Effects of autoimmune antibodies anti-lipoprotein lipase, anti-low density lipoprotein, and anti-oxidized low density lipoprotein on lipid metabolism and atherosclerosis in systemic lupus erythematosus

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ABSTRACT

Introduction: Premature development of atherosclerosis in systemic lupus erythematosus has been widely reported. Anti-lipoprotein lipase antibody may be one cause contributing to this disorder. **Objective:** To assess the extent of coronary risk due to autoimmune antibodies in terms of carotid plaque in lupus patients. **Patients and Methods:** We compared 114 documented lupus patients with 111 normal controls matched for sex and age. Anti-lipoprotein lipase (A-LPL), anti-oxidized low density lipoprotein (A-OXLDL), and anti-low density lipoprotein (A-LDL) were measured by enzme-linked immunoabsorbent assay. Low density lipoprotein-triglyceride (LDL-Trig) and high density lipoprotein-triglyceride (HDL-Trig) were also measured. Plaque was measured by bilateral carotid ultrasound. **Results:** 45.6% of patients tested positive for A-LPL, and 34.4% for A-OXLDL. 44% of normal controls tested positive for A-LPL, and 20% for A-OXLDL. Risk increased sharply in subgroups with increased antibody levels. Patients with A-LPL and A-OXLDL > 0.40 (n = 12) showed coronary risk correlations of: A-LPL x LDL-Trig = 0.7008, P = 0.0111; bilateral ultrasound vs total cholesterol = 0.62205, P = 0.0308; LDL-Trig *vs* myocardial infarction (MI) = 0.76562, P = 0.0037; total triglycerides *vs* MI = 0.78191, P = 0.0027); LDL-Trig/LDL-cholesterol *vs* MI = 0.80493, P = 0.0016; A-OXLDL *vs* USBL = 0.71930, P = 0.0084. Correlations of SLEDAI with risk variables were highly significant only in subgroups of elevated antibody levels (SLEDAI x A-OXLDL = 0.70366, P = 0.0107)**. Conclusion:** A-LPL initiates the development of LDL mutations, followed by antibody production, plaque formation and coronary risk in some SLE patients.

Keywords: systemic lupus erythematosus, dyslipidemia, triglycerides, lipoprotein lipase, atherosclerosis.

INTRODUCTION

Previous studies have shown a relationship between antibodies to lipoprotein lipase and elevated triglycerides in patients with systemic lupus erythematosus (SLE).[1-4] The Pearson correlation 0.84 (P = 0.0001) of anti-lipoprotein lipase (A-LPL) was reported by this laboratory in 2002.[1] A-LPL also correlated at 0.85 (P = 0.0001) with low density lipoprotein-triglyceride (LDL-Trig), and 0.85 (P = 0.001) with Apo B respectively. Apo E correlated with a-LPL at 0.87 (P = 0.0002). These lipid-lipoprotein particles are representative of the very low density lipoprotein (VLDL) and LDL density classes which play central roles in lipid metabolism.

The correlation strength of this relationship among these lipid particles prompted us to examine other potential antibodies within the VLDL, LDL regions. Our findings suggest that

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these antibodies may be part of the mechanism underlying the premature atherosclerosis characteristic of SLE.

It has been reported that circulating triglycerides alone present a direct risk for the development of atherosclerosis.[5,6] LDL-Trig is also reported to be an independent risk factor of coronary artery disease and inflammatory agent.[7] This accentuates the overall risk of excess triglyceride in circulation, particularly in combination with other developing mutant lipoprotein forms that inhibit lipid metabolism. Our focus was to relate those effects on the established lipid transport mechanism in terms of plaque formation and coronary events.

