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Association of lipoprotein subfractions and glycoprotein acetylation with coronary plaque burden in SLE

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ABSTRACT

Objective Subjects with SLE display an enhanced risk of atherosclerotic cardiovascular disease (CVD) that is not explained by Framingham risk. This study sought to investigate the utility of nuclear MR (NMR) spectroscopy measurements of serum lipoprotein particle counts and size and glycoprotein acetylation (GlycA) burden to predict coronary atherosclerosis in SLE.

Methods Coronary plaque burden was assessed in SLE subjects and healthy controls using coronary CT angiography. Lipoproteins and GlycA were quantified by NMR spectroscopy.

Results SLE subjects displayed statistically significant decreases in high-density lipoprotein (HDL) particle counts and increased very low-density lipoprotein (VLDL) particle counts compared with controls. Non-calcified coronary plaque burden (NCB) negatively associated with HDL subsets whereas it positively associated with VLDL particle counts in multivariate adjusted models. GlycA was significantly increased in SLE sera compared with controls. In contrast to high-sensitivity C reactive protein, elevations in GlycA in SLE significantly associated with NCB and insulin resistance (IR), though the association with NCB was no longer significant after adjusting for prednisone use.

Conclusions Patients with SLE display a proatherogenic lipoprotein profile that may significantly contribute to the development of premature CVD. The results demonstrate that NMR measures of GlycA and lipoprotein profiles, beyond what is captured in routine clinical labs, could be a useful tool in assessing CVD risk in patients with SLE.

Key messages

- Measures of glycoprotein acetylation (GlycA) and lipoprotein profiles, beyond what is captured in routine clinical labs, could be a useful tool in assessing cardiovascular risk in patients with lupus.
- In patients with lupus, GlycA is a better predictor of insulin resistance than high-sensitivity C reactive protein.

SLE is an autoimmune disorder primarily affecting women of childbearing age that is characterised by immune dysregulation, multiorgan involvement and systemic inflammation. The Framingham Offspring Study estimates that women aged 35–44 years with SLE have a 50-fold increase in the risk of myocardial infarction compared with age-matched and gender-matched women without SLE.[1] Additionally, the Framingham risk equation does not fully account for the enhanced risk of cardiovascular disease (CVD) and CVD mortality in SLE.[2]

Previous studies in SLE cohorts have demonstrated that routine cholesterol measurements, including high-density lipoprotein (HDL) and low-density lipoprotein (LDL), do not differ between SLE and controls or between SLE subjects with or without coronary artery involvement. As such, CVD risk may be better explained by aberrant proatherogenic lipoprotein particle numbers.[3–5] Proton nuclear MR (NMR) spectroscopy is an automated method that quantifies plasma lipoproteins and can be used to determine the size and concentration of lipoprotein particle subfractions in plasma to assess CVD.[6 7] In addition to lipoprotein parameters, NMR also provides quantifications of serum glycoprotein acetylation (GlycA), which is an emerging composite inflammatory biomarker that predicts CV events in other patient populations.[8]

Previous studies have analysed lipoprotein particle subfractions in SLE and found no associations between these subfractions and coronary artery calcification measured via Agatston Scores.[9] However, whether associations exist with non-calcified plaque burden (NCB), typically associated with higher risk of plaque rupture, remains to be determined.[10–12] We now report an analysis of

NMR determinations of lipid subfractions and GlycA and their association with subclinical coronary artery disease in SLE by assessing both calcified burden and NCB.

PATIENTS AND METHODS

Patients

The study protocol was conducted in accordance with principles stated in the Declaration of Helsinki. Subjects were recruited from the National Institute of Arthritis and Muskuloskeletal and Skin Diseases Lupus and Community Health Center clinics. All of the patients fulfilled revised criteria for SLE.[13] Healthy adults were recruited from the National Institutes of Health healthy volunteer cohort. Detailed clinical characteristics and inclusion and exclusion criteria for this cohort have been recently described.[14] In brief, 64 SLE subjects were enrolled in the study, 36 of which underwent coronary CT angiography (CCTA) as those with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73m^2 body surface were excluded from this assessment. A total of 30 controls were included in the study, 18 of which underwent CCTA. Homoeostatic model assessment (HOMA) was used to quantify insulin resistance (IR) (HOMA-IR = ((glucose (nmol/ml)+insulin (µIU/ml))/22.5)).

Coronary CT angiography nuclear MR

CCTA assessment was performed as previously described.[14] Coronary plaque quantifications were controlled for the artery length by dividing total vessel plaque volume by total vessel length.

Nuclear MR

NMR assessment of lipoproteins and GlycA was performed on an FDA approved Vantera clinical NMR analyser (LabCorp, North Carolina, USA). Using the LipoProfile-3 algorithm, the average particle size and concentrations of HDL, LDL and very low density lipoprotein (VLDL) were measured (LabCorp, North Carolina, USA).

Statistical analysis

Statistical analysis was performed using STATA V.12.0 software (STATACorp, College Station, Texas, USA). A p value≤0.05 was considered statistically significant. Normality was assessed on continuous variables by Shapiro-Wilk and by skewness and kurtosis to determine appropriate parametrical or non-parametrical analyses. Descriptive statistics are presented as mean and SD for parametrical data or median and IQR for non-parametrical data. To compare SLE and controls, Student's t-test was used for parametrical data and Mann-Whitney U test was used for non-parametrical data. Standardised univariate and multivariate regressions were performed and β-coefficients and p values were reported. Bonferoni correction was reported for multiple comparisons.

