.5)
Mucutaneous manifestations	185 (92.5)
Discoid rash	15 (7.5)
Photosensitivity	114 (57)
Malar rash	146 (73)
Oral/nasal ulcers	167 (83.5)
Alopecia	59 (29.5)
Musculoskeletal manifestations	199 (99.5)
Myositis	17 (8.5)
Myalgia	113 (56.5)
Arthritis	183 (91.5)
Arthralgia	199 (99.5)
Nephritis	120 (60)
Abdominal manifestations	9 (4.5)
Mesenteric vasculitis	1 (0.5)
Jaundice	1 (0.5)
Ascites	9 (4.5)
Peritonitis	1 (0.5)
Hematemesis and melena	0 (0)
Vasculitis	37 (18.5)
Neurological manifestations	39 (19.5)
Lupus headache	15 (7.5)
Stroke	8 (4)
Psychosis	23 (11.5)
Seizures	8 (4)
Pleurisy	179 (89.5)
Hypertension	105 (52.5)
Diabetes	19 (9.5)

Table 3 Laboratory features of systemic lupus erythematosus patients (*n* = 200)

Laboratory parameters	Range	Mean ± SD
Hb (g/dl)	6–17	11.5 ± 1.7
WBC × 10^3 (cell/mm^3)	2.2–24	7.4 ± 1.4
PLT × 10^3 (cell/mm^3)	42–949	284 ± 166
Urea (mg/dl)	7–205	35.5 ± 25.6
Creatinine (mg/dl)	0.3–5.8	0.8 ± 0.5
ESR (first hour) (mm/h)	4–150	46.4 ± 31.5
TG (mg/dl)	40–585	169.6 ± 89.4
Cholesterol (mg/dl)	40–568	200.9 ± 73.4
ALT (U/dl)	4–190	25.1 ± 21.7
AST (U/dl)	6–149	22.4 ± 14.1
ALP (U/dl)	24–306	73.4 ± 34.5
GGT (U/dl)	6–1481	40 ± 107
Direct bilirubin	0–0.6	0.1 ± 0.07
Total bilirubin	0.1–1.7	0.3 ± 0.1
Albumin (g/dl)	1–5.6	3.7 ± 0.6
PT (s)	10–46	13.9 ± 5
PC (%)	25–172	94.5 ± 18.5
INR	0.8–3.2	1.1 ± 0.3
FBS (mg/dl)	60–342	99 ± 36.8
Anemia [*n* (%)]	105 (52.5)	
Leukopenia [*n* (%)]	23 (11.5)	
Thrombocytopenia [*n* (%)]	6 (3)	
Hyperlipidemia [*n* (%)]	72 (36)	

ALP, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; PC, prothrombin concentration; PLT, platelet; PT, prothrombin time; TG, triglycerides; WBCs, white blood cells.

were used by 176 patients (88%), methotrexate was used by four patients (2%), NSAIDs were received by 198 (99%) of our patients (they all received them only on need), and antihypertensive drugs were received by 105 patients (52.5%).

Laboratory features of SLE patients are illustrated in Table 3.

The immune profile of SLE patients is shown in Table 4.

Table 4 Immune profile of all patients

	n (%)
Positive ANA	195 (97.5)
Positive anti-dsDNA	164 (82)
Consumed C3	51 (25.5)
Consumed C4	38 (19)

ANA, antinuclear antibodies; C3, complement 3; C4, complement 4.

Our results showed that the SLEDAI score of all patients ranged from 0 to 50 with a mean of 11.2 ± 7.1.

According to the level of liver enzymes [alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT)], all patients were then divided into two groups:

(1) The first group included patients who had one or more liver enzymes elevated above their normal levels. This group included 13 (6.5%) patients.
(2) The second group included patients whose liver enzymes were within their normal levels. This group included 187 (93.5%) patients.

On comparing both groups regarding their demographic data, there were no significant differences between them (Table 5).

The SLEDAI score of SLE patients ranged from 0 to 50, with a mean of 11.2 ± 7.1.