The presence of plaque measured by ultrasound of the carotid arteries has been shown to be a useful predictor of coronary artery disease and is associated with clinical risk of coronary artery disease events such as angina and myocardial infarction.[8,9] In our present study, we used carotid plaque scores as a measure of atherosclerosis in 114 SLE patients and 111 normal subjects. Additionally, complete lipid profiles on serum, LDL and HDL were performed, as well as antibody levels for A-LPL, anti-oxidized low density lipoprotein (A-OXLDL), and anti-low density lipoprotein (A-LDL) on all subjects. The collected data was used to evaluate the role of these autoimmune antibodies in the development of premature atherosclerosis characteristic of SLE patients.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the Oklahoma Medical Research Foundation and all subjects signed informed consent forms. The patient population was predominantly female totaling 114 subjects including 10 males matched for sex and age ranging from age 16 to 87 with an average age of 43. The majority of patients had a long term duration of disease, and consequently were on the usual variety of autoimmune medications. However, none of the study subjects were taking lipid lowering medications. No lipid exclusion limits were imposed on patients or controls. All patients were tested and met the diagnostic criteria for SLE of the American College of Rheumatology.[10] They also tested positive for "The Reichlin Profile", anti-nuclear antibody (ANA), anti-double strand DNA (dsDNA) and extractable nuclear antibodies (ENA). Controls were recruited from within our local health science center, selected to match the patient group for sex and age, and otherwise were in a healthy state of well being, taking no lipid lowering medications.

Carotid ultrasound

Plaque scores (measured on a scale from 0 to 10) were performed and provided by the Cardiovascular section of the Department of Medicine, University of Oklahoma Health Sciences Center. Study subjects were given a duplex carotid screen (both arteries) by Doppler sonography. The atherosclerotic burden of plaque was expressed as the sum of values measured in both arteries. Only study subjects having a value entry of the ultrasound test were included for statistical correlations of study groups.

Assays of autoimmune antibodies

The same standard enzyme-linked immunoabsorbent assay (ELISA) methodology for measurements of the anti-LPL, anti-OXLDL, and anti-LDL was used in this study. Only the reactant antigens and antibodies differ. This consisted of coating the plate with the antigen then adding the subject serum at a 100 fold dilution with incubation overnight followed by two washes, then adding the anti-human IgG with the O.D. read at 280 nm. This laboratory reference method was applied for measurement of all patients and controls.[1]

Antibody/Lipid determination

The measurements of cholesterol and triglycerides were performed in accordance with the manual of Laboratory Operations, Lipid and Lipoprotein Analysis, Revised 1982 Methodology, Lipid Research Clinics Program.[11] Enzymatic lipid reagents used in the study were purchased from Roche Laboratories and used on a Cobas Mira Plus autoanalyzer manufactured by Roche Laboratories as described in Reichlin, *et al*.[1]

The accuracy and precision of the assays were maintained by an ongoing successful performance in a national analytical surveillance program.

Analytical HDL/LDL isolation

Of serum, 0.25 mL was aliquoted into 1.5 mL conical centrifuge tubes (SARSTED) with 0.25 mL of 0.9% Na Cl. 15µL of 0.92 M sodium heparin (ICN) and 25µL of 1 M Mn Cl_2 were added. Test samples and control samples were mixed briefly by vortex then stored overnight in an ice bath. The samples were vortexed briefly then centrifuged at 10,000 rpm in a Sorvall centrifuge. The HDL supernate was removed and set aside. The precipitates were combined with 0.25 mL of PBS-Tween-20 (SIGMA), vortexed to a homogeneous suspension and stored overnight in the cold room. The samples were then centrifuged at 10,000 rpm to pack the insoluble precipitate and

float the LDL supernate. The LDL supernate was removed and stored with the HDL to be analyzed by routine cholesterol and triglyceride serum assays.Measured and derived methods using the 1:5 VLDL-cholesterol:triglyceride ratio of the Friedwald estimation for LDL-cholesterol (LDL-Chol) determination were applied for all samples in the study. A comparison of 1,100 samples analyzed for verification of LDL-Chol values by the measured method with the derived method yielded a correlation coefficient of 0.82 with a significant P value of < 0.0001.

Preparative LDL isolation

Isolation of the low density lipoprotein was performed according to the method of Lee *et al*. [12] with two additional centrifugation washes at density 1.070 Na Cl to exclude albumin. Ultracentrifugation runs were performed for 26 hours at 45,000 rpm in a Beckman J-25 ultracentrifuge. The isolated LDL fractions were dialyzed for two days in .05% EDTA, PBS prior to use. *LDL Oxidation*

For the oxidation of LDL, a slightly modified version of the copper oxidation method by Palinski *et al*, 1990, was used.[13] 200 µL of the intact LDL at 3.80 mg/mL was added with 5 µL of 1 M copper sulfate in 1 mL of PBS for each preparation of the study. The mixture was incubated overnight in a water bath at 37°C, then centrifuged at 10,000 rpm in a Sorvall RC5C centrifuge. The supernate was removed and dialyzed in 0.10% EDTA PBS for two days.

