

Longitudinal Evaluation of Lipoprotein Variables in Systemic Lupus Erythematosus Reveals Adverse Changes with Disease Activity and Prednisone and More Favorable Profiles with Hydroxychloroquine Therapy

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ABSTRACT. Objective. Systemic lupus erythematosus (SLE) is associated with accelerated atherosclerotic cardiovascular disease. Patients with SLE have adverse lipoprotein variables, but little is known about how these change with treatment and disease activity. The nuclear magnetic resonance LipoProfile test contains a glycoprotein signal—termed GlycA, an inflammatory marker, which has not been evaluated in SLE. We assessed patients longitudinally to determine how lipoproteins and GlycA change with active SLE.

Methods. Sera from selected clinical visits of patients in the Hopkins Lupus Cohort were analyzed for lipoprotein and GlycA levels. Univariate and multivariate analyses were performed to evaluate lipoprotein variables and their relationship to ethnicity, disease activity, prednisone use, and hydroxychloroquine (HCQ) therapy.

Results. Fifty-two patients were included over 229 visits. Adverse changes in lipoprotein variables with disease activity were demonstrated. For each point increase in the Systemic Lupus Erythematosus Disease Activity Index, there was a decrease in high-density lipoprotein (HDL) even after adjusting for corticosteroid use. Prednisone was associated with higher very low-density lipoprotein, low-density lipoprotein, HDL, and triglycerides. HCQ was associated with more favorable variables. GlycA levels were higher than in normal populations and increased with disease activity.

Conclusion. Adverse changes in lipoprotein profiles were associated with SLE activity and prednisone therapy. This gives insight into mechanisms of atherosclerosis in SLE. Favorable lipoprotein variables occurred in those taking HCQ. GlycA increased with disease activity and was higher than in healthy populations. (J Rheumatol First Release February 1 2016; doi:10.3899/jrheum.150437)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS DYSLIPIDEMIA DISEASE ACTIVITY
NUCLEAR MAGNETIC RESONANCE LIPOPROTEIN PROFILE
GlycA HYDROXYCHLOROQUINE

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Systemic lupus erythematosus (SLE) is associated with accelerated atherosclerotic cardiovascular (CV) disease (CVD) and mortality¹. Epidemiological data indicate a CV risk that is more than 2.66-fold higher than that of Framingham controls. Both SLE and traditional CV risk factors are involved².

Dyslipidemia in the general population, measured by conventional methods, is an important CV risk factor³ and is common in SLE⁴. The conventional lipid abnormalities typically reported in SLE are elevated triglycerides (TGC) and low high-density lipoprotein cholesterol (HDL-C)^{5,6}. Routine lipid measurements do not distinguish between SLE and normal controls, and they do not help identify patients with SLE with atherosclerosis^{7,8,9}. However, conventional

lipid variables seem to worsen with disease activity. Chung, *et al* found a negative correlation between disease activity and HDL-C levels¹⁰. In pediatric patients, higher low-density lipoprotein (LDL) levels are associated with disease activity¹¹. Urquizu-Padilla, *et al*¹² demonstrated a trend toward more atherogenic conventional lipid profiles with disease activity, which reached significance for the total cholesterol/HDL-C ratio only. These studies were cross-sectional and measured only standard lipid variables. A further consideration in the assessment of dyslipidemia is the atheroprotective apolipoprotein A (apoA), which is HDL predominant, and apolipoprotein B (apoB), which is principally LDL-containing and proatherogenic.

Nuclear magnetic resonance (NMR) spectroscopy provides the opportunity to determine the size and concentration of lipoprotein classes and subclasses. It has been used to establish the relationship between lipoproteins and CV risk in many populations^{13,14,15,16,17}. NMR lipoprotein analysis revealed that patients with SLE have larger very LDL (VLDL) particles (VLDL-P) and lower levels of large HDL compared with controls¹⁸. Further, in SLE with established atherosclerosis based on carotid intima-media thickness, the numbers for very small, small, and medium LDL and intermediate-density lipoprotein (IDL) particle (IDL-P) were higher⁹, suggesting pathogenicity. Changes in lipoproteins with disease activity longitudinally have not been evaluated.