The SLEDAI score in group 1 ranged from 2 to 22, with a mean of 10.23 ± 6.55, and in group 2, it ranged from 2 to 50, with a mean of 11.29 ± 7.17. There was no significant difference between both groups regarding their mean SLEDAI score.

Vasculitis affected more patients in group 1 than in group 2, and there was a significant difference between both groups (P = 0.04). Proteinuria and pyuria were present more often in patients of group 2 than in group 1, and there were significant

Table 5 Comparison between both groups regarding their demographic data

	Group 1 (*n* = 13)	Group 2 (*n* = 187)	*P* value	Significance
Sex [*n* (%)]				
Male	0 (0.0)	17 (9.1)	0.6	Not significant
Female	13 (100)	170 (90.9)		
Age (mean ± SD) (years)	32.08 ± 11.15	29.74 ± 8.41	0.54	Not significant
BMI (mean ± SD) (kg/m^2)	28.21 ± 5.94	27.3 ± 4.46	0.52	Not significant
Age of onset of disease (mean ± SD) (years)	26.92 ± 11.98	23.55 ± 7.7	0.27	Not significant
Duration of disease (mean ± SD) (years)	5.31 ± 4.14	6.2 ± 4.93	0.57	Not significant

Table 6 Comparison between both groups regarding their systemic lupus erythematosus disease activity index score

	Group 1 (*n* = 13) [*n* (%)]	Group 2 (*n* = 187) [*n* (%)]	*P* value	Significance
Visual disturbance	1 (7.7)	14 (7.5)	1	Not significant
Stroke	0 (0)	1 (0.5)	1	Not significant
Seizures	0 (0)	2 (1.1)	1	Not significant
Psychosis	2 (15.4)	15 (8)	0.3	Not significant
Cranial nerves affection	0 (0)	1 (0.5)	1	Not significant
Organic brain lesion	0 (0)	0 (0)		
Lupus headache	0 (0)	7 (3.7)	1	Not significant
Pleurisy	11 (84.6)	122 (65.2)	0.22	Not significant
Pericarditis	2 (15.4)	11 (5.9)	0.2	Not significant
Oral/nasal ulcers	3 (23.1)	13 (7)	0.07	Not significant
Alopecia	2 (15.4)	21 (11.2)	0.64	Not significant
Vasculitis	3 (23.1)	10 (5.3)	0.04	Significant
New rash	3 (23.1)	22 (11.8)	0.21	Not significant
Myositis	0 (0)	1 (0.5)	1	Not significant
Fever	3 (23.1)	12 (6.4)	0.06	Not significant
Arthritis	2 (15.4)	17 (9.1)	0.35	Not significant
DNA	10 (76.9)	153 (81.8)	0.83	Not significant
Consumed C3 and C4	3 (23.1)	48 (25.7)	1	Not significant
Proteinuria	1 (7.7)	89 (47.6)	0.007	Significant
Pyuria	0 (0)	61 (32.6)	0.01	Significant
Hematuria	1 (7.7)	35 (18.7)	0.47	Not significant
Urinary casts	1 (7.7)	22 (11.8)	1	Not significant
Leukopenia	2 (15.4)	21 (11.2)	0.64	Not significant
Thrombocytopenia	0 (0)	6 (3.2)	1	Not significant
SLEDAI score (mean ± SD)	10.23 ± 6.55	11.29 ± 7.17	0.59	Not significant

SLEDAI, systemic lupus erythematosus disease activity index.

differences between both groups (*P* = 0.007 and 0.01, respectively). There were no significant differences in other items of the SLEDAI score (Table 6).

Comparison between both groups regarding their laboratory data revealed that there were significant differences between both groups in their ALT (*P* = 0.00), AST (*P* = 0.00), ALP (*P* = 0.004), and GGT (*P* = 0.006), which were markedly elevated in group 1 compared with group 2, and there were no significant differences between both groups in other laboratory data (Table 7).