The oxidized sample was tested by immunodiffusion against anti-Apo B as compared with the intact LDL and shown to present a comparatively faint disrupted precipitin line.

Data management

Data file storage, statistical analysis and regression plots were performed using SAS software, Version 9.1, purchased from SAS Institute Inc. of Cary, North Carolina.

RESULTS

Table 1 shows the comparison of A-LPL (+) and (-) patients with controls and the stages of associated risk variables. The majority of significant variables were comprised of triglyceride containing particles. Total cholesterol, LDL-Chol and HDL-Chol were not dramatically different among groups. HDL-Chol was mildly so.

Statistical review of a subgroup of A-OXLDL (+) patients (n = 41) also showed a very similar mean A-LPL value for the A-LPL antibody (average A-LPL = 0.41; A-OXLDL = 0.41). However, a subgroup of patients selected for an A-LPL (+) response (n = 52; average A-LPL = 0.514; A-OXLDL = 0.286) showed a mean value of half or less for the A-OXLDL antibody. The same is true for the controls; however, the A-OXLDL levels for that group are lower yet at approximately one third (A-LPL (+) n = 49 (average = 0.54; A-OXLDL = 0.17); (A-OXLDL (+), n = 23 (average A-LPL = 0.37; A-OXLDL = 0.31).

Table 1. A-LPL positive/negative levels in patient and control groups

Variable	Mean	SD	Mean	SD	*t*-test (P value)
	Normal Control A-LPL (-) (n = 62)		**Normal Control A-LPL (+) (n = 9)**		
Plaque	0.37	0.87	0.40	0.90	0.43
Total Chol	187.7	38.8	195.8	33.3	0.0499
Total Trigl	120.4	53.5	129.9	27.5	0.4669
LDL-Chol	105.9	31.2	112.6	23.5	0.0718
LDL-Trig	73.4	73.4	84.4	59.8	0.3881
Trig/Chol	0.65	0.31	0.65	0.34	0.4075
LDL-Trig/LC	0.70	0.34	0.72	0.43	0.4144
HDL-Trig/HC	0.79	0.74	0.76	0.32	0.3932
A-OXLDL	0.14	0.12	0.17	0.11	0.0145
A-LPL	0.28	0.17	0.54	0.19	<0.0001
HDL-Chol	53.8	53.8	56.4	15.4	0.2244
HDL-Trig	39.5	39.5	40.5	14.3	0.2058
	Lupus A-LPL (-) (n = 62)		**Lupus A-LPL (+) (n = 52)**		
Plaque	0.74	1.18	1.19	1.95	0.2223
Total Chol	196.8	59.0	202.1	50.6	0.2446
Total Trig	149.9	79.3	191.2	118.6	0.0099
LDL-Chol	111.4	42.3	121.3	35.8	0.0668
LDL-Trig	98.8	69.3	126.3	70.6	0.0083
Trig/Col	0.78	0.42	0.94	0.44	0.0141
LDL-Trig/LC	0.88	0.55	1.04	0.50	0.0333
HDL-Trig/HC	0.85	0.38	0.93	0.39	0.0949
A-OXLDL	0.19	0.15	0.28	0.13	0.0108
A-LPL	0.25	0.13	0.51	0.16	<0.0001
HDL-Chol	54.1	20.5	50.8	16.6	0.1943
HDL-Trig	42.0	12.4	44.2	16.4	0.3338
	Normal Control A-LPL (-) (n = 62)		**Lupus A-LPL (+) (n = 52)**		
Plaque	0.37	0.87	1.19	1.95	0.0032
Total Chol	187.7	38.8	202.1	50.6	0.0521
Total Trig	120.4	53.5	191.2	118.6	<0.0001
LDL Chol	105.9	31.2	121.3	35.8	0.0209
LDL Trig	73.4	73.4	126.3	70.6	<0.0001
Trig/Chol	0.65	0.31	0.94	0.44	0.0001
LDL-Trig/LC	0.70	0.34	1.04	0.50	0.0002
HDL-Trig/HC	0.79	0.74	0.93	0.39	0.0025
A-OXLDL	0.14	0.12	0.28	0.20	<0.0001
A-LPL	0.28	0.17	0.51	0.16	<0.0001
HDL-Chol	53.8	53.8	50.8	16.6	0.0728
HDL-Trig	39.5	39.5	44.2	16.4	0.0237

Total Chol, total cholesterol; Total Trig, total triglyceride; LDL-Chol, low density lipoprotein-cholesterol; LDL-Trig, low density lipoprotein-triglyceride; Trig/Chol, triglyceride/cholesterol; LDL-Trig/LC, low density lipoprotein-triglyceride/low density lipoprotein cholesterol; HDL-Trig/HC, high density lipoprotein-triglyceride/high density lipoprotein-cholesterol; A-OXLDL, anti-oxidized lipoprotein lipase; A-LPL, anti-lipoprotein lipase; HDL-Chol, high density lipoprotein-cholesterol; HDL-Trig, high density lipoprotein-triglyceride.