RESULTS

SLE subjects display an atherogenic lipoprotein particle profile

Demographic and clinical characteristics of this cohort have been recently described (table 1).[14] No patient included in the study had nephrotic range proteinuria or proteinuria >500 mg/dL. There were no differences in total cholesterol or triglyceride levels between SLE and controls. However, SLE subjects demonstrated significantly lower levels of HDL cholesterol (54.1±16 mg/dL SLE vs 66.9±16 mg/dL control, p<0.001) and smaller HDL particle size (9.6 nm (9.2–9.9 nm) SLE vs 9.9 nm (9.5–10.1 nm) control, p=0.013) compared with controls (table 2). HDL particle counts were significantly lower in SLE compared with controls (30.0±5.9 umol/L vs 35.0±7.7 umol/L, respectively, p<0.001), and these differences seemed to be accounted by significant decreases in medium and large HDL particle counts in SLE (table 2). LDL cholesterol levels were not significantly different between SLE and controls, but LDL particle count was elevated in SLE (1094.0 nmol/L (871–1220 nmol/L) SLE vs 843.5 nmol/L (675–1219 nmol/L) control, p=0.029). This elevation appeared to be driven by significant increases in small LDL particle count (419.5 nmol/L (211–653 nmol/L) SLE vs 271.0 nmol/L (0–389 nmol/L) control, p=0.027). There were no significant differences in LDL particle size between SLE and controls. SLE subjects demonstrated elevated VLDL triglycerides (59.9 mg/dL (44–87 mg/dL) SLE vs 47.8 mg/dL (36–58 mg/dL) control, p=0.031) and a trend towards increased VLDL particle counts (41.1 nmol/L (29–61 nmol/L) SLE vs 33.3 nmol/L (21–47 nmol/L) control, p=0.067). These differences seemed to be accounted by significant increases in medium and large medium VLDL particle counts (table 2). SLE subjects also demonstrated significantly decreased intermediate-density lipoprotein particle counts compared with controls (53.5 nmol/L (25–124 nmol/L) SLE vs 130.5 nmol/L (62–190 nmol/L) control, p=0.001). There were no differences in VLDL particle size in SLE compared with controls. Overall, SLE subjects displayed a dysregulated lipoprotein particle profile.

NCB significantly associates with atherogenic lipoprotein profiles in SLE

CCTA quantified both dense calcified plaque burden and NCB, the latter being significantly elevated in SLE compared with controls (86±33 mm^2 SLE vs 76±19 mm^2 control, p<0.001), as recently described in this cohort.[14] NCB associated with HDL subfractions whereas dense calcified plaque associated with LDL subfractions. VLDL subfractions associated with both calcified and non-calcified plaque. Specifically, NCB negatively associated with HDL cholesterol (β=−0.331, p=0.001), medium and large HDL particle count (β=−0.214, p=0.029 and β=−0.292, p=0.003, respectively), and HDL particle size (β=−0.226, p=0.021). NCB positively associated with small HDL particle count (β=0.231, p=0.019). The

Table 1 Demographics and clinical characteristics[14]

Characteristics	Lupus (N=64)	Control (N=30)	P values
Demographics			
Age (years)	45±12	37±11	**<0.001**
Female gender, N (%)	56 (88%)	29 (97%)	0.15
Type-2 DM	4 (6%)	0 (0%)	0.25
Hyperlipidaemia	11 (17%)	0 (0%)	**0.02**
Hypertension	37 (58%)	0 (0%)	**<0.001**
Statin use	6 (9%)	0 (0%)	0.12
Race			
Caucasian	25 (39%)	16 (53%)	0.69
African-American	13 (20%)	5 (17%)	
Asian	6 (9%)	2 (7%)	
Other	20 (31%)	7 (23%)	
Ethnicity			
Hispanic	27 (42%)	10 (33%)	0.43
Non-Hispanic	35 (55%)	20 (67%)	
History			
Smoking			
Current tobacco use, N (%)	4 (7%)	0 (0%)	0.22
Previous smoker, N (%)	7 (11%)	4 (14%)	0.51
Physical activity, N (%)	19 (42%)	9 (50%)	0.90
Lupus history			
Disease duration (years)	15±12	–	–
SLEDAI	3.8±3.0	–	–
SLICC	2 (0–3)	–	
History of thrombotic event	13 (20%)	–	–
Medications			
Hydroxychloroquine	57 (89%)	–	–
Azathioprine	16 (25%)	–	–
Methotrexate	10 (16%)	–	–
Mycophenolate mofetil	19 (30%)	–	–
Prednisone	48 (75%)	–	–
Clinical parameters			
BMI	28.4±6.2	24.1±4.4	**<0.001**
Framingham Risk Score	0 (0–1)	0 (0–0)	0.14
Glucose (mg/dL)	90.1±13.0	92.0±9.4	0.23
Insulin (mcU/ml)	15.0 (9–20)	8.0 (6–11)	**<0.001**
HOMA-IR	3.3 (1.9–4.6)	1.7 (1.4–2.5)	**0.002**
C reactive protein (mg/L)	1.6 (0.8–3.9)	1.1 (0.7–3.2)	0.18
Urine creatinine (mg/dl)	110 (66–181)	133 (52–166)	0.90
Urine protein (mg/dl)	32 (18–44)	13 (11–17)	**<0.001**
Protein/creatinine ratio	0.2 (0.2–0.4)	0.1 (0.1–0.1)	**<0.001**
WBC count	5.1 (3.9–6.4)	5.2 (4.5–6.4)	0.53
Neutrophil %	61±12	56±10	**0.03**

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HOMA-IR, homoeostatic model assessment insulin resistance; SLEDAI, SLE Disease Activity Index; SLICC, Systemic Lupus International Collaborating Committee.

association of HDL particle size and small and medium HDL particle counts persisted after multivariate regressions adjusting for Framingham risk (table 3). The association of NCB with HDL cholesterol and large HDL particle count also persisted after multivariate regressions adjusting for Framingham risk, HOMA-IR, past 20-day cumulative prednisone dose and SLE Disease Activity Index (SLEDAI) (table 3). NCB positively associated with large VLDL particle count (β=0.277, p=0.004) and VLDL particle size (β=0.283, p=0.004) that remained significant in multivariate models (table 3). Associations adjusted for race, ethnicity and BMI are described in table 3. Dense calcified plaque positively associated with LDL cholesterol (β=0.378, p=<0.001) and total LDL particle count (β=0.352, p=<0.001); the association was driven primarily by large LDL particle counts (β=0.336, p=<0.001). The association of dense calcified plaque with LDL cholesterol, total LDL particle count and large LDL particle count persisted after multivariate regressions adjusting for Framingham risk, HOMA-IR and past 20-day cumulative prednisone dose. Dense calcified plaque positively associated with overall VLDL particle count (β=0.220, p=0.025); this association was driven by small VLDL particle count (β=0.329, p=0.001), and negatively associated with VLDL particle size (β=−0.238, p=0.015). As previously reported, the Agatston Score for coronary calcification had no associations with lipoprotein particle subfractions.[9]

GlycA is elevated in SLE and displays significant associations with NCB

Circulating GlycA was significantly increased in SLE (table 2) and positively associated with IR (β=0.407, p=0.001), Systemic Lupus International Collaborating Committee (SLICC) (β=0.331, p=0.010), erythrocyte sedimentation rate (β=0.611, p=<0.001) and NCB (β=0.198, p=0.044) (table 4 and table 5). The association between GlycA and NCB persisted after multivariate regression analysis adjusting for Framingham risk and lipoproteins, suggesting that the association of GlycA and NCB is independent of the association that lipoproteins showed with plaque (table 3). As previously

Table 2 Lipoprotein particle subfractions and GlycA in SLE and healthy controls as assessed by NMR

Lipoproteins	SLE (n=64)	Control (n=30)	P values
Baseline parameters			
Total cholesterol, mg/dL	163.5 (148–191)	164.0 (145–202)	0.764
Triglycerides, mg/dL	86.5 (67–123)	77.0 (61–91)	0.131
HDL cholesterol, mg/dL	**54.1±16**	**66.9±16**	**<0.001**
LDL cholesterol, mg/dL	99.0 (84–124)	85.5 (72–125)	0.359
VLDL triglycerides, mg/dL	**59.9 (44–87)**	**47.8 (36–58)**	**0.031**
GlycA	**405.0 (365–470)**	**357.5 (301–411)**	**0.001**
Particle counts			
HDL particle count, umol/L	**30.0±5.9**	**35.0±7.7**	**<0.001**
Small HDL particle count, umol/L	12.7±7.7	10.1±6.7	0.057
Medium HDL particle count, umol/L	**8.1 (4–12)**	**14.2 (9–21)**	**<0.001**
Large HDL particle count, umol/L	**6.9 (5–10)**	**10.5 (9–12)**	**0.001**
LDL particle count, nmol/L	**1094.0 (871–1220)**	**843.5 (675–1219)**	**0.029**
Small LDL particle count, nmol/L	**419.5 (211–653)**	**271.0 (0–389)**	**0.027**
Large LDL particle count, nmol/L	419.5 (317–577)	445.0 (249–687)	0.805
IDL particle count, nmol/L	**53.5 (25–124)**	**130.5 (62–190)**	**0.001**
VLDL particle count, nmol/L	**41.1 (29–61)**	**33.3 (21–47)**	**0.067**
Small VLDL particle count, nmol/L	26.6 (18–38)	20.8 (14–34)	0.192
Medium VLDL particle count, nmol/L	**13.5 (7–25)**	**6.8 (2–14)**	**0.007**
Large medium VLDL particle count, nmol/L	**14.7 (7–27)**	**8.7 (3.7–15.1)**	**0.017**
Large VLDL particle count, nmol/L	2.3 (1.2–4.1)	1.8 (1.3–3.7)	0.961
Particle Size			
HDL particle size, nm	**9.6 (9.1–9.9)**	**9.9 (9.5–10.1)**	**0.013**
LDL particle size, nm	21.0 (20.4–21.4)	21.1 (20.7–21.6)	0.295
VLDL particle size, nm	47.6 (43–51)	48.5 (45–54)	0.441

Student's t-test used unless otherwise noted (mean±SD).
Parameters reaching significance ($p \leq 0.05$) highlighted in bold; after controlling for multiple comparisons only those with $p \leq 0.00009$ remain significant.
*Mann-Whitney test used (median (IQR)).
GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear MR; VLDL, very low-density lipoprotein.

reported, GlycA associated with a cumulative prednisone dose in a univariate regression and no longer associated with NCB when prednisone was added to the multivariate model (tables 2 and 3).[15] To determine if GlycA could provide value beyond current markers of inflammation, it was compared with high-sensitivity C reactive protein (hsCRP) in univariate regressions associating these markers with disease parameters. While hsCRP associated better with disease duration and traditional risk factors of atherosclerosis (Framingham Risk), GlycA was a better predictor than hsCRP of IR, SLICC, total plaque burden and NCB (table 4).