On comparing both groups regarding their immune profile (ANA, anti-dsDNA, C3, and C4), there were no significant differences as shown in Table 8.

On comparing both groups with respect to the drugs used by the patients, all patients in groups 1 and 2 were receiving steroids. AZA was used by nine patients (69.2%) in group 1 and 104 patients (55.6%) in group 2. CYC was used by four patients (30.8%) in group 1 and 29 patients (15.5%) in group 2. MMF was used by 21 patients (11.3%) in group 2 and no patients in group 1. Antimalarials were used by 11 patients (84.6%) in group 1 and 167 patients (89.3%) in group 2. Methotrexate was used by four patients (2.1%) in group 2 and no patients in group 1. NSAIDs were used by all patients in group 1 (used on need only) and in 185 patients (98.9%) in group 2 (used on need only). Antihypertensive drugs were used in eight patients (61.5%) in group 1 and in 97 patients (51.9%) in group 2. There were no significant differences between both groups regarding the number of patients using these drugs.

Patients in group 1 (who had elevated levels of one or more of their liver enzymes) were subjected to further investigations (Table 9).

(1) There were two patients with a positive test for HCV antibodies (15.4%), and no patient showed positive tests for hepatitis A or B virus antibodies. PCR was performed for HCV-positive patients and revealed one patient with low viremia and the other was below the detection limit. Their abdominal U/S showed fatty hepatomegaly. Their SLEDAI scores were 4 and 2.
(2) There were two patients (15.4%) with possible AIH; their score was 6 in the simplified diagnostic criteria for AIH. Liver biopsy was performed to prove the diagnosis of AIH, but it was difficult as the two patients were pregnant. The two patients were ANA positive, had elevated IgG, and negative viral hepatitis; one was antismooth muscle antibody positive and both had negative anti-liver–kidney microsomal antibody. Their abdominal U/S showed bright

Table 7 Comparison between both groups regarding their laboratory data

Laboratory data	Group 1 (n = 13)		Group 2 (n = 187)		P value	Significance
	Range	Mean ± SD	Range	Mean ± SD		
Hb (g/dl)	9–15	12.25 ± 1.7	6–17	11.47 ± 1.8	0.13	Not significant
WBC × 10^3 (cell/mm^3)	1.5–15	7.29 ± 1.2	2.2–24	7.41 ± 1.43	0.13	Not significant
PLT × 10^3 (cell/mm^3)	157–480	298 ± 161	42–949	279 ± 166	0.13	Not significant
Urea (mg/dl)	17–45	28.6 ± 10	7–205	36 ± 26	0.46	Not significant
Creatinine (mg/dl)	0.5–1.1	0.7 ± 0.18	0.3–5.8	0.8 ± 0.5	0.57	Not significant
ESR (first hour) (mm/h)	5–110	58.23 ± 35.8	4–150	45.6 ± 31.1	0.19	Not significant
TG (mg/dl)	100–233	164.2 ± 50.1	40–585	170 ± 91.6	0.68	Not significant
Cholesterol (mg/dl)	119–358	192.5 ± 66.5	40–568	201.5 ± 71	0.56	Not significant
ALT (U/dl)	14–190	67.8 ± 60.4	4–65	22.2 ± 116	0.00	Significant
AST (U/dl)	42–149	60.8 ± 27.9	6–37	19.8 ± 7.2	0.00	Significant
ALP (U/dl)	51–306	129.6 ± 82	24–120	69.5 ± 24.6	0.004	Significant
GGT (U/dl)	6–1481	188 ± 399	10–55	29.7 ± 20.8	0.006	Significant
Direct bilirubin	0.04–0.6	0.13 ± 0.14	0–0.4	0.1 ± 0.06	0.89	Not significant
Total bilirubin	0.16–1.7	0.44 ± 0.41	0.1–1	0.33 ± 0.14	0.88	Not significant
Albumin (g/dl)	2.7–4.5	3.75 ± 0.55	1–5.6	3.7 ± 0.7	0.84	Not significant
PT (s)	10–20	13.1 ± 2.3	10–46	13.9 ± 5.2	0.7	Not significant
PC (%)	60–124	97.3 ± 16.3	25–172	94.3 ± 18.7	0.94	Not significant
INR	0.89–1.6	1.05 ± 0.17	0.8–3.2	1.11 ± 0.39	0.56	Not significant
FBS (mg/dl)	75–170	105.3 ± 26.7	60–342	98.7 ± 37.4	0.11	Not significant