The highest O.D. levels of autoimmune antibodies measured were from anti-LPL. The most significant impact on lipid profiles was shown by elevated triglycerides in whole serum and among the measured density classes LDL and HDL.

Bilateral measurements of carotid plaque done by ultrasound (USBL) were highest in patient groups measuring positive for A-LPL.

In Table 2 the highest correlation with plaque is shown with triglyceride measured in the HDL fraction of patients with A-LPL (+), in contrast to subjects of both SLE and control groups having low levels of A-LPL for which a correlation with plaque is not shown. Patients which were negative for the A-LPL antibody showed a significant negative correlation for the USBL x HDL-TG variable by comparison. Patients measuring > 0.45 for the A-LPL antibody (n = 37) showed significant correlations of incidence of MI with lipid distribution ratios of serum density classes.

Table 2. Correlation of ultrasound carotid plaque score and incidence of myocardial infarction in lupus subgroups of anti-LPL levels with lipid variables

Correlation variables	Lupus A-LPL (-) (n = 67)	P value
USBL x Total Chol	0.0749	0.5467
USBL x Total Trig	0.0044	0.9716
USBL x HDL-Trig/HDL-Col	-0.1560	0.2148
USBL x HDL-Trig	-0.2866	0.0206
	Lupus A-LPL (+) (n = 52)	
USBL x Total Chol	0.2659	0.0567
USBL x Total Trig	0.2927	0.0352
USBL x HDL-Trig/HDL-Chol	0.3130	0.0239
USBL x HDL-Trig	0.4372	0.0012
	Lupus A-LPL > 0.45 O.D. (n = 37)	
MI x Trig/Chol	0.4231	0.0091
MI x LDL-Trig	0.3822	0.0196
IM x LDL-Trig/LDL-Chol	0.5052	0.0014
MI x HDL-Trig/HDL-Chol	0.4358	0.0076

USBL, bilateral ultrasound; Total Chol, total cholesterol; Total Trig; total triglyceride; HDL-Trig/HDL-Chol, high density lipoprotein-triglyceride/high density lipoprotein-cholesterol; MI, myocardial infarction; A-LPL, anti-lipoprotein lipase.

We found the greatest percent distribution in favor of triglyceride in the LDL fraction of patients. Comparison by *t* test of the LDL-Trig and the LDL distribution ratio were highly significant compared to the normal group (P = 0.0001), although LDL-Chol was not significant.

Beyond the increasing risk for coronary events with increasing A-LPL shown in Table 2, a subset of 21 patients containing antibodies to both A-LPL and A-OXLDL higher than baseline at > 0.3500 O.D. units showed a correlation coefficient of MI x LDL-Trig/LDL-Chol = 0.75897, P ≤ 0.0001 (data not shown).

Given that LPL activity is a major point at issue, the density classes LDL and HDL were isolated to permit cholesterol and triglyceride, including the distribution within and among patients and normals. Table 3 shows the *t* test comparative results of the Trig/Chol ratios of SLE patients with normal controls at the right margin of the table. These data reflect the percent distribution of Trig:Chol within serum, LDL and HDL and the *t* test comparison of each analyte in each fraction in addition to the Trig:Chol ratio in each fraction. The distribution ratios of Trig:Chol shown in Table 3 are comparatively close in values within groups, but significantly higher in patients throughout the density class spectrum, compared with the normal group. The overall average Trig:Chol ratio of SLE patients was 0.8982, significantly in favor of triglyceride, as compared with 0.7153 for normal controls. These data show significantly higher levels of triglycerides in SLE patients in serum and among the density classes, while cholesterol was only mildly so in HDL.