Associations of SLE disease markers with lipoprotein profiles

SLEDAI, a measure of recent or current disease activity, was negatively associated with HDL particle count (β=−0.354, p=0.006) and, in particular, with small HDL particle counts (β=−0.281, p=0.026) (table 5 and table 6). The SLICC Disease Index, a measure of accrued damage over time, did not associate with the lipoprotein profile. Protein:creatinine ratio in SLE was positively associated with VLDL triglycerides (β=0.280, p=0.038) and VLDL particle counts (β=0.436, p=0.001), particularly small VLDL particle counts (β=0.498, p=<0.001) (table 5 and table 6). C3 complement levels positively associated with small HDL particle counts (β=0.377, p=0.002), total LDL particle counts (β=0.332, p=0.008) and small LDL particle counts (β=0.320, p=0.010), and negatively associated with large HDL particle counts (β=−0.333, p=0.008) and HDL particle size (β=−0.456, p=<0.001) (table 6). C4 complement levels were positively associated with small HDL particle count (β=0.259, p=0.040). Anti-double stranded (ds) DNA and anti-extractable nuclear antigen (ENA) antibody levels negatively associated with overall HDL particle counts (β=−0.264,

Table 3 Multivariate regressions of non-calcified burden with HDL and VLDL subfractions and GlycA

Model	HDL cholesterol	HDL particle size	Small HDL particle count	Medium HDL particle count	Large HDL particle count	Large VLDL particle count	VLDL particle size	GlycA
Unadjusted	**−0.331 (0.001)**	**−0.226 (0.021)**	**0.231 (0.019)**	**−0.214 (0.029)**	**−0.292 (0.003)**	**0.278 (0.004)**	**0.283 (0.004)**	**0.198 (0.044)**
Model 1	**−0.330 (0.001)**	**−0.226 (0.022)**	**0.230 (0.019)**	**−0.216 (0.027)**	**−0.291 (0.003)**	**0.278 (0.005)**	**0.281 (0.002)**	**0.199 (0.044)**
Model 2	**−0.328 (0.001)**	**−0.260 (0.009)**	**0.290 (0.003)**	**−0.250 (0.011)**	**−0.304 (0.002)**	**0.284 (0.005)**	**0.248 (0.008)**	0.143 (0.138)
Model 3	**−0.344 (0.008)**	0.026 (0.828)	−0.040 (0.722)	−0.239 (0.067)	−0.183 (0.149)	**0.379 (0.004)**	0.220 (0.071)	0.122 (0.338)
Model 4	**−0.353 (<0.001)**	**−0.242 (0.013)**	**0.233 (0.018)**	**−0.222 (0.024)**	**−0.310 (0.001)**	**0.279 (0.004)**	**0.292 (0.003)**	**0.195 (0.047)**
Model 5	**−0.319 (0.001)**	−0.141 (0.151)	0.187 (0.072)	**−0.193 (0.039)**	**−0.259 (0.009)**	**0.214 (0.024)**	**0.309 (0.001)**	0.042 (0.696)
Model 6	**−0.337 (0.002)**	−0.172 (0.138)	**0.221 (0.050)**	−0.183 (0.132)	**−0.301 (0.008)**	**0.231 (0.04)**	**0.298 (0.007)**	0.138 (0.320)
Model 7	**−0.305 (0.010)**	−0.055 (0.628)	0.148 (0.202)	−0.167 (0.149)	**−0.232 (0.045)**	0.180 (0.098)	**0.324 (0.002)**	−0.042 (0.775)
Model 8	**−0.440 (<0.001)**	−0.073 (0.534)	0.063 (0.586)	−0.146 (0.222)	**−0.307 (0.010)**	**0.222 (0.035)**	**0.318 (0.002)**	0.018 (0.901)
Model 9	**−0.477 (<0.001)**	−0.089 (0.479)	0.070 (0.560)	−0.142 (0.214)	**−0.323 (0.006)**	**0.225 (0.035)**	**0.334 (0.001)**	–
Model 10	–	–	–	–	–	–	–	**0.214 (0.024)**

Model 1 – adjusted for ethnicity.
Model 2 – adjusted for ethnicity + race.
Model 3 – adjusted for ethnicity + race + BMI.
Model 4 – adjusted for Framingham risk.
Model 5 – adjusted for Framingham risk + HOMA-IR.
Model 6 – adjusted for Framingham risk + 20-day prednisone dose.
Model 7 – adjusted for Framingham risk + HOMA-IR + 20-day prednisone dose.
Model 8– adjusted for Framingham risk + HOMA-IR + 20-day prednisone dose + SLEDAI.
Model 9 – adjusted for Framingham risk + HOMA-IR + 20-day prednisone dose + SLEDAI + GlycA.
Model 10 – adjusted for HDL cholesterol + HDL particle size + small HDL particle count + medium HDL particle count + large HDL particle count + large VLDL particle count + VLDL particle size.
Parameters reaching significance ($p<0.05$) highlighted in bold; after controlling for multiple comparisons only those with $p<0.00009$ remain statistically significant.
BMI, body mass index; GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment insulin resistance; SLEDAI, SLE Disease Activity Index; VLDL, very high-density lipoprotein.

Table 4 Univariate regressions for GlycA and hsCRP

Parameter	GlycA (n=64)	hsCRP (n=63)
Demographic and clinical characteristics		
Age	0.013 (0.901)	0.199 (0.118)
Gender	0.011 (0.934)	0.090 (0.485)
Smoking, N (%)	0.240 (0.060)	**0.534 (<0.001)**
Clinical and laboratory values		
BMI, kg/m^2	**0.328 (0.008)**	0.221 (0.081)
Systolic BP, mm Hg	0.033 (0.794)	0.052 (0.687)
Diastolic BP, mm Hg	0.023 (0.854)	−0.155 (0.225)
Total cholesterol, mg/dL	−0.008 (0.950)	−0.127 (0.322)
LDL, mg/dL	0.008 (0.952)	−0.051 (0.695)
HDL, mg/dL	−0.139 (0.272)	−0.226 (0.075)
Triglycerides, mg/dL	0.187 (0.143)	0.043 (0.739)
Framingham Risk Score	0.040 (0.752)	**0.310 (0.013)**
HOMA-IR	**0.407 (0.001)**	0.234 (0.065)
Glucose, mg/dL	**0.270 (0.031)**	0.093 (0.470)
Insulin, mcU/ml	**0.433 (<0.001)**	0.247 (0.051)
Erythrocyte sedimentation rate, mm/hour	**0.611 (<0.001)**	**0.284 (0.025)**
High-sensitivity C reactive protein, mg/L	**0.578 (<0.001)**	–
Protein/creatinine ratio	0.226 (0.097)	−0.071 (0.611)
WBC count	**0.441 (<0.001)**	0.233 (0.068)
SLE characteristics		
SLEDAI	0.011 (0.934)	0.043 (0.740)
SLICC	**0.331 (0.010)**	**0.293 (0.024)**
Disease duration, years	0.226 (0.073)	**0.456 (<0.001)**
Hydroxychloroquine, N (%)	0.079 (0.533)	0.026 (0.841)
Azathioprine, N (%)	0.205 (0.104)	−0.092 (0.471)
Methotrexate, N (%)	−0.187 (0.140)	−0.014 (0.911)
Mycophenolate mofetil, N (%)	−0.043 (0.735)	−0.114 (0.372)
Cumulative 20-day steroid dose, mg	**0.410 (0.016)**	−0.178 (0.314)
Coronary plaque burden		
Total burden, (× 100) mm2	**0.217 (0.027)**	−0.131 (0.184)
Calcified burden, (× 100) mm^2	0.092 (0.355)	−0.077 (0.438)
Non-calcified burden, (×100) mm^2	**0.198 (0.044)**	−0.117 (0.238)

Univariate regressions reported as β-coefficient (p value). Parameters reaching significance (p≤0.05) highlighted in bold; after controlling for multiple comparisons only those with p≤0.00009 remain statistically significant.
BMI, body mass index; GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment insulin resistance; LDL, low-density lipoprotein; SLEDAI, SLE Disease Activity Index; SLICC, Systemic Lupus International Collaborating Committee; WBC, white blood cell count; hsCRP, high-sensitivity C reactive protein.

p=0.037 and β=−0.273, p=0.032, respectively). Anti-La autoantibodies negatively associated with large HDL particle counts (β=−0.262, p=0.043), while anti-ribonuclear protein (RNP) autoantibodies negatively associated with both total HDL particle count (β=−0.295, p=0.022), and LDL particle size (β=−0.273, p=0.035) (table 6). Anti-Smith antibodies and SLE disease duration demonstrated no associations with lipoprotein particle subfractions. A past 20-day prednisone dose did associate with NMR parameters, however other medications did not show associations (table 7). Overall, dysregulation in lipoprotein fractions by NMR was significantly associated with lupus activity and specific autoantibody profiles. Of note, only p values less than 0.00009 in this study are statistically significant after controlling for multiple comparisons.

DISCUSSION

We report that SLE subjects with overall mild to moderate disease activity display a proatherogenic lipoprotein profile characterised by lower levels and smaller size of HDL particles and increases in VLDL and LDL particle number. Our findings are in agreement with previous studies that have shown decreases in HDL and increases in VLDL particle counts and triglycerides in SLE.[16] As previously suggested, our findings indicate that lupus disease activity is associated with a more proatherogenic lipid profile.[16]

To our knowledge, this is the first study to associate the aberrant lipoprotein profile in SLE with burden of non-calcified coronary plaque. The shift towards smaller HDL particle size in SLE could support a proatherogenic environment that contributes to the enhanced NCB in SLE. This is significant because NCB can predict CV events in other patient populations and is considered higher risk for unstable plaque development.[10–12] Although we observed a significant association between LDL particles and dense calcified plaque in fully adjusted models, we did not see an association between LDL and NCB. This is in contrast to previous studies that have identified LDL as a predictor of NCB in other patient populations.[17 18] Those studies were not focused on patients with autoimmune conditions, suggesting that the pathways underlying atherogenesis in SLE could be distinct. Our group has previously reported that modifications to HDL in SLE cause it to become proinflammatory and atherogenic due to its impaired cholesterol efflux capacity (CEC).[19] Indeed, small HDL particle numbers associate with impaired CEC and we recently found that impaired CEC associates with NCB in SLE.[14 20]

An association between VLDL and plaque burden, measured by carotid intima-media thickness, was previously reported in SLE.[21] Here, we found that large VLDL particle counts and VLDL particle size positively associated with both NCB and calcified plaque, providing additional evidence that VLDL may act as an independent predictor of subclinical coronary artery disease in SLE. It has been

