SUPPLEMENTAL MATERIALS

Supplemental Tables S1-S4

Supplemental Figures S1-S3

Table S1. Prevalence of diabetes relative to LD in SLE. P values reflect two-tailed χ^2 test relative to normal LFT cohorts.

Diabetes	**Normal LFT**	**iLD**	**LD**	**iLD + LD**
All patients				
Present	11	8	8	16
Absent	208	118	82	200
P value		0.4204	0.6291	0.3267
Males				
Present	1	0	0	0
Absent	15	8	15	23
P value		1.0000	1.0000	0.4103
Females				
Present	10	8	8	16
Absent	193	118	67	185
P value		0.6226	0.1006	0.2304

Table S2. Increased proteinuria in anti-DNA antibody-positive SLE patients. P values reflect two-tailed χ^2 test.

	Anti-DNA (+)	Anti-DNA (-)	P value
Proteinuria (+)	14	29	*0.003*
Proteinuria (-)	36	235	

Table S3. Prevalence of LD disease in SLE with respect to use of rapamycin (Rapa) and N-acetylcysteine (NAC) relative to conventional immunosuppressant medications: azatioprine (AZA), cyclosporine A (CsA) and cyclophosphamide (CTX). P values reflect analyses with two-tailed Fisher's exact test.

	Normal LFT	LD	p
Rapa	6	0	
AZA	6	7	0.0237
CsA	1	4	0.0060
CTX	0	2	0.0047
NAC	4	0	
AZA	6	7	0.0557
CsA	1	4	0.0164
CTX	0	2	0.0143

Table S4: Comparison of studies on LD in SLE

Year/Reference	N	LD Pre	LD Criteria	Alcohol excluded	Hepatitis excluded	Drug associations	Immunological Associations	Additional Notes	Adjusted LD Pre
1980/[1]	206	20.9%	2 fold > ULN in 4 determinations of total bilirubin, AST, ALT, LDH, or ALP. At least 2 other tests had to be abnormal	No	No	Salicylates & steroids used more by patients without LD	LD associated with mucosal ulcer, arthritis, cytopenia, and thyroid disease	Did not exclude patients with previous history of liver disease. LD sometimes noted 4 years before SLE diagnosis. 45% of LD and SLE were noted in the same year	N/A
1981/[2]	81	55%	Elevation in AST, ALT, ALP, or serum bilirubin	No	No	N/A	N/A	Excluded patients with previous history of liver disease. Number of LD with heart failure, salicylate hepatotoxicity, and non-hepatic pathologies noted	8.6%
1984/[3]	260	23%	Elevation in AST, ALT, or ALP	Yes	No	NSAIDs (excluding aspirin), AZA, & corticosteroids did not result in abnormal LFTS or worsen pre-existing conditions	AST was concordant with SLE disease activity	Excluded SLE patients with haemolysis and myositis. Number of LD with salicylate hepatotoxicity, hepatitis B (no HCV), heart failure, and alcohol noted	10.0%
2010/[4]	242	18.6%	3 month Sustained LFT elevation or confirmed on 2 consecutive visits	No	No	Prednisone associated to LD normalization	Prevalence of serological and clinical SLE markers reported for lupus hepatitis group	Number of LD due to lupus hepatitis, drug toxicity, AIH, NAFLD, and viral/alcoholic hepatitis noted	6.6%
2011/[5]	141	32.6%	2-fold >ULN in 2: AST, ALT, bilirubin, LDH, or ALP	No	No	Herbal & anti-Tb medication associated with toxic hepatitis (5 fold increase > ULN in LFTs)	Prevalence of ANA, immunologic, renal, & hematologic involvement reported	Number of LD due to myositis, hemolytic anemia, and myocarditis noted	24.0%
2013/[6]	504	9.3%	Elevation in AST, ALT, ALP, GGT, or total bilirubin	Yes	Yes	89.4% LD normalized after immuno-regulatory treatment	LD associated with hypcomplementemia, SMA, ↑IgA, and ↑IgM	LD patients demonstrated hepatomegaly, cirrhosis, & liver atrophy	7.4%
2013/[7]	206	59.7%	Elevation in 2: AST, ALT, GGT, or ALP	No	No	31.7% of LD identified to be drug induced, with antibiotics being the main culprit	Mean WBC, CH50, anti-dsDNA antibody, & SLEDAI were not significantly different btw LD and normal	Number of patients with LD caused by alcohol, HCV noted	29.7%
Present study	435	20.7%	2-fold ≥ ULN AST or ALT	Yes	Yes	Prednisone associated to LD normalization.	LD associated with SMA, proteinuria, anti-DNA antibodies, hypocomplementemia, leukopenia, thrombocytopenia. SLEDAI was higher in LD	Separated SLE patients into 2 levels of liver dysfunction to better detect differences. Excluded patients with alcohol abuse, viral hepatitis, HIV, parvovirus B19, and thyroid disease. Compared drugs taken during time of LD and time of normalization to assess hepatotoxicity of immunosuppressants.	20.7%