Table 3. Average lipid distribution ratios of lupus patients and normal controls

	Lupus patients (n = 119)			Normal controls (n = 117)			
	Trig / Chol (%)	(mg/dl)	Trig:Chol Ratio	Trig / Chol (%)	(mg/dl)	Trig:Chol Ratio	*t* test P value
Serum	(100%)	168.0	= 0.8535	(100%)	124.6	= 0.6546	< 0.0001
	(100%)	199.1		(100%)	191.3		< 0.0001
							0.2533
LDL	(70.4%)	110.8	= 0.9520	(60.6%)	78.3	= 0.7117	0.0001
	(57.8%)	115.0		(56.7%)	108.8		0.0001
							0.2189
HDL	(30.3%)	43.0	= 0.8891	(36.1%)	39.9	= 0.7797	0.0191
	(27.5%)	52.7		(29.2%)	54.9		0.0019
							0.0316

Correlations of LDL lipids (Table 4) with all three autoimmune antibodies measured in subject samples above baseline show an increased risk in both patients and controls where a combination of antibodies are positive. The subset of patients in Table 4 having both A-LPL and A-OXLDL > 0.40 (n = 12) shows the highest correlations among LDL associated antibodies, LDL risk variables and coronary risk.

In Table 5, correlation of SLEDAI values of the total patient group risk factors (n = 111) were mildly significant (SLEDAI x MI 0.2597, P = 0.0066; SLEDAI x CVA 0.2412, P = 0.0119; and SLEDAI x LDL-Chol 0.1958, P = 0.0422). The patient group's average SLEDAI score was 19.5. Correlations of SLEDAI > 25 and < 25 subgroups show stronger correlations with risk variables in the elevated SLEDAI group, and weaker correlations in the lower SLEDAI group.

Table 4. Correlations of autoimmune antibodies with coronary risk variables

Correlation variables	Lupus A-OXLDL (+) (n = 67) (range 0.16 – 0.83)	P value
LDL-Chol x A-LPL	0.4190	0.0064
LDL-Chol x A-LDL	0.4774	0.0018
LDL-Chol x A-OXLDL	0.4267	0.0068
%LDL-Trig x A-LPL	0.4014	0.4126
HDL-Trig x A-LDL	0.4126	0.0091
%LDL-Trig x MI	0.3158	0.0430
	Normal control A-OXLDL (-) (n = 88)	
LDL-Chol x A-LPL	0.2159	0.0433
LDL-Chol x A-LDL	-0.0244	0.8212
LDL-Chol x A-OXLDL	0.1245	0.2480
%LDL-Trig x A-LPL	0.0727	0.5008
HDL-Trig x A-LDL	0.0354	0.7464
%LDL-Trig x MI	No MI	No MI
	Autoimmune antibodies normal control A-OXLDL (+) (n = 23) (range 0.16 – 0.61)	
LDL-Chol x A-LPL	0.1974	0.3665
LDL-Chol x A-LPL	0.2672	0.2178
LDL-Chol x A-OXLDL	0.5258	0.0100
%LDL-Trig x A-LPL	-0.4080	0.0533
HDL-Trig x A-LDL	0.4740	0.0223
%LDL-Trig x IM	No MI	No MI
	Lupus patients with A-LPL and A-OXLDL > 0.400 O.D. (n = 12)	
Total Chol x Carotid Plaque (USBL)	0.6225	0.0380
Total Serum Trig x MI	0.7819	0.0027
LDL-Trig/LDL-Chol x MI	0.8049	0.0016
LDL-Trig x MI	0.7656	0.0037
HDL-Trig/HDL-Chol x MI	0.7031	0.0108
LDL-Chol x CVA	0.6825	0.0145
Anti-LPL x LDL-Trig	0.7480	0.0081
Anti-OXLDL x Carotid Plaque (USBL)	0.7193	0.0084

LDL-Chol, low density lipoprotein-cholesterol; A-LPL, anti-lipoprotein lipase; A-LDL, anti-low density lipoprotein; A-OXLDL, anti-oxidized low density lipoprotein; %LDL-Trig, percent of low density lipoprotein of total triglyceride; USBL, bilateral ultrasound; MI, myocardial infarction; HDL-Trig/HDL-Chol, high density lipoprotein-triglyceride/high density lipoprotein cholesterol; CVA, cerebrovascular accident; LDL-Trig, low density lipoprotein-triglyceride.

