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Relation Among Lipoprotein Subfractions and Carotid Atherosclerosis in Alaskan Eskimos (From the GOCADAN study)

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Abstract

Studies have been inconsistent as to whether lipoprotein particle subfraction measures are useful indicators of cardiovascular risk. This study evaluated the relation between lipoprotein particle concentrations and size, analyzed by nuclear magnetic resonance (NMR) spectroscopy, and measures of carotid atherosclerosis in a population with high cardiovascular risk but little hyperlipidemia. In this cross-sectional, population-based sample of Alaska Eskimos ≥35yrs (n=656), higher carotid intimal medial thickness (IMT) was associated with higher low-density lipoprotein cholesterol (LDL-C) (p=0.03) and total LDL particle concentration (LDL-P) (p=0.04), independently of other traditional risk factors; the effects of LDL-C and LDL-P on IMT were additive (p=0.015). Carotid plaque was associated with higher levels of LDL-C (p=0.01), higher concentrations of large LDL particles (p=0.003), and a reduction in the size of the very-low-density lipoprotein (VLDL) particles (p=0.03). The effects of LDL-C and large LDL particles on plaque score were additive. In conclusion, carotid IMT was associated with higher LDL particle concentrations; the association was strongest in those with higher LDL-C levels. Plaque was associated with higher concentrations of LDL-C, large LDL particles, and smaller VLDL particles. It may be beneficial to determine lipoprotein subfractions in populations with little hyperlipidemia.

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Keywords

atherosclerosis; lipoproteins; cardiovascular disease; risk factors; plaque

INTRODUCTION

The Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) population can provide unique insight into studies of the determinants of atherosclerosis. Although many Alaska Eskimos maintain a traditional diet and lifestyle, rates of CVD are high[1,2,3,4] and systematic measures of carotid atherosclerosis indicate that plaque prevalence is > in other U.S. groups.[5] Smoking rates[6] and subclinical inflammation[7] are high; on the other hand LDL-C and triglyceride (TG) levels are not elevated and HDL-C levels are high.[8] The aim of this study was to evaluate the relations between lipoprotein subfraction particle concentrations and size and measures of carotid atherosclerosis in this population with high cardiovascular risk but little hyperlipidemia.

METHODS

The GOCADAN study population includes 1214 family members ≥ age 18 who are residents of 8 villages and the town of Nome in the Norton Sound Region of Alaska and were recruited in 2000–2004.[9,10] Each participant underwent a physical examination, personal interview, collection of biological specimens, and other diagnostic tests. Permission was granted by each community to conduct the study; written informed consent was obtained from all participants. Details of the study have been published.[9,10]

The current analysis focused on 796 GOCADAN participants, ≥ age 35. Those missing carotid ultrasound examination (n=61) and lipoprotein particle data (n=56) were excluded as well as participants who were diagnosed as having diabetes according to 1998 World Health Organization criteria[11] (n = 40) or were receiving hypolipidemic agents (n = 69), leaving 656 persons in the final dataset.

Anthropometric measurements, including height, weight, and waist circumference, were performed with participants fasting, according to standard procedures.[9] Weight was measured to the nearest tenth pound. Waist circumference was measured with an anthropometric tape applied at the level of the umbilicus, with the subject supine, and approximated to the nearest quarter inch. Sitting blood pressure was measured on the right brachial artery using a mercury sphygmomanometer after the participant rested for 5 minutes. Three readings were taken, with the mean of the second and third measurements used as the final measure. Smoking habits were evaluated via questionnaire and participants were categorized as current, former, and never-smokers.[9]

Samples of whole blood, plasma, serum, and urine were collected from each participant and stored at −80° C until used. All laboratory methods have been published.[9] Plasma lipids were analyzed by a conventional enzymatic chemistry analyzer (Virtos 950, Ortho-Clinical Diagnostics, Rochester, NY, USA) using a dry multilayered analytical element coated on a polyester support.[12,13] LDL-C was calculated by the Friedewald formula.[14] Apolipoprotein

B (Apo B) and apolipoprotein A1 (apo A1) were measured.[15] Fasting plasma glucose was measured by the exokinase method on the Hitachi 717 (Roche Diagnostics, Indianapolis, IN, USA).