Glycosylated proteins can also be measured by NMR. The NMR signal originating from the N-acetyl methyl groups of the N-acetylglucosamine residues located on the carbohydrate chains of circulating acute-phase proteins such as α -1-acid glycoprotein, haptoglobin, α -1 antitrypsin, α -1 acid glycoprotein, and transferrin has been identified as GlycA¹⁹. GlycA performs similarly to high-sensitivity C-reactive protein (hsCRP) in the prediction of CV events in healthy individuals²⁰. In SLE, hsCRP has been associated with organ damage²¹ and has also been shown in some, but not all, studies to change with disease activity^{22,23}. Elevations in CRP have been associated with CV events in healthy populations and in some SLE populations. We have reported that hsCRP strongly associates with obesity, but not with the incidence of myocardial infarction²¹. Here, we examined whether GlycA levels increased with active disease to help establish whether this could be a more useful biomarker in the prediction of CV events in SLE.

Patients with SLE were evaluated longitudinally to assess the association between clinical variables (disease activity and treatment) and both lipoprotein variables and GlycA levels.

MATERIALS AND METHODS

Patients were identified as part of the Hopkins Lupus Cohort. Ours is a prospective study of predictors of flare, atherosclerosis, and health status in SLE. The cohort included all patients at the Hopkins Lupus Center who had a clinical diagnosis of SLE and gave informed consent to participate in the study. Enrolled subjects were followed quarterly or more frequently if clinically necessary. The history, laboratory testing, and damage accrual data were recorded at the time of entry into the cohort and updated at subsequent

visits. The Hopkins Lupus Cohort was approved yearly by the Johns Hopkins University School of Medicine Institutional Review Board and complied with the Health Insurance Portability and Accountability Act.

At each visit, plasma samples were collected and disease activity measured using the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)²⁴. The SELENA-SLEDAI measures SLE disease activity within the preceding 10 days. It includes 24 clinical and laboratory variables weighted by organ system. Disease activity can range from 0–105. Plasma was stored at -70°C .

Our analysis was based on sera selected from multiple visits of 52 patients. Patients and patient visits were selected based on the availability of stored sera. An effort was made to choose patients and visits such that each patient had at least 1 visit with high disease activity and 1 visit with low disease activity. Sera were analyzed for lipoprotein particle and GlycA concentrations using NMR performed on the Vantera Clinical Analyzer following the methods outlined by Otvos, *et al* and Matyus, *et al*^{19,25,26}.

Patients were evaluated longitudinally to determine how lipoprotein variables change with time, treatment, and other clinical variables. Univariate and multivariate analyses were performed using a linear mixed-effects model with a random effect for patient. The relationships between lipoprotein particle size and concentration and the following variables were examined: SLEDAI, ethnicity, prednisone, hydroxychloroquine (HCQ), and renal disease.

RESULTS

We evaluated 52 patients over 229 visits. The demographic

Table 1. Clinical characteristics and demographics.

Characteristics	n (%)
Sex	
Male	3 (6)
Female	49 (94)
Ethnicity	
White	24 (46)
African American	23 (44)
Other	5 (10)
Age, yrs	
< 30	13 (25)
30–44	16 (31)
45–59	16 (31)
60+	7 (13)
Duration of SLE at first assessment, yrs	
< 2	19 (37)
2–5	18 (35)
5+	15 (29)
No. visits	
3	1 (2)
4	43 (83)
5+	8 (15)
Treated with prednisone 10 mg/day or more	
No visits	1 (2)
Some visits	43 (83)
All visits	8 (15)
HCQ therapy	
No visits	14 (27)
Some visits	10 (19)
All visits	28 (54)
History of diabetes	3 (6)
History of hypertension	10 (19)

SLE: systemic lupus erythematosus; HCQ: hydroxychloroquine.

data for the group are outlined in Table 1. The median lag time between visits was 91 days. Eight individuals (15%) were consistently receiving doses of prednisone in excess of 10 mg per day, while 43 (83%) were receiving this dose at some of their visits. Twenty-eight individuals (54%) were consistently taking HCQ, 10 (19%) were taking it at some visits, and 14 (27%) were not taking HCQ at all. In terms of CV risk factors, 3 individuals (6%) had a history of diabetes, 10 (19%) were diabetic, and 17 (33%) were obese.

Based on univariate longitudinal analysis, concentrations of apoB-containing lipoproteins [total LDL and small LDL particles (LDL-P)] increased significantly with each point increase in SLEDAI (Table 2). Decreases in apoA-containing lipoproteins [total HDL particles (HDL-P), large HDL-P, medium HDL-P, and HDL-C] were demonstrated with each point increase in SLEDAI. GlycA increased with each point increase in the SLEDAI. Mean GlycA levels in this cohort were higher than those reported for a normal population¹⁹.