Table 5 Univariate regressions of NMR parameters and lupus history

NMR parameters	SLEDAI (n=63)	SLICC (n=59)	Disease duration (n=64)	Protein/ creatinine ratio (n=55)	Framingham risk (n=64)	HOMA-IR (n=64)
Baseline parameters						
Total cholesterol	**−0.250 (0.049)**	−0.072 (0.586)	−0.084 (0.509)	0.111 (0.419)	0.030 (0.814)	−0.011 (0.928)
Triglycerides	−0.008 (0.951)	−0.075 (0.570)	−0.095 (0.454)	0.236 (0.083)	0.138 (0.277)	**0.453 (<0.001)**
HDL cholesterol	−0.231 (0.069)	−0.134 (0.312)	−0.021 (0.868)	−0.019 (0.890)	−0.237 (0.059)	**−0.315 (0.011)**
LDL cholesterol	−0.144 (0.260)	−0.017 (0.900)	−0.084 (0.509)	0.050 (0.715)	0.313 (0.301)	−0.013 (0.917)
VLDL triglycerides	0.057 (0.657)	−0.059 (0.660)	−0.123 (0.332)	**0.280 (0.038)**	0.097 (0.445)	**0.521 (<0.001)**
GlycA	0.011 (0.934)	**0.331 (0.010)**	0.226 (0.073)	0.226 (0.097)	0.040 (0.752)	**0.407 (0.001)**
Particle counts						
HDL particle count	**−0.345 (0.006)**	−0.197 (0.135)	0.001 (0.999)	0.048 (0.728)	0.002 (0.990)	−0.103 (0.418)
Small HDL particle count	**−0.281 (0.026)**	0.012 (0.927)	−0.107 (0.402)	0.101 (0.461)	0.132 (0.300)	0.144 (0.257)
Medium HDL particle count	0.051 (0.691)	−0.155 (0.241)	0.178 (0.159)	−0.043 (0.753)	0.046 (0.721)	−0.038 (0.767)
Large HDL particle count	−0.085 (0.509)	−0.106 (0.424)	−0.046 (0.719)	−0.054 (0.694)	**−0.286 (0.022)**	**−0.350 (0.005)**
LDL particle count	−0.029 (0.822)	−0.036 (0.787)	−0.127 (0.318)	0.109 (0.429)	**0.332 (0.007)**	0.180 (0.154)
Small LDL particle count	0.127 (0.320)	−0.049 (0.712)	−0.036 (0.779)	0.094 (0.496)	**0.403 (0.001)**	**0.314 (0.012)**
Large LDL particle count	−0.162 (0.203)	0.010 (0.942)	−0.154 (0.225)	0.044 (0.748)	−0.073 (0.567)	−0.158 (0.214)
IDL particle count	−0.130 (0.308)	0.005 (0.971)	0.083 (0.517)	−0.104 (0.451)	−0.104 (0.413)	−0.083 (0.515)
VLDL particle count	0.048 (0.711)	−0.013 (0.924)	−0.170 (0.179)	**0.436 (0.001)**	0.013 (0.918)	**0.534 (<0.001)**
Small VLDL particle count	0.044 (0.730)	0.051 (0.699)	−0.165 (0.193)	**0.498 (<0.001)**	−0.078 (0.542)	**0.414 (<0.001)**
Medium VLDL particle count	0.016 (0.902)	−0.069 (0.605)	−0.101 (0.428)	0.256 (0.059)	0.069 (0.587)	**0.421 (<0.001)**
Large medium VLDL particle count	0.033 (0.797)	−0.074 (0.578)	−0.112 (0.380)	0.247 (0.069)	0.102 (0.424)	**0.457 (<0.001)**
Large VLDL particle count	0.084 (0.515)	−0.013 (0.921)	−0.066 (0.605)	0.068 (0.622)	0.194 (0.125)	**0.414 (0.001)**
Particle size						
HDL particle size	0.011 (0.932)	−0.078 (0.557)	0.056 (0.659)	−0.081 (0.554)	**−0.329 (0.008)**	**−0.353 (0.004)**
LDL particle size	−0.191 (0.133)	0.030 (0.821)	0.151 (0.237)	−0.129 (0.347)	**−0.267 (0.033)**	**−0.316 (0.011)**
VLDL particle size	−0.073 (0.569)	−0.036 (0.789)	0.067 (0.600)	−0.182 (0.185)	0.740 (0.580)	−0.003 (0.979)

Univariate regressions reported as β-coefficient (p value).
Parameters reaching significance ($p \leq 0.05$) highlighted in bold; after controlling for multiple comparisons only those with $p \leq 0.00009$ remain statistically significant.
GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment insulin resistance; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear MR; SLEDAI, SLE Disease Activity Index; SLICC, Systemic Lupus International Collaborating Committee; VLDL, very low-density lipoprotein.