ALP, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; PC, prothrombin concentration; PLT, platelet; PT, prothrombin time; TG, triglycerides; WBCs, white blood cells.

Table 8 A comparison between both groups regarding their immune profile

	Group 1 (n = 13) [n (%)]	Group 2 (n = 187) [n (%)]	P value	Significance
Positive ANA	13 (100)	182 (97.3)	1	Not significant
Positive DNA	10 (76.9)	154 (82.4)	0.7	Not significant
Consumed C3	3 (23.1)	48 (25.7)	1	Not significant
Consumed C4	2 (15.4)	36 (19.3)	1	Not significant

ANA, antinuclear antibodies; C3, complement 3; C4, complement 4.

hepatomegaly. Their SLEDAI scores were 12 and 5.

(3) Antimitochondrial antibodies were tested to exclude primary biliary cirrhosis and was negative in all patients.
(4) Abdominal U/S performed on patients showed bright hepatomegaly in five patients (38.5%), fatty liver in five patients (38.5), hepatosplenomegaly in two patients (15.4%), ascites in two patients (15.4%), and gall bladder stone in one patient (7.7%).
(5) The antiphospholipid profile of patients revealed the following:
    (a) Anticardiolipin IgG positive in four patients (30.8%) and IgM positive in three patients (23.1%).
    (b) Lupus anticoagulant positive in two patients (15.4%).
    (c) Anti-B_2 glycoprotein positive in three patients (23.1%).
    (d) Three patients (23.1%) were diagnosed to have antiphospholipid syndrome. Their abdominal U/S showed two patients with fatty hepatomegaly and one patient with bright hepatomegaly but no evidence of vascular occlusion.
(6) In addition to the drugs mentioned above, our patients were found to use other drugs as follows: one patient (7.7%) was receiving statin, one patient (7.7%) was receiving an anticoagulant, one patient (7.7) was receiving an antiepileptic and two patients (15.2%) were receiving antipsychotics. All these drugs are hepatotoxic. Their abdominal U/S showed the following: three patients with bright hepatomegaly, two patients with fatty hepatomegaly, and one patient with ascites.
(7) CPK was within normal levels for all patients.

Discussion

SLE may be associated with liver abnormalities secondary to the presence of a coexisting autoimmune liver disease (particularly primary biliary cirrhosis or AIH), the direct involvement of the liver parenchyma or the impact of medical treatments on the liver [2].

Numerous histopathological patterns can be found in liver biopsies of SLE patients, including small-artery vasculitis reported in up to 21% of the patients, nonalcoholic fatty liver diseases in 20–73%, nodular regenerative hyperplasia in 5.7%, chronic persistent or active hepatitis in 2.4%, and cirrhosis in 1.1% or fibrosis

Table 9 Investigations carried out in group 1

Investigations	*n* (%)
Viral hepatitis	2 (15.4)
HCV	Low viremia [1 (7.7)]
PCR	Below DL [1 (7.7)]
HBV	0 (0)
HAV	0 (0)
Criteria of AIH	
Positive ANA	13 (100)
Positive ASMA	3 (23)
Positive ALKMA	0 (0)
Elevated IgG	2 (15.4)
Absence of viral hepatitis	11 (84.6)
AMA	0 (0)
U/S findings	
Bright hepatomegaly	5 (38.5)
Fatty liver	5 (38.5)
HSM	2 (15.4)
Ascites	2 (15.4)
Gall bladder stone	1 (7.7)
APL profile	
Anticardiolipin IgG	4 (30.8)
Anticardiolipin IgM	3 (23.1)
Lupus anticoagulant	2 (15.4)
Anti-B_2 glycoprotein	3 (23.1)
Antiphospholipid syndrome	3 (23.1)
Other used drugs	
Statins	1 (7.7)
Anticoagulants	1 (7.7)
Antipsychotic	2 (15.2)
Antiepileptic	1 (7.7)