In terms of ethnic differences, African American patients had lower total, medium, and small HDL-P. VLDL size was lower and HDL size was lower. The African American population also had lower VLDL, lower TG, and higher levels of GlycA compared with the other SLE groups.

Prednisone use, per 5 mg change, was associated with significantly higher levels of apoB-containing lipoproteins, including total VLDL-P, medium VLDL, small VLDL-P,

total LDL-P, and IDL-P. Large LDL-P and chylomicrons also increased significantly (Table 2). There was an increase in HDL-P, TGC, VLDL and chylomicron, and in GlycA. In those who were taking HCQ, VLDL-P and chylomicrons were lower, as were small VLDL-P. Total and large HDL-P were higher, as were HDL size and HDL-C. With renal involvement, total and small LDL-P were higher.

After adjustment for other variables in a multivariate model, the positive association between SLEDAI and LDL-P was no longer statistically significant. After this adjustment, however, the negative association between SLEDAI and several HDL variables persisted (Table 3). The positive association between SLEDAI and GlycA also persisted. African American ethnicity remained significantly associated with lower VLDL, LDL, and HDL variables (total VLDL and chylomicrons, large VLDL-P and chylomicrons, medium VLDL-P and VLDL size, total LDL-P, small LDL-P, total HDL-P, medium HDL-P, and small HDL-P). HDL size was higher in this population. There were lower TGC in African American patients and higher GlycA levels. Prednisone use was associated with higher total and large VLDL-P and chylomicrons. Small, medium, and total VLDL-P were increased, as were IDL-P, large LDL-P, and total and small HDL-P. TGC were also increased with each 5-mg increase in prednisone. HCQ therapy was associated with a decrease in VLDL variables and an increase in total HDL, HDL size, and

Table 2. Univariate relationships between clinical characteristics and lipoprotein subtypes.

Lipoprotein Subtypes	SLEDAI, Per 1 Unit Change		African American vs Not		Prednisone Per 5 mg/day Change		HCQ, Yes vs No		Renal Involvement, Yes vs No	
	Mean Change	p	Mean Change	p	Mean Change	p	Mean Change	p	Mean Change	p
Total VLDL-P and chylomicrons	0.07	0.44	-7.6	0.12	3.1	< 0.0001	-10.4	0.018	-1.7	0.67
Large VLDL-P and chylomicrons	-0.003	0.93	-1.46	0.0077	0.09	0.11	-0.8	0.063	-0.003	0.99
Medium VLDL-P	0.10	0.52	-6.04	0.0023	0.47	0.037	-1.2	0.48	0.8	0.55
Small VLDL-P	-0.03	0.93	-0.04	0.99	2.66	< 0.0001	-8.97	0.013	-2.48	0.47
Total LDL-P	12.64	0.022	-148.3	0.076	37.39	< 0.0001	-92.00	0.16	112.14	0.022
IDL-P	-1.04	0.67	4.13	0.87	8.56	0.020	-0.12	0.61	-28.94	0.20
Large LDL-P	1.93	0.60	-39.16	0.51	19.97	0.0005	-31.25	0.47	42.22	0.19
Small LDL-P	12.43	0.0035	-113.5	0.087	9.80	0.15	-37.60	0.45	105.90	0.0049
Total HDL-P	-0.21	0.043	-7.38	0.0002	0.31	0.061	2.47	0.066	-0.33	0.72
Large HDL-P	-0.13	0.019	0.09	0.94	-0.09	0.26	1.68	0.015	-0.51	0.29
Medium HDL-P	-0.27	0.0057	-3.98	0.0010	-0.20	0.20	1.30	0.22	-1.57	0.071
Small HDL-P	0.11	0.29	-3.54	0.016	0.50	0.0025	0.11	0.93	1.35	0.16
VLDL size	-0.02	0.85	-4.13	0.0016	-0.16	0.36	0.21	0.86	0.65	0.52
LDL size	-0.02	0.14	0.12	0.47	0.02	0.50	-0.02	0.86	-0.17	0.10
HDL size	-0.01	0.40	0.37	0.0074	-0.02	0.13	0.26	0.0039	-0.026	0.68
TGC	-0.02	0.97	-24.66	0.0030	3.38	< 0.0001	-12.80	0.067	-0.15	0.98
VLDL and chylomicron TGC, total	-0.01	0.98	-21.23	0.0040	2.80	0.0005	-11.69	0.052	-0.09	0.98
HDL-C	-0.60	0.012	-6.74	0.19	0.08	0.82	6.03	0.045	-1.97	0.33
GlycA	4.15	0.0047	44.14	0.054	6.05	0.0089	-32.56	0.061	21.27	0.10