Table 6 Univariate regressions of NMR parameters and autoantibodies

NMR Parameters	C3 (n=63)	C4 (n=63)	anti-dsDNA (n=63)	anti-ENA (n=62)	Ro (n=60)	La (n=60)	Sm (n=60)	CCP (n=21)	RNP (n=60)
Baseline parameters									
Total cholesterol	0.050 (0.697)	0.027 (0.836)	−0.059 (0.648)	0.051 (0.695)	−0.096 (0.467)	−0.098 (0.457)	−0.030 (0.820)	−0.210 (0.360)	−0.032 (0.810)
Triglycerides	−0.116 (0.367)	−0.140 (0.273)	0.125 (0.330)	0.011 (0.931)	0.014 (0.914)	−0.081 (0.540)	−0.037 (0.778)	−0.220 (0.338)	−0.082 (0.535)
HDL cholesterol	−0.167 (0.192)	−0.004 (0.974)	−0.230 (0.069)	−0.236 (0.065)	−0.112 (0.394)	−0.218 (0.094)	0.029 (0.827)	−0.137 (0.554)	−0.174 (0.184)
LDL cholesterol	0.159 (0.214)	0.140 (0.274)	−0.033 (0.795)	0.089 (0.493)	−0.153 (0.243)	−0.054 (0.681)	−0.076 (0.562)	−0.290 (0.202)	0.025 (0.849)
VLDL triglycerides	−0.115 (0.371)	−0.144 (0.262)	0.158 (0.216)	0.026 (0.844)	0.049 (0.710)	−0.033 (0.801)	−0.035 (0.793)	−0.193 (0.402)	−0.091 (0.489)
GlycA	**0.287 (0.022)**	0.166 (0.193)	0.045 (0.728)	0.064 (0.623)	0.005 (0.973)	0.180 (0.170)	−0.005 (0.969)	−0.171 (0.460)	−0.006 (0.964)
Particle counts									
HDL particle count	0.195 (0.125)	0.220 (0.083)	**−0.264 (0.037)**	**−0.273 (0.032)**	−0.093 (0.482)	−0.155 (0.238)	−0.046 (0.724)	−0.259 (0.257)	**−0.295 (0.022)**
Small HDL particle count	**0.377 (0.002)**	**0.259 (0.040)**	0.057 (0.665)	0.056 (0.667)	0.064 (0.627)	−0.056 (0.669)	0.039 (0.766)	−0.276 (0.225)	−0.036 (0.788)
Medium HDL particle count	−0.021 (0.871)	−0.001 (0.992)	−0.273 (0.031)	−0.221 (0.085)	−0.101 (0.445)	0.117 (0.375)	−0.141 (0.281)	0.084 (0.717)	−0.185 (0.157)
Large HDL particle count	**−0.333 (0.008)**	−0.123 (0.336)	−0.127 (0.323)	−0.207 (0.106)	−0.108 (0.412)	**−0.262 (0.043)**	0.048 (0.714)	−0.017 (0.941)	−0.106 (0.421)
LDL particle count	**0.332 (0.008)**	0.180 (0.158)	0.091 (0.476)	0.169 (0.189)	−0.090 (0.495)	0.002 (0.991)	−0.085 (0.520)	−0.143 (0.537)	0.114 (0.387)
Small LDL particle count	**0.320 (0.010)**	0.106 (0.409)	0.227 (0.074)	0.108 (0.405)	0.008 (0.953)	0.043 (0.742)	−0.061 (0.643)	0.008 (0.973)	0.099 (0.451)
Large LDL particle count	0.039 (0.760)	0.104 (0.415)	−0.130 (0.311)	0.057 (0.657)	−0.082 (0.533)	−0.041 (0.756)	−0.035 (0.788)	−0.236 (0.304)	0.022 (0.865)
IDL particle count	−0.153 (0.232)	−0.060 (0.641)	−0.174 (0.171)	0.056 (0.664)	−0.134 (0.309)	−0.037 (0.781)	0.041 (0.754)	0.001 (0.998)	−0.063 (0.631)
VLDL particle count	−0.127 (0.322)	−0.126 (0.325)	0.123 (0.339)	0.087 (0.500)	0.146 (0.265)	0.005 (0.970)	−0.032 (0.807)	−0.178 (0.440)	−0.030 (0.820)
Small VLDL particle count	−0.106 (0.409)	−0.050 (0.695)	−0.039 (0.764)	0.136 (0.292)	0.224 (0.086)	0.062 (0.638)	−0.015 (0.907)	−0.121 (0.600)	0.040 (0.764)
Medium VLDL particle count	−0.129 (0.314)	−0.178 (0.164)	**0.254 (0.044)**	0.004 (0.978)	0.010 (0.937)	−0.057 (0.668)	−0.026 (0.842)	−0.197 (0.391)	−0.073 (0.577)
Large medium VLDL particle count	−0.101 (0.433)	−0.156 (0.223)	0.241 (0.057)	0.003 (0.983)	0.010 (0.938)	−0.055 (0.675)	−0.037 (0.779)	−0.179 (0.438)	−0.089 (0.499)
Large VLDL particle count	0.094 (0.463)	0.001 (0.998)	0.017 (0.895)	−0.007 (0.956)	0.031 (0.812)	0.023 (0.862)	−0.054 (0.682)	−0.103 (0.658)	−0.116 (0.376)
Particle Size									
HDL particle size	**−0.456 (<0.001)**	−0.257 (0.042)	−0.106 (0.408)	−0.211 (0.099)	−0.006 (0.963)	−0.101 (0.444)	0.044 (0.741)	0.135 (0.558)	−0.103 (0.433)
LDL particle size	−0.200 (0.115)	−0.027 (0.834)	−0.186 (0.145)	−0.249 (0.051)	−0.152 (0.247)	−0.068 (0.603)	0.042 (0.752)	−0.284 (0.212)	**−0.273 (0.035)**
VLDL particle size	−0.010 (0.941)	−0.126 (0.325)	−0.047 (0.712)	−0.019 (0.882)	−0.072 (0.585)	−0.038 (0.774)	−0.054 (0.683)	−0.066 (0.776)	−0.131 (0.320)

Univariate regressions reported as β-coefficient (p value).
Parameters reaching significance ($p<0.05$) highlighted in bold; after controlling for multiple comparisons only those with $p\leq0.00009$ remain significant.
CCP, anti-cyclic citrullinated peptide; GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear MR; VLDL, very low-density lipoprotein; anti-ENA, anti-extractable nuclear antigen; anti-RNP, anti-ribonuclear protein; anti-dsDNA, anti-double stranded DNA.