AIH, autoimmune hepatitis; ALKMA, anti-liver–kidney microsomal antibodies; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; APL, antiphospholipid; ASMA, antismooth muscle antibodies; DL, detection limit; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSM, hepatosplenomegaly; IgG, immunoglobulin G; IgM, immunoglobulin M; U/S, ultrasound.

in 0.8% [5]. Moreover, cases of giant cell hepatitis, granulomatous hepatitis, massive hepatic necrosis, cholangitis, isolated portal hypertension, the Budd–Chiari syndrome, and liver infarction have also been described. End-stage liver disease is a very infrequent finding, whereas cases of Budd–Chiari syndrome have been reported in association with the antiphospholipid syndrome. Moreover, antiphospholipid antibodies have been shown to be involved in small-artery intrahepatic damage and in the pathogenesis of nodular regenerative hyperplasia [3].

Abnormal liver function tests are common in patients with SLE — being reported in 3–29% of the patients [3], often during disease exacerbations, and 4.4% of patients with SLE may have serious chronic liver diseases, including chronic active hepatitis and liver cirrhosis. The most common liver histologic manifestation of SLE is steatosis, which may not be associated with corticosteroid therapy.

In this study, 13 patients (out of 200) had levels of one or more liver enzymes elevated above their normal levels, with a prevalence of 6.5%.

This prevalence is nearly similar to that in a study conducted by Huang *et al.* [9] in which the prevalence of elevated liver enzymes in SLE patients was 8.7%.

Our study was different from that conducted by Khalifa *et al.* [10], in which the prevalence of elevated liver enzymes was 15%.

There is also disagreement with the study conducted by Efe *et al.* [11]; this study included 147 SLE patients, and 36 (24.5%) of them had abnormal liver enzymes.

In a study conducted by Her *et al.* [12], the prevalence of elevated liver enzymes in SLE patients was 32.6%.

Also, in a study conducted by Bruce *et al.* [13], out of 238 SLE patients, 43 (21%) had elevated liver enzymes.

This difference between this study and other studies may be due to the difference in inclusion criteria as they added bilirubin, lactate dehydrogenase, and prothrombin time and concentration to the items of liver affection; it may be also due to the fact that most of our patients were receiving immunosuppression and all of them were receiving steroids; this may cause a masking of manifestations of liver affection in some diseases such as AIH, SLE hepatitis, and primary biliary cirrhosis. Also, in these studies, patients had a long duration of follow-up, and so liver affection had more chance to be detected.

In this study, comparison between SLE patients with and without elevated liver enzymes revealed that there were no significant differences regarding demographic data (age, sex, age of onset, disease duration, BMI, hypertension, and diabetes mellitus).

However, BMI, hypertension, and diabetes mellitus were more frequent in patients with elevated liver enzymes than in those with normal liver enzymes; this relatively agrees with Huang *et al.* [9], who reported a statistically significant difference between both groups regarding these items.

Disease activity was assessed using the SLEDAI score and there was no significant difference between both groups regarding the mean of the SLEDAI score, which agrees with Huang *et al.* [9].

Patients were divided into two groups: group 1 with elevated levels of one or more liver enzymes and group 2 with normal liver enzymes.

On comparing both groups regarding their demographic data, we found no statistically significant differences between both groups.

However, the mean of BMI in group 1 was higher than in group 2, but with no statistical significance ($P = 0.52$); hypertension was more frequent in group 1 (61.5%) than in group 2 (51.9%), but this difference also did not reach statistical significance ($P = 0.57$); also, diabetes was more frequent in group 1 (15.4%) than in group 2 (9.1%) with no statistically significant difference between both groups ($P = 0.3$). This relatively agrees with Huang *et al.* [9] who reported that hypertension is more frequent in patients with elevated liver enzymes than in those with normal liver enzymes ($P = 0.03$), and that BMI was higher in patients with elevated liver enzymes than in those with normal liver enzymes ($P = 0.04$), but they reported a statistically significant difference between both groups in both hypertension and BMI. Also, diabetes was more frequent in patients with elevated liver enzymes than in those with normal liver enzymes with no statistical significance ($P = 0.34$). Hypertension, diabetes mellitus, and increased BMI, as a part of the metabolic syndrome, may predispose one to alteration of liver enzymes by increased risk of development of fatty liver [9].

The SLEDAI score in group 1 ranged from 2 to 22, with a mean of 10.23 ± 6.55. In group 2, it ranged from 2 to 50, with a mean of 11.29 ± 7.17. There was no significant difference in the mean of SLEDAI scores between both groups ($P = 0.59$). This was in agreement with Huang *et al.* [9] who reported that there was no statistical difference between patients with elevated liver enzymes and those with normal liver enzymes in the mean of SLEDAI scores ($P = 0.9$).

Regarding the immune profile of our patients, there were no significant differences between both groups in ANA, anti-dsDNA, C3, and C4, and this agreed with Huang *et al.* [9] who reported no significant differences between patients with elevated liver enzymes and those with normal liver enzymes in their immune profile.

In the current work, laboratory data of our patients revealed a highly significant difference between group 1 and group 2 in their liver enzymes: ALT ($P = 0.00$), AST ($P = 0.00$), ALP ($P = 0.004$), and GGT ($P = 0.006$). This was in agreement with Huang *et al.* [9] who also reported a highly significant difference between both groups in their liver enzymes: ALT ($P = 0.001$), AST ($P = 0.018$), and ALP ($P = 0.015$).

In the current work, laboratory data also reported that hyperlipidemia was more frequent in group 1 (53.8%) than in group 2 (34.7%), but this difference did not reach statistical significance ($P = 0.27$), which agreed with Huang *et al.* [9] who reported higher plasma cholesterol and triglyceride levels in patients with elevated liver enzymes than in those with normal liver enzymes.

Regarding drugs received by our patients, all patients in group 1 and group 2 were receiving steroids; all patients in group 1 were receiving immunosuppression, 69.2% were receiving AZA, and 30.8% were receiving CYC, and in group 2, about 80% of patients were receiving immunosuppression, 55.6% were receiving AZA, 15.5% were receiving CYC, and 11% were receiving MMF. The difference between both groups in the use of immunosuppression did not reach statistical significance. This did not agree with Huang *et al.* [9] who reported a statistically significant difference in the use of immunosuppression between patients with normal liver enzymes and those with elevated liver enzymes, and that a larger number of patients with elevated liver enzymes received AZA and methotrexate compared with patients with normal liver enzymes. This difference between both studies may be due to the fact that a larger number of our patients were receiving immunosuppression (more than 80%), whereas in the other study, only 60% of the patients were receiving immunosuppression.

Patients in group 1 who had elevated levels of one or more liver enzymes were subjected to further investigations.

These investigations revealed the following.

There were two patients, out of the 13 patients with elevated liver enzymes, 15.4% suffering from HCV infection. This percentage was nearly similar to that in a study conducted by El-Garf *et al.* [14] to determine the prevalence of HCV infection in SLE patients, which included 98 patients known to have SLE, and all of them were screened for HCV infection: 20 patients (20.4%) were found to have positive tests for HCV antibodies.

The percentage of AIH was nearly similar to that in the study conducted by Efe *et al.* [11] who studied AIH in patients with SLE; this study included 147 SLE patients: 36 of them had elevated liver enzymes, and 19.4% of those with elevated liver enzymes proved to have AIH; also, it was similar to the study conducted by Vaidehi *et al.*, [15] which included 40 SLE patients with abnormal liver enzymes: six (15%) of them proved to have AIH.

Results of U/S were comparable to that in the study conducted by Huang *et al.* [9] who reported fatty liver in 41% of SLE patients with elevated liver enzymes

by U/S. Also, the results were comparable to the study conducted by Khalifa *et al.* [10] who reported hepatomegaly in 33% of SLE patients with elevated liver enzymes; they reported ascites in 16.6% of patients. In a study conducted by Bruce *et al.* [13], 238 SLE patients were included in the study, and 43 (21%) had liver affection: among those with liver affection, 39% had hepatomegaly and 6% had splenomegaly.

In our study, six patients had no obvious cause for elevated liver enzymes other than SLE and drugs: four of them (30.8%) had a history of recent drug use.

One patient had a history of recent use of statins, and there are several forms of side effects attributed to the use of atorvastatin, as reported by Liu *et al.* [16], including hepatocellular injury, cholestatic injury, a mixed pattern of atorvastatin-associated hepatocellular and cholestatic injury, autoimmune-type reaction, and fulminant liver failure.

There was also one patient with a history of recent use of phenytoin, and as reported by Altuntas *et al.* [17], increased γ-glutamyl transferase and SAP levels are very often observed in the absence of hepatic injury among people taking phenytoin; acute hepatitis, including severe cholestatic hepatitis, is a very rare but important side effect of phenytoin.

There were two patients with a history of recent use of antipsychotic drugs; Jeffrey and Allan [18] reported that asymptomatic mild transient elevation of liver enzymes occurs infrequently with both first-generation and second-generation antipsychotic drugs. These drugs include chlorpromazine, haloperidol, risperidone, quetiapex, clozapine, and tricyclic antidepressants [19].

Hence, liver enzyme abnormalities in those four patients out of the 13 with elevated liver enzymes (30.8%) could be attributed to drugs. This result was comparable to that in the study conducted by Her *et al.* [12] who studied 141 SLE patients, and 46 (32%) of them had abnormal liver enzymes and 11 (24%) of them had drug-induced hepatitis.

It was also similar to the study conducted by Huang *et al.* [9] in which the prevalence of drug-induced hepatotoxicity was 26% (35 out of 134 SLE patients with elevated liver enzymes).

In the other two patients (15.4%), there were no causes of liver enzyme abnormalities other than SLE itself, and this differs from the study conducted by Piga *et al.* [20], which included 242 SLE patients, and of them, 45 (18.6%) had elevated liver enzymes, and 14 of them (31%) were due to SLE. It also differs from the study conducted by Caramaschi *et al.* [21] who studied 86 SLE patients for liver affection, and there were 20 patients (23%) with liver abnormalities; 14 (70%) of them proved to be due to lupus activity.

This difference between our study and other studies may be due to the fewer number of patients who had elevated liver enzymes, and may also be due to the fact that all of our patients were receiving steroids and immunosuppression, and so only two of our SLE patients with elevated liver enzymes had severe activity and the remaining 11 patients had mild to moderate activity according to their SLEDAI score.

Conclusion

(1) In the current study, the prevalence of elevated liver enzymes in patients with SLE (attending the Rheumatology and Rehabilitation Department, Cairo University) was found to be 6.5%.
(2) The most common liver abnormality found in SLE patients who had elevated liver enzymes was fatty liver, affecting 38.5% of the patients. Drug-induced hepatotoxicity was found to affect 30.8% of the patients, and HCV, AIH, and SLE were found to affect 15.4% for each cause.

Recommendations

(1) Observation of liver enzymes in SLE patients is very important as alteration in liver enzymes in SLE is not uncommon and it indicates an underlying liver affection.
(2) Close observation of drugs received by SLE patients is recommended (especially in those with liver affection).
(3) Control of dyslipidemia, hypertension, and diabetes mellitus in patients with SLE is recommended to decrease the frequency of fatty liver.

Acknowledgements

Conflicts of interest

None declared.

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