Significant data are in bold face. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HCQ: hydroxychloroquine, VLDL: very low-density lipoprotein; VLDL-P: VLDL particle; LDL: low-density lipoprotein; LDL-P: LDL particle; IDL-P: intermediate-density lipoprotein particle; HDL: high-density lipoprotein; HDL-P: HDL particle; TGC: triglycerides; NMR: nuclear magnetic resonance; HDL-C: NMR-derived HDL cholesterol.

Table 3. Multivariate relationships between clinical characteristics and lipoprotein subtypes*.

Lipoprotein Subtypes	SLEDAI, Per 1 Unit Change		African American vs Not		Prednisone, Per 5 mg/day Change		HCQ, Yes vs No		Renal Involvement, Yes vs No	
	Mean Change	p	Mean Change	p	Mean Change	p	Mean Change	p	Mean Change	p
Total VLDL-P and chylomicrons	-0.05	0.93	-12.22	0.0051	3.4	<0.0001	-9.0	0.028	-1.8	0.73
Large VLDL-P and chylomicrons	-0.01	0.81	-1.67	0.0021	0.11	0.052	-0.87	0.038	0.16	0.72
Medium VLDL-P	0.02	0.93	-6.84	0.0005	0.54	0.021	-1.55	0.33	1.39	0.42
Small VLDL-P	-0.10	0.84	-3.63	0.32	2.72	<0.0001	-6.93	0.045	-3.26	0.46
Total LDL-P	2.68	0.71	217.24	0.0079	37.18	<0.0001	105.42	0.086	96.82	0.12
IDL-P	0.12	0.97	-1.61	0.95	9.06	0.020	-5.48	0.82	-31.70	0.29
Large LDL-P	-5.48	0.26	-68.73	0.26	21.31	0.0003	-34.45	0.42	69.09	0.11
Small LDL-P	7.59	0.19	-147.0	0.029	7.78	0.25	-55.45	0.27	63.20	0.21
Total HDL-P	-0.42	0.0028	-7.25	0.0002	0.44	0.0075	2.27	0.073	2.32	0.056
Large HDL-P	-0.16	0.023	0.59	0.60	-0.06	0.49	1.75	0.0092	0.68	0.27
Medium HDL-P	-0.25	0.053	-3.45	0.0038	-0.04	0.78	1.38	0.17	0.07	0.95
Small HDL-P	-0.05	0.74	-4.32	0.0042	0.55	0.0013	-0.05	0.96	1.54	0.22
VLDL size	-0.08	0.61	-4.06	0.0030	-0.09	0.62	-0.17	0.88	1.56	0.25
LDL size	-0.01	0.47	0.14	0.43	0.02	0.41	0.003	0.98	-0.11	0.43
HDL size	-0.01	0.49	0.43	0.0030	-0.02	0.096	0.27	0.0024	0.01	0.91
TGC	-0.53	0.50	-30.39	0.0001	4.31	<0.0001	-12.93	0.043	4.30	0.54
VLDL and chylomicron TGC, total	-0.35	0.68	-25.87	0.0002	3.18	0.0001	-12.22	0.030	2.91	0.63
HDL-C	-0.86	0.0042	-5.31	0.29	0.31	0.39	5.87	0.039	4.34	0.093
GlycA	3.87	0.051	30.55	0.18	4.23	0.064	-32.08	0.059	-3.63	0.83

* Each row in the table is a separate multivariate linear model with lipoprotein subtype as the dependent variable, and the column variables as the independent variables. Significant data are in bold face. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HCQ: hydroxychloroquine, VLDL: very low-density lipoprotein; VLDL-P: VLDL particle; LDL: low-density lipoprotein; LDL-P: LDL particle; IDL-P: intermediate-density lipoprotein particle; HDL: high-density lipoprotein; HDL-P: HDL particle; TGC: triglycerides; NMR: nuclear magnetic resonance; HDL-C: NMR-derived HDL cholesterol.

large HDL-P. TGC were decreased by HCQ therapy. Using the multivariate model, none of the previously mentioned associations with renal involvement remained significant.

DISCUSSION

To our knowledge, our study represents the first time that NMR lipoprotein variables have been assessed longitudinally in adults with SLE in relation to SLE disease activity and treatment. Each unit increase in the SLEDAI resulted in an increase in apoB-containing lipoproteins (total and small LDL-P) and a decline in apoB-containing HDL-P, which remained significant in multivariate analysis. Thus, more pathogenic lipoprotein variables occurred with SLE disease activity. In the general population, the atherogenic lipoprotein phenotype is often characterized by elevations in apoB-containing lipoproteins, including VLDL and small LDL-P concentrations, and lower levels of apoA-containing lipoproteins (HDL)²⁷.

Prednisone use is often cited as a key factor in the development of atherosclerosis in SLE and is predictive of damage accrual and CV events². In univariate and multivariate analyses, increases were demonstrated in VLDL variables and TGC with increases in the dose of prednisone. HDL was also shown to increase, predominantly the smaller particles. Increases in VLDL are associated with increased atherosclerosis

in the general population, while HDL elevations are usually considered protective. However, dysfunctional proinflammatory HDL have been found in women with SLE and associated with increased carotid intima-media thickness. Many of the atherogenic changes with disease activity were also influenced by prednisone and did not persist once this was controlled for. In the rheumatoid arthritis literature, prednisone has been shown to increase HDL without other alterations in standard lipid profiles^{28,29}. Given the longterm, robust data inciting prednisone therapy as a significant factor in the development of atherosclerosis and in the incidence of CV events, this increase cannot be considered cardioprotective. The proatherogenic increments may cancel any protective effects of an increase in HDL. In SLE, proinflammatory HDL occurs, which increases the risk of atherosclerosis³⁰.

Patients with SLE have been shown to have larger VLDL-P and lower levels of large HDL-P. Elevated LDL is a well-known risk factor for CVD and the smaller LDL-P are implicated as being more atherogenic^{13,31}. González, *et al*⁹ previously evaluated NMR lipid variables in SLE at a single point in time. They found that chylomicrons, VLDL (total, large, medium, and small), and LDL (very small and small, but not large) were associated with carotid intima-media thickness. In our longitudinal study, we found pathogenic alterations in lipoprotein variables longitudinally with disease

activity. Increased SLE disease activity resulted in an atherogenic lipid profile with a dose-response relationship for every point increase in the SLEDAI. Total LDL-P tended to increase with an increase in TGC with flare. This is in keeping with a previous study where disease activity heralded an increase in TGC⁶.

HCQ therapy is the cornerstone of the medical management of SLE and has been shown to have a beneficial effect on traditional lipid variables in SLE and in other rheumatic diseases^{32,33,34}. In this group, HCQ therapy was associated with lower TGC and VLDL. HDL variables were also higher in those taking HCQ. This is in keeping with a tendency for a more favorable lipid profile in those taking HCQ and may reflect one of the mechanisms by which it prolongs survival.

There were ethnic differences demonstrated with lower VLDL-P total, medium VLDL-P, and small HDL variables in African American patients with SLE. Lower HDL is associated with CV risk, but lower VLDL components are thought to be favorable. There were also lower TGC, which is generally considered protective against CVD. It is unknown whether these cumulative differences contribute to CV risk in this population. The differences persisted on multivariate analysis.

GlycA increased significantly with each point increase in the SLEDAI in both univariate and multivariate analyses. GlycA has been shown to be a marker for CV events in healthy populations²⁰, similar to hsCRP. The levels seen in our study are higher than those demonstrated in normal individuals, in keeping with a population at high risk for atherosclerosis. A limitation in this evaluation of GlycA is that we did not include data on CRP in this population as a comparator. A further limitation in our work is that we did not evaluate statin therapy in this group.

The factors contributing to atherosclerosis in SLE are not fully understood. Herein we demonstrated longitudinally, for the first time in adult SLE, adverse changes in NMR lipoprotein profiles with prednisone therapy and disease activity. Importantly, we also demonstrated improvements in lipoprotein variables with HCQ therapy. GlycA levels, which have been shown to predict CV events, increased with each unit increase in the SLEDAI and were higher than the general population, in keeping with a population at high risk for CV events.

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