Table 7 Univariate regressions of NMR parameters and medications

NMR parameters	Prednisone (n=64)	20-day prednisone dose (n=34)	Hydroxychloroquine (n=64)	Statins (n=64)
Baseline parameters				
Total cholesterol	0.045 (0.724)	0.243 (0.166)	0.082 (0.519)	−0.042 (0.740)
Triglycerides	0.143 (0.261)	**0.405 (0.018)**	0.178 (0.160)	−0.133 (0.294)
HDL cholesterol	0.048 (0.707)	−0.021 (0.904)	0.009 (0.946)	0.123 (0.333)
LDL cholesterol	0.013 (0.918)	0.333 (0.054)	0.078 (0.542)	−0.107 (0.398)
VLDL triglycerides	0.162 (0.200)	**0.430 (0.011)**	0.172 (0.174)	−0.150 (0.236)
GlycA	0.214 (0.089)	**0.410 (0.016)**	0.079 (0.553)	0.133 (0.294)
Particle counts				
HDL particle count	−0.217 (0.086)	−0.206 (0.243)	−0.067 (0.596)	0.136 (0.285)
Small HDL particle count	−0.236 (0.060)	0.049 (0.784)	−0.111 (0.384)	−0.034 (0.790)
Medium HDL particle count	−0.079 (0.536)	**−0.374 (0.029)**	0.033 (0.795)	0.104 (0.415)
Large HDL particle count	0.200 (0.112)	0.048 (0.787)	0.050 (0.694)	0.121 (0.341)
LDL particle count	−0.050 (0.694)	0.321 (0.065)	0.046 (0.717)	−0.135 (0.289)
Small LDL particle count	−0.114 (0.370)	0.025 (0.889)	−0.027 (0.834)	−0.088 (0.488)
Large LDL particle count	0.046 (0.716)	**0.338 (0.050)**	0.112 (0.380)	−0.038 (0.764)
IDL particle count	0.124 (0.327)	0.011 (0.951)	−0.028 (0.826)	−0.083 (0.516)
VLDL particle count	0.179 (0.157)	**0.468 (0.005)**	0.115 (0.365)	−0.114 (0.368)
Small VLDL particle count	0.136 (0.283)	**0.340 (0.049)**	0.093 (0.467)	−0.027 (0.831)
Medium VLDL particle count	0.172 (0.173)	**0.419 (0.014)**	0.074 (0.561)	−0.162 (0.202)
Large medium VLDL particle count	0.156 (0.219)	**0.424 (0.013)**	0.095 (0.453)	−0.161 (0.203)
Large VLDL particle count	0.033 (0.793)	0.194 (0.271)	0.183 (0.149)	−0.048 (0.706)
Particle size				
HDL particle size	0.184 (0.147)	−0.063 (0.725)	0.036 (0.778)	0.069 (0.588)
LDL particle size	0.063 (0.619)	0.003 (0.985)	0.121 (0.342)	0.086 (0.498)
VLDL particle size	0.094 (0.459)	0.112 (0.529)	0.081 (0.523)	0.022 (0.863)

Univariate regressions reported as β-coefficient (p value).
Parameters reaching significance ($p \leq 0.05$) highlighted in bold; after controlling for multiple comparisons only those with $p \leq 0.00009$ remain statistically significant.
GlycA, glycoprotein acetylation; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear MR; VLDL, very low-density lipoprotein.

suggested that decreased lipoprotein lipase activity, potentially due to autoantibodies targeting this enzyme in SLE, promotes lipoprotein dysregulation and increased VLDL and LDL levels.[22] Given the associations identified here between VLDL and NCB, future studies should investigate the role that lipoprotein lipase has in VLDL deposition and atherosclerotic progression. In addition, traditional clinical laboratory tests do not capture the detailed assessments of lipoprotein subfraction counts and sizes. Our data suggest that, in SLE, small HDL particles have a positive association with proatherogenic pathways while the opposite is observed with larger HDL particles. It may therefore be beneficial for clinicians to determine the relative abundance of small HDL particles when determining potential CV risk in patients with SLE. This reinforces the notion that using NMR to obtain a detailed assessment of lipoprotein parameters may help better characterise CVD risk in lupus.

In other patient populations, GlycA confers additional value beyond traditional biomarkers of inflammation, like hsCRP, in predicting long-term CV and all-cause mortality.[8] In support of this, GlycA but not hsCRP was significantly elevated in SLE. Although this increase in GlycA has been shown to predict systemic inflammation in SLE, its association to subclinical coronary artery disease had not been identified because of the reliance on coronary calcification scores.[23] We now found that GlycA associates with NCB but not with calcified plaque. Moreover, a comparison between GlycA and hsCRP revealed that GlycA significantly associated with IR and plaque burden in SLE, while hsCRP did not. Taken together, our findings suggest that GlycA may be a better tool to assess CV risk in SLE than hsCRP. Indeed, previous studies have shown that CRP is suppressed by type I interferons and this may explain the poor association of this acute

phase reactant to lupus disease activity and organ-specific complications.[24]

Although GlycA represents a composite NMR signal of multiple acetylated glycoproteins, it has been suggested that neutrophils are an important source of two major protein contributors to the GlycA signal, α1-acid glycoprotein and haptoglobin.[8] It has also been shown that elevated GlycA is associated with neutrophil activity.[8] In this cohort, we have previously identified elevated levels of a pathogenic neutrophil subset, known as low density granulocytes, which display an activated phenotype and associate with NCB in SLE.[14] These neutrophils could potentially serve as a significant source for the elevated GlycA in SLE and the extent to which they contribute to the GlycA signal should be investigated. The association of GlycA with NCB did not persist after controlling for prednisone dose. These findings suggest that there is a possible link between GlycA and corticosteroid use and that GlycA may be useful in tracking vascular damage caused by steroids. In addition, this could be a confounding effect as patients with more severe disease tend to take higher doses of steroids. The associations of GlycA with inflammatory markers and plaque imply that the inflammatory pathways producing acetylated glycoproteins may play a role in driving atherogenesis. Future studies should seek to determine the putative role that the pathways associated with this marker have in other aspects of lupus pathogenesis.

Although our study was limited by a relatively small sample size and included patients with mild to moderate disease activity, GlycA and lipoprotein profiles still independently predicted NCB in SLE. However, due to the exploratory nature of this cross-sectional analysis, after controlling for multiple comparisons, only p values less than 0.0009 remain statistically significant. Our study was not appropriately powered to meet this requirement and is therefore subject to type 1 error. Future studies should confirm these findings in larger cohorts and study the predictive value of GlycA and lipoprotein profiles in subjects with more severe disease. Longitudinal assessments of these parameters are also required to further understand the pathogenicity of lipoprotein subsets in SLE and the extent to which GlycA fluctuates with changes in vascular damage and predicts progression to coronary events.

Contributors MMP, PMC, SS, MS performed experiments; AKD, JBB, JHC, TS, MYC and NNM were involved in statistical analysis and/or coronary CT quantification; YT-O, SS, AF, MC, SG, SH,were involved in patient assessment and recruitment and clinical phenotyping; ZM managed the database; AR and MS were involved in interpretation of lipoprotein data; MMP, PMC and MJK designed the study and wrote the manuscript.

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