Published in final edited form as:

J Rheumatol. 2016 April ; 43(4): 745–750. doi:10.3899/jrheum.150437.

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

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Abstract

Objectives—Systemic lupus erythematosus (SLE) associates with accelerated atherosclerotic cardiovascular disease. SLE patients have adverse lipoprotein parameters, but little is known about how these change with treatment and disease activity. The NMR 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 parameters and their relationship to ethnicity, disease activity, prednisone use and hydroxychloroquine therapy.

Results—52 patients were included over 229 visits. Adverse changes in lipoprotein parameters with disease activity were demonstrated. For each point increase in SLEDAI there was a decrease in high-density lipoprotein (HDL) even after adjusting for corticosteroid use. Prednisone associated with higher VLDL, LDL, HDL and triglycerides. Hydroxychloroquine associated with more favorable parameters. GlycA levels were higher than in normal populations and increased with disease activity.

Conclusion—Adverse changes in lipoprotein profiles associated with SLE activity and prednisone therapy. This gives insight into mechanisms of atherosclerosis in SLE. Favorable lipoprotein parameters occurred in those taking hydroxychloroquine. GlycA increased with disease activity and was higher than in healthy populations.

Keywords

Systemic lupus erythematosus; Dyslipidemia; Disease activity; NMR lipoprotein profile; GlycA; Hydroxychloroquine

Introduction

Systemic lupus erythematosus (SLE) associates with accelerated atherosclerotic cardiovascular disease and mortality (1). Epidemiological data indicate a cardiovascular risk which is more than 2.66 fold higher than Framingham controls. Both SLE and traditional cardiovascular risk factors play a role (2).

Dyslipidemia in the general population, measured by conventional methods, is an important cardiovascular risk factor (3) and is common in SLE (4). The conventional lipid abnormalities typically reported in SLE are elevated triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) (5, 6). Routine lipid measurements do not distinguish between lupus and normal controls, nor do they help identify lupus patients with atherosclerosis (7-9). However, conventional lipid parameters seem to worsen with disease activity. Chung *et al* found a negative correlation between disease activity and HDL-C levels (10). In pediatric patients higher low-density lipoprotein (LDL) levels associated with disease activity (11). Urquizu-Padilla *et al* (12) demonstrated a trend toward more atherogenic conventional lipid profiles with disease activity, which reached significance for the total cholesterol (TC)/HDL-C ratio only. These studies were cross-sectional and measured only standard lipid parameters. A further consideration in the assessment of dyslipidemia, is the atheroprotective apolipoprotein A (apoA), which are HDL predominant and apolipoprotein B (apoB) which are 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 cardiovascular risk in many populations (13-17). NMR lipoprotein analysis revealed that SLE patients have larger very low density lipoprotein (VLDL) particles and lower levels of large HDL compared to controls (18). Further, in SLE, with established atherosclerosis based on carotid intimal medial thickness, very small, small and medium LDL and IDL particle numbers were higher (9), 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 alpha 1-acid glycoprotein, haptoglobin, alpha 1 anti trypsin, alpha 1 acid glycoprotein and transferrin has been identified as GlycA (19). GlycA performs similarly to high sensitivity C reactive protein (hsCRP) in the prediction of cardiovascular events in healthy individuals (20). In SLE, hsCRP has been associated with organ damage (21) 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 cardiovascular 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 infarction (21). 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 cardiovascular events in lupus.

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

Methods

Patients were identified as part of the Hopkins Lupus Cohort. This is a prospective study of predictors of flare, atherosclerosis, and health status in SLE. The cohort includes all patients at the Hopkins Lupus Center who have a clinical diagnosis of SLE and give informed consent to participate in the study. Enrolled subjects are followed quarterly or more frequently if clinically necessary. The history, laboratory testing, and damage accrual data are recorded at the time of entry into the cohort and updated at subsequent visits. The Hopkins Lupus Cohort has been approved yearly by the Johns Hopkins University School of Medicine Institutional Review Board and complies with the Health Insurance Portability and Accountability Act.

At each visit, plasma samples were collected and disease activity measured using the SELENA revision of the Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI score (SELENA-SLEDAI)(24). The SELENA- SLEDAI measures lupus 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 degrees.

This 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 has at least one visit with high disease activity and one visit with low disease activity. Sera were analyzed for lipoprotein particle and GlycA concentrations using NMR performed on the Vantera Clinical Analyzer using the methods outlined by Otvos *et al* and Matyus *et al* (19, 25, 26). Patients were evaluated longitudinally to determine how lipoprotein parameters 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, and renal disease.

Results

We evaluated 52 patients over 229 visits. The demographic data for the group are outlined in Table 1. The median lag time between visits was 91 days. Eight individuals (15%) were consistently on doses of prednisone in excess of 10 mg per day, whilst 15 (29%) were on this dose at some of their visits. Twenty-eight individuals (54%) were consistently taking hydroxychloroquine, 10 (19%) were taking it at some visits and 14 (27%) were not taking hydroxychloroquine at all. In terms of cardiovascular 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-P) increased significantly with each point increase in SLEDAI (Table 2). Decreases in apoA-containing lipoproteins (total HDL-P, large HDL-P, medium

HDL-P and HDL-C) were demonstrated with each point SLEDAI increase. GlycA increased with each point increase in SLEDAI. Mean GlycA levels in this cohort were higher than those reported for a normal population (19).

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, triglycerides and higher levels of GlycA compared to 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, triglycerides, VLDL and chylomicron and in GlycA. In those who were taking hydroxychloroquine, VLDL-P and chylomicrons were lower, as were small VLDL-P. Total and large HDL-P were higher as was 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 particles was no longer statistically significant. After this adjustment, however, the negative association between SLEDAI and several HDL parameters persisted (Table 3.). The positive association between SLEDAI and GlycA also persisted. African American ethnicity remained significantly associated with lower VLDL, LDL and HDL parameters (total VLDL & chylomicrons, large VLDL-P & 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 triglycerides 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. Triglycerides were also increased with each 5 mg increase in prednisone. Hydroxychloroquine therapy was associated with a decrease in VLDL parameters and an increase in total HDL, HDL size and large HDL-P. Triglycerides were decreased by hydroxychloroquine therapy. Using the multivariate model, none of the previously mentioned associations with renal involvement remained significant.

Discussion

This study represents the first time that NMR lipoprotein parameters have been assessed longitudinally in adults with SLE in relation to lupus disease activity and treatment. Each unit increase in SLEDAI resulted in an increase in apoB-containing lipoproteins (total and small LDL-P) and a decline in apoB-containing HDL particles, which remained significant in multivariate analysis. Thus, more pathogenic lipoprotein parameters 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 particle 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 cardiovascular events (2). In univariate and

multivariate analyses, increases were demonstrated in VLDL parameters and triglycerides 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, whilst HDL elevations are usually considered protective. However, dysfunctional proinflammatory HDL have been found in women in SLE and associated with increased carotid intima medial 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 long-term, robust data inciting prednisone therapy as a significant factor in the development of atherosclerosis and in the incidence of cardiovascular events, this increase cannot be considered as being cardio-protective. The proatherogenic increments may cancel any protective effects of an increase in HDL. In SLE, proinflammatory HDL occurs which increases the risk of atherosclerosis (30).

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 cardiovascular disease and the smaller LDL particles are implicated as being more atherogenic (13, 31). Gonzalez *et al* (9) previously evaluated NMR lipid parameters 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 medial thickness. In this longitudinal study, we found pathogenic alterations in lipoprotein parameters longitudinally with disease activity. Increased SLE disease activity resulted in an atherogenic lipid profile with a dose response relationship for every point increase in SLEDAI. Total LDL-P tended to increase with an increase in triglycerides with flare. This is in keeping with a previous study where disease activity heralded an increase in triglycerides (6).