Abbreviations: LD, liver disease; LD Pre, LD Prevalence; Adjusted LD Pre, Adjusted LD Prevalence that has been calculated based on our study criteria; ULN, upper limit of normal; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; GGT: γ-glutamyl transpeptidase; AZA: azathioprine; Anti-Tb: anti-tuberculosis drugs;

References cited in Table S4

1. Runyon BA, LaBrecque DR, Anuras S. The spectrum of liver disease in systemic lupus erythematosus. Report of 33 histologically-proved cases and review of the literature. *Am.J.Med.* 1980;**69**:187-94.

2. Gibson T,.Myers AR. Subclinical liver disease in systemic lupus erythematosus. *J.Rheumatol.* 1981;**8**:752-9.

3. Miller MH, Urowitz MB, Gladman DD *et al*. The liver in systemic lupus erythematosus. *Q.J.Med.* 1984;**53**:401-9.

4. Piga M, Vacca AF, Porru GF *et al*. Liver involvement in systemic lupus erythematosus: incidence, clinical course and outcome of lupus hepatitis. *Clin.Exp.Rheumatol.* 2010;**28**:504-10.

5. Her M, Lee Y, Jung E *et al*. Liver enzyme abnormalities in systemic lupus erythematosus: a focus on toxic hepatitis. *Rheumatol Int* 2011;**31**:79-84.

6. Zheng RH, Wang JH, Wang SB *et al*. Clinical and immunopathological features of patients with lupus hepatitis. *Chin.Med.J.* 2013;**126**:260-6.

7. Takahashi A, Abe K, Saito R *et al*. Liver Dysfunction in Patients with Systemic Lupus Erythematosus. *Intern.Med.* 2013;**52**:1461-5.

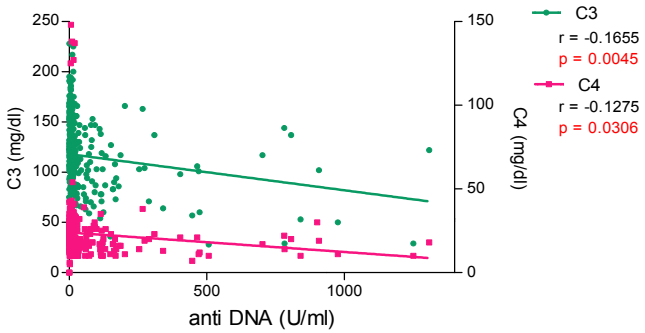
LEGENDS TO SUPPLEMENTAL FIGURES

Figure S1. Inverse correlation of anti-DNA antibody titers with hypocomplementemia C3 and C4 in 435 patients with SLE. Pearson r values and corresponding two-tailed p values are indicated each correlation dot plot.

Figure S2. Liver biopsy of 53-year-old Caucasian female. Hematoxylin and eosin staining revealed mild, chronic portal inflammation at 10-fold (panel A), 20-fold (panel-B), and 40-fold original magnifications (panels C and D). Areas of inflammation are demarcated by rectangles. Infiltrating eosinophils (Eo, panel C) and lymphocytes (Ly, panel D) and plasma cells (PC, panel D) are indicated with arrows. Mallory bodies are shown in panel E. Macro and microvesicular fat vacuoles and steatosis are evident in panels E and F. Reticulin (panels G and H) and trichrome staining no significant fibrosis or change in tissue architecture (panel I).

Figure S3. Histological evidence of inflammation in liver biopsy of a 29-year-old Caucasian female lupus patient with LD. Hematoxylin and eosin staining revealed massive inflammatory cell infiltrates at 4-fold, 10-fold, at 40-fold original magnifications (panels A-C). Infiltrating lymphocytes (Ly), plasma cells (PC) and eosinophils (Eo) are indicated with arrows in panel C. Reticulin stain demonstrates the loss of tissue architecture in the area of lymphocytic infiltration (panel D). Trichrome staining shows aberrant mitotic figures (panel E) and apoptotic hepatocyte (panel F). Bile duct proliferation is noted within areas of lymphocytic infiltration at 4-fold, 10-fold, at 40-fold original magnifications (panels G-I). Bile duct cell with mitotic figures (MF) is marked by arrow.

Figure S1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p = 0.0045
C4
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p = 0.0306
C3 (mg/dl)
C4 (mg/dl)
anti DNA (U/ml)
250
200
150
100
50
0
150
100
50
0
0
500
1000

Figure S2

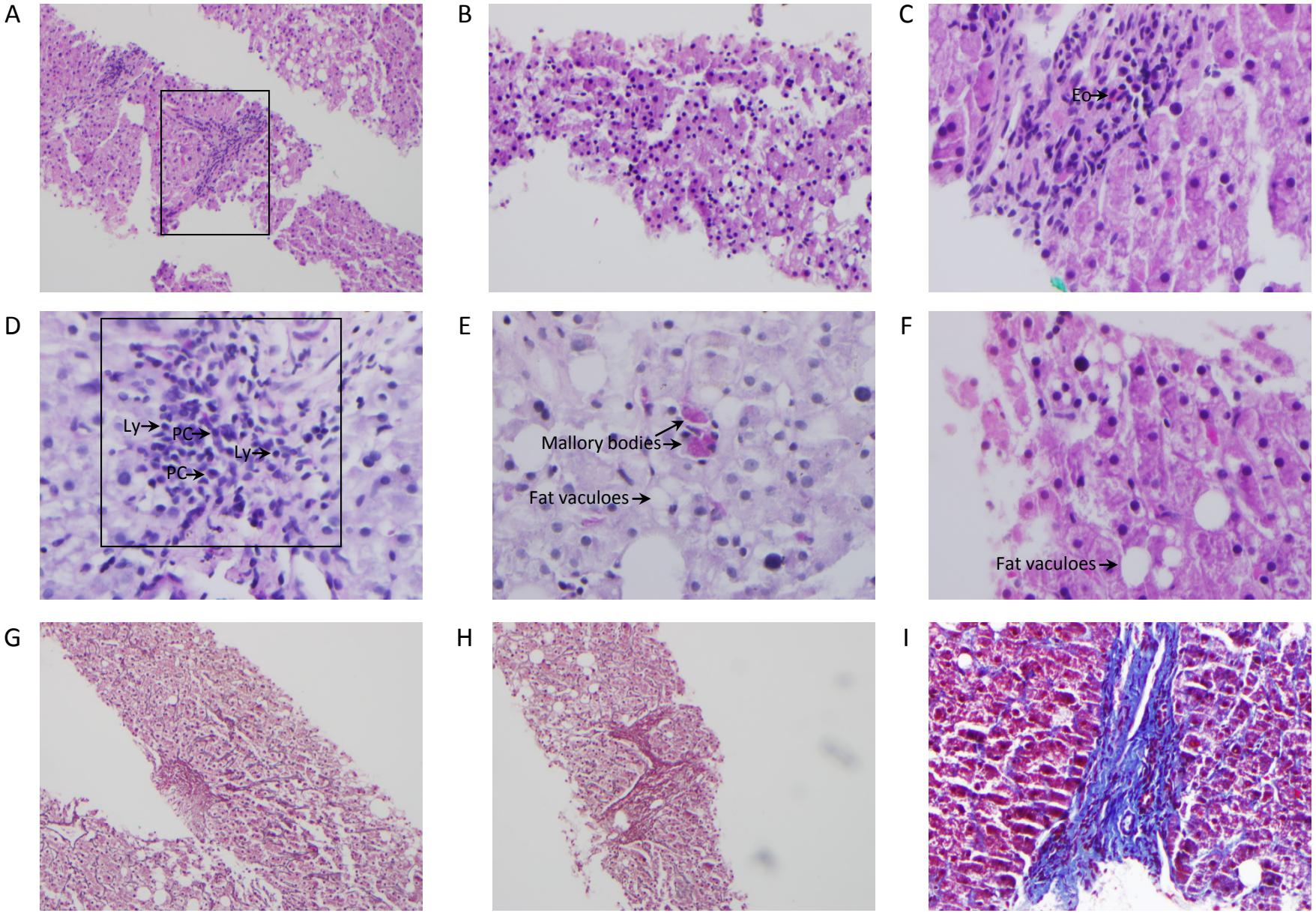
A
B
C
Eo
D
Ly
PC
Ly
PC
E
Mallory bodies
Fat vaculoes
F
Fat vaculoes
G
H
I

Figure S3