Table 5. Correlations of risk variables in SLEDAI subgroups

Correlation variables	SLEDAI ≥ 25 (n = 30)	P value
SLEDAI x Total Trig	0.4440	0.0140
Plaque x Total Chol	0.5091	0.0041
SLEDAI x HDL-Trig	0.5948	0.0005
Plaque x LDL-Chol	0.5452	0.0018
Plaque x LDL-Trig	0.3899	0.0331
SLEDAI x MI	0.3693	0.0446
CVA x MI	0.5649	0.0011
	SLEDAI < 25 (n = 81)	
SLEDAI x Total Trig	-0.0094	0.9350
Plaque x Total Chol	0.0807	0.4739
SLEDAI x HDL-Trig	0.0874	0.4527
Plaque x LDL-Chol	0.0721	0.5224
Plaque x LDL-Trig	0.1086	0.3345
SLEDAI x MI	0.2997	0.0077
CVA x MI	-0.0362	0.7479
	SLEDAI ≥ 25 + A-LPL > .35 O.D. (n = 10)	
SLEDAI x Plaque	0.8586	0.0015
SLEDAI x LDL-Chol	0.7387	0.0147
Plaque x LDL-Chol	0.6837	0.0293
Plaque x Trig/A-LPL	0.7962	0.0054
Plaque x Total Trig	0.6395	0.0465

SLEDAI, systemic erythematosus disease activity index; Total Trig, total triglyceride; Total Chol, total cholesterol; HDL-Trig, high density lipoprotein-triglyceride; LDL-Chol, low density lipoprotein-cholesterol; LDL-Trig, low density lipoprotein-triglyceride; MI, myocardial infarction; CVA, cerebrovascular accident; A-LPL, anti-lipoprotein lipase.

Figure 1 shows the highest relationship with measured plaque formations to be in lupus patients with high levels of both A-LPL and A-OXLDL, compared with all other groups.

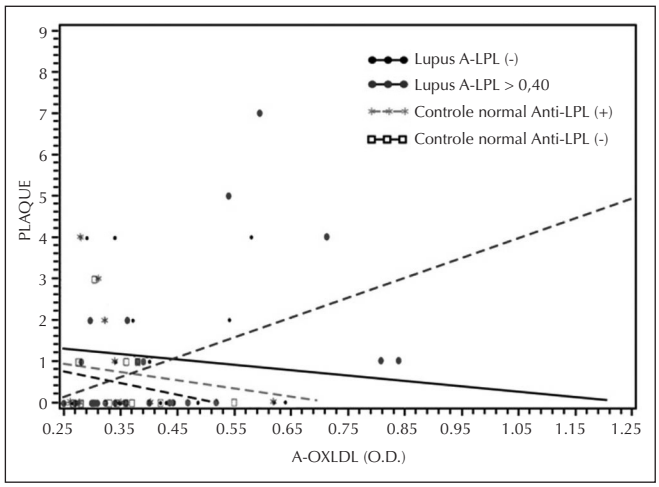

Figure 1. Relationship of anti-oxidized low density lipoprotein (A-OXLDL) with carotid artery plaque among subgroups of patients and controls at different levels of anti-lipoprotein lipase (A-LPL).

DISCUSSION

A general review of the data in this study shows approximately 47% of patients to be A-LPL positive, with approximately 36% positive for the A-OXLDL antibody. The levels and distribution of antibodies observed are consistently higher for A-LPL than A-OXLDL in the antibody positive group.

It is well established that lipid-lipoprotein particles among density classes are metabolically processed forming a sequence of diminishing size and lipid distribution, beginning with LPL activity on triglyceride in chylomicron and continuing through HDL, resulting in increasing density and loss of lipid due to enzymic activities during the course of normal lipid transport.[14-17] LPL being first in the sequence of transport, combined with the observations of antibody levels and distribution as described, we interpret that the A-LPL antibody develops first, with A-OXLDL developing later as a result of A-LPL impeding transport and promoting mutation, which subsequently produces mutant autoimmune antibodies which collectively contribute greatly to the lipid dysfunction and lipid excess in circulation in some SLE patients.

Analysis of the SLEDAI data offers interesting results. The patient population is made largely of a long disease duration cohort with variable activity management efficiencies. The overall average SLEDAI is elevated at 19.0, although does not significantly correlate with risk variables and events as a group. However, as shown in Table 5, subgroups of the population of SLEDAI > 25 x < 25 begin to show consistent patterns of risk according to these groups. Further, in a subgroup of more severe conditions having SLEDAI > 25 combined with A-LPL above the background baseline of 0.35 OD, the correlations of SLEDAI with plaque and other known coronary risk variables become more dramatic. We conclude these data are supportive of previous reports[3,18] of increased lipid dysfunction during high disease activity.

Results of this study support closer attention being focused on autoimmune antibodies as a potentially increased risk for premature development of atherosclerosis in some SLE patients. Elevated levels and distribution of triglyceride in serum and density classes may be an indication, of autoimmune activity on lipid transport. However, equally important, the results also emphasize the need for further study to explore the presence and roles of other autoimmune antibodies contributing to this risk.

While only the higher concentrations of antibodies showed strong correlations with coronary risk variables, we suggest that constant exposure to low levels of specific antibodies also present a risk for development of vascular disease in SLE patients and may also develop as a source of coronary risk in normal subjects over time.

REFERÊNCIAS

REFERENCES

1. Reichlin M, Fesmire J, Quintero-Del-Rio AI, Wolfson-Reichlin M. Autoantibodies to lipoprotein lipase and dyslipidemia in systemic lupus erythematosus. Arthritis Rheum 2002; 46:2957-63.
2. de Carvalho JF, Borba EF, Viana VST, Bueno C, Leon EP, Bonfá E. Anti-Lipoprotein Lipase Antibodies. Arthritis Rheum 2004; 50(11):3610-5.
3. de Carvalho JF, Viana VST, Neto EFB, Leon EP, Bueno C, Bonfá E. Longitudinal fluctuation of anti-lipoprotein lipase antibody is related with disease activity in systemic lupus erythematosus patients without anti-dsDNA antibodies. Rev. Bras. Reumatol 2009; 49(1):39-47.
4. Kodera M, Hayakawa I, Komura K, Yanaba K, Hasegawa M, Takehara K *et al*. Anti-lipoprotein lipase antibody in systemic sclerosis: Association with elevated serum triglyceride concentrations. J Rheumatol 2005; 32(4):629-36.
5. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007; 298:299-308.
6. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK *et al*. Relation of triglyceride metabolism and coronary artery disease, studies in the postprandial state. Arterioscler Thromb 1992; 12(11):1336-45.

7. März W, Scharnagl H, Winkler K, Tiran A, Nauck M. Low-density lipoprotein triglycerides associated with low-grade systemic inflammation, adhesion molecules and angiographic coronary artery disease: The Ludwig Shafen Risk and Cardiovascular Health Study. Circulation 2004; 110: 3068-3074.
8. Zanolla CN, Franceschini L, Cacici G, De Cristan B, Arieti M, Vassanelli C. Usefulness of ultrasonographic markers of carotid atherosclerosis (intima-media thickness, unstable carotid plaques and severe carotid stenosis) for predicting presence and extent of coronary artery disease. J Cardiovasc Med 2009; 10(12):906-12.
9. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-medial thickness as a predictor of coronary and cerebrovascular disease. Curr Cardiol Rep 2009; 11(1):21-7.
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF *et al*. The revised criteria for the classification of systemic lupus erytematosus. Arth Rheum 1982; 25:1271-7.
11. Lipid Research Clinics Program. Manual of Laboratory Operations: Lipid and Lipoprotein Analysis. Second Edition, Bethesda, MD: National Heart, Lung and Blood Institute, NIH, U.S. Dept. of Health and Human Services, 1982.
12. Lee DM, Downs D. A quick and large-scale density gradient subfractionation method for low density lipoproteins. J Lipid Res 1982; 23(1):14-27.
13. Palinski W, Ylä-Herttuala S, Rosenfeld ME, Butler SW, Socher SA, Parthasarathy S *et al*. Antisera and monoclonal antibodies specific for epitopes generated during oxidative modification of low density lipoprotein. Arteriosclerosis 1990; 10(3):325-35.
14. Havel RJ, Eder HA, Bradgon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 1955; 34(9):1345-53.
15. Blackett PR, Kittredge D. Hyperlipidemia in children. South Med J 1993; 86:1083-92.
16. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6):499-502.
17. Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin Chem 1990; 36(1):15-9.
18. Borbá EF, Bonfá E. Dyslipoproteinemias in systemic lupus erythematosus: Influence of disease activity and anticardiolipin antibodies. Lupus 1997; 6:533-9.