Hydroxychloroquine therapy is the cornerstone of the medical management of SLE and has been shown to have a beneficial effect on traditional lipid parameters in SLE and in other rheumatic diseases (32-34). In this group, hydroxychloroquine therapy associated with lower triglycerides and VLDL. HDL parameters were also higher in those taking hydroxychloroquine. This is in keeping with a tendency for a more favorable lipid profile in those taking hydroxychloroquine and may reflect one of the mechanisms by which it prolongs survival.

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

GlycA increased significantly with each point increase in SLEDAI in both univariate and multivariate analyses. GlycA has been shown to be a marker for cardiovascular events in healthy populations (20) 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 have not included data on CRP in this population as a comparator. A further limitation in the work is that we have not evaluated statin therapy in this group.

Conclusion

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 parameters with hydroxychloroquine therapy. GlycA levels, which have been shown to predict cardiovascular events, increased with each unit increase in SELDAI and were higher than the general population, in keeping with a population at high risk for cardiovascular events.

Acknowledgments

Support: The Hopkins Lupus Cohort is supported by NIH AR 43727

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Table 1

Clinical characteristics and demographics.

Characteristic		Number (%)
Sex	Male	3 (6)
	Female	49 (94)
Ethnicity	Caucasian	24 (46)
	African American	23 (44)
	Other	5 (10)
Age (years)	<30	13 (25)
	30-44	16 (31)
	45-59	16 (31)
	60+	7 (13)
Duration with SLE at first assessment (years)	<2	19 (37)
	2-5	18 (35)
	5+	15 (29)
Number of visits	3	1 (2)
	4	43 (83)
	5+	8 (15)
Treated with Prednisone 10mg/day or more	No visits	1 (2)
	Some visits	43 (83)
	All visits	8 (15)
Hydroxychloroquine therapy	No visits	14 (27)
	Some visits	10 (19)
	All visits	28 (54)
History of Diabetes		3 (6)
History of Hypertension		10 (19)

Table 2

Univariate relationships between clinical characteristics and lipoprotein subtypes.

Lipo protein Subtype	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-Value	Mean change	P-Value	Mean change	P-Value	Mean change	P-Value	Mean change	P-Value
Total VLDL-P & Chylomicrons	0.07	0.44	-7.6	0.12	3.1	<0.0001	-10.4	0.018	-1.7	0.67
Large VLDL-P & 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
Triglycerides	-0.02	0.97	-24.66	0.0030	3.38	<0.0001	-12.80	0.067	-0.15	0.98
VLDL & Chylomicron triglyceride (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

SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, HCQ= hydroxychloroquine, VLDL= Very low density lipoprotein, LDL= Low density lipoprotein, IDL= Intermediate density lipoprotein, HDL= high density lipoprotein, TG = NMR-derived triglycerides, HDL-C = NMR-derived HDL cholesterol

Table 3

Multivariate relationships between characteristics at a visit lipoprotein subtypes¹.

Lipo protein Sub-type	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-value	Mean Change	P-value	Mean Change	P-value	Mean Change	P-value	Mean Change	P-value
Total VLDL-P & Chylomicrons	-0.05	0.93	-12.22	0.0051	3.4	< 0.0001	-9.0	0.028	-1.8	0.73
Large VLDL-P & 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
Triglycerides	-0.53	0.50	-30.39	0.0001	4.31	< 0.0001	-12.93	0.043	4.30	0.54
VLDL & Chylomicron triglyceride (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

¹ Each row in the table is a separate multivariate linear model with lipo-protein subtype as the dependent variable, and the column variables as the independent variables.

SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, HCQ= hydroxychloroquine, VLDL= Very low density lipoprotein, LDL= Low density lipoprotein, IDL= Intermediate density lipoprotein, HDL= high density lipoprotein, TG = NMR-derived triglycerides, HDL-C = NMR-derived HDL cholesterol