Detailed lipoprotein subclassification (type [LDL, VLDL, HDL], size [small, intermediate, large], and concentration) was performed on plasma-EDTA isolated by centrifugation (3,000 rpm, 10 min, 4° C) and stored at −80° C for the NMR spectroscopy,[16] using a rapid, automated, commercially available assay (LipoScience Inc., Raleigh, NC, USA). Lipoprotein quantification was achieved on freshly thawed untreated specimens (400 μl) in a 3-step process consisting of an automatic measurement of the plasma NMR spectrum, followed by computer deconvolution (curve fitting) of the spectral data and calculation of the subclass concentrations and size. Details of the NMR methodology have been published.[16, 17]

In this analysis, the data are presented as molar particle concentrations, because the focus of the study was on the occurrence of lipoprotein subclasses and their distribution rather than abnormal lipid composition. To simplify the analysis, the 15 NMR lipoprotein subfractions (V1−V6, intermediate-density lipoprotein [IDL], L1−L3, H1−H5) were grouped into 3 size groups (large, intermediate, and small) for each lipoprotein class. This resulted in the following spectra: large VLDL (V5 + V6, 60–220 nm), intermediate VLDL (V3 + V4, 35–60 nm), and small VLDL (V1 + V2, 27–35 nm); large LDL (L3, 21.3–22.7 nm), intermediate LDL (L2, 19.8–21.2 nm), and small LDL (L1, 18.3–19.7 nm); and large HDL (H4 + H5, 8.8–13 nm), intermediate HDL (H3, 8.2–8.8 nm), and small HDL (H1 + H2, 7.3–8.2 nm).[17] Data on IDL particles (25 nm) are not reported in this study. For all the analyses, intermediate and small LDL particles were grouped together and considered small particles, as in other studies.[18,19]

At the baseline exam, carotid ultrasound studies were performed to evaluate intimal medial thickness (IMT) and to determine the presence and location of plaque, using standardized published protocols,[20] by a centrally trained sonographer and interpreted at a core reading center (Cornell Medical Center, NY) by a single skilled physician reader blinded to participant characteristics. Carotid IMT was measured from B-mode guided M-mode images obtained at end diastole. Far wall IMT was measured using electronic callipers operated on several cycles and averaged. Carotid IMT was never measured at the level of discrete plaque. Plaque was defined as focal protrusion into the vessel lumen at least 50% > the surrounding wall; plaque score was defined as the number of segments (0–8) of each carotid artery containing plaque.

The Spearman rank correlation coefficients were calculated for lipoproteins, lipids, and carotid atherosclerosis. Comparisons among groups were evaluated by analysis of variance (ANOVA) for continuous variables and by logistic regression for categorical variables, adjusted for potential confounders, including age, gender, BMI, systolic blood pressure, and current smoking. The natural log transformation was applied to variables that were highly skewed. The back-transformed mean values are shown in the tables, where indicated. However, the transformed variables were used in the statistical analyses. All probability

values were 2-tailed, and values < 0.05 were considered statistically significant. Data were analyzed using SAS version 9.1.

RESULTS

Women comprised a greater proportion of the study population (Table 1) BMI, and systolic and diastolic blood pressures were mostly normal, with a low portion of participants receiving antihypertensive drugs. Plasma lipid concentrations were on average lower than those of the general U.S. population, with high HDL-C. A large percentage of the population smoked and almost half had at least 1 focal plaque.

Lipoprotein subfractions are reported in Table 2. The majority of the VLDL and HDL particles were small, whereas the LDL particles were equally distributed.

To evaluate the relationship between lipoprotein concentration and size vs. IMT and plaque score, the cohort was analyzed according to tertiles of IMT and plaque score groups (0, 1, and 2–7). The same was done for standard lipids, and all data were adjusted for age, gender, BMI, systolic blood pressure, and current smoking. Both IMT and plaque score increased with increasing LDL-C (Table 3). Conversely, plasma triglycerides decreased with increasing IMT and plaque score, reaching statistical significance for plaque score (Table 3). Apo B levels tended to increase with increasing IMT tertiles and plaque score, but without reaching statistical significance. No associations were found with HDL-C and apo A1 (Table 3).

When relations among ultrasound variables and lipoprotein subfractions concentration and size were assessed (Table 4), higher IMT tertile was associated with a significant increase in total LDL particle concentration. Both large and small LDL particles showed corresponding but non-significant increases with increasing IMT tertile. Higher plaque score was associated with higher levels of large LDL particles (Table 4). No relationship was found between IMT or plaque score and LDL particle size. With increasing plaque score there was a significant linear decrease in large VLDL concentration and a nonsignificant decrease in intermediate particles. Therefore, higher plaque score was associated with a smaller VLDL size. No relation was found between IMT tertiles and VLDL particle concentrations and size. IMT and plaque score were not associated with HDL particle concentrations or size (Table 4).

To evaluate the independent and/or combined effect of LDL-C and total LDL particle concentration on IMT, we divided the population into 4 groups based on their quartiles of LDL-C and LDL-P: 1) those with low LDL-C and low LDL particle concentration (group 1, n = 248); 2) those with high LDL-C and low LDL particle concentration (group 2, n = 80); 3) those with low LDL-C and high LDL particle concentration (group 3, n = 81); and 4) those with high LDL-C and high LDL particle concentration (group 4, n = 247) using a 2-way analysis of variance (Figure 1). The groups with only 1 lipid abnormality (high LDL-C or high LDL particle concentration, groups 2 and 3, respectively) had an intermediate value of IMT, not significantly different from group 1 (both normal LDL-C and LDL particle

concentration). On the contrary, participants with both high LDL-C and high LDL particle concentration (group 4) showed higher IMT values ($p = 0.015$ vs group 1).

The same analyses were performed for plaque score, using large LDL particle concentration instead of total LDL particle concentration (Figure 2). Again, only the group with both abnormalities showed a significantly higher plaque score compared with the group with no abnormality ($p = 0.006$, group 4 vs group 1).

DISCUSSION

This study, performed in a population with a high prevalence of CVD despite mostly favorable lipid and blood pressure patterns and a physically active lifestyle, showed several findings:

- LDL particle concentration was relatively low and LDL were large in this population.
- A high proportion of the GOCADAN participants had plaque.
- Higher IMT levels were significantly associated with higher levels of LDL-C and total LDL particle concentration, independently of other traditional cardiovascular risk factors (i.e., age, BMI, systolic blood pressure, and current smoking). These 2 lipid abnormalities appeared to be additive in their effects on IMT.
- Carotid plaque was associated with higher levels of LDL-C, higher levels of large LDL particles, higher concentrations of small VLDL, and smaller VLDL size. The effects of LDL-C and LDL particle size on plaque score were additive.
- IMT and plaque score were not associated with HDL-C or HDL subfraction concentrations.

Reports relating LDL particle concentration and/or size and IMT have varied: 2 studies found no relations with LDL size,[21,22] whereas another found a significant relation with LDL size in asymptomatic participants with familial combined hyperlipidemia.[23] Another study in a multiethnic population, examining both LDL size and particle concentrations, found a significant relation both with large and small LDL particle concentrations,[18] while the current analysis found a significant relation with total LDL particle concentration and trends with large and small particles when analyzed separately. The population studied by Mora et al.[18] was larger and differed from our population in that it included a large percentage of diabetic participants and had higher concentrations of small LDL particles.

An intriguing finding is the inverse relation of plaque score with plasma triglycerides. This association was accompanied by inverse associations with large VLDL and VLDL size. To our knowledge there have been no other reported analyses of the relations among lipoprotein particles and plaque score. However, small VLDL particles can more easily enter the subendothelial space, and some studies[24,25] have suggested an atherothrombotic role for VLDL remnants; this may explain the observed relation with plaque, whose formation is more specifically linked with thrombotic processes than IMT.

The current analysis indicated possible differences in lipoprotein determinants of IMT and occurrence and/or worsening of plaque. LDL particle concentration may be more closely related to IMT, whereas small VLDL and large LDL may be more closely related to plaque score. The relationship of plaque score with large LDL instead of total or small LDL is consistent with some studies, including that of Mora et al.,[18] suggesting that large LDL particles, not only small ones, may be implicated in the evolution of the atherosclerotic process and CVD. Furthermore, it must be emphasized that large LDL particle concentrations were significantly and inversely associated with VLDL size. Therefore, the association of large LDL particles with plaque score could be mediated through their association with small VLDL.

The lack of association of HDL-C, apo A1, or HDL particle concentration with carotid atherosclerosis is of interest because of the high levels of HDL-C characterizing our population and because CVD rates are high despite the high HDL-C levels. More studies are needed to understand HDL-C metabolism in this group.

The strengths of this study include the population-based sampling of a relatively homogeneous group, standardization of carotid measures, and availability of lipoprotein subfraction data in a large percentage of the participants. Also, the high prevalence of carotid disease in this cohort is not confounded by hyperlipidemia, thus allowing evaluation of the possible role of different lipoprotein particles and sizes as additional cardiovascular risk factors in a population with average plasma lipids within the normal range. The multiple carotid measures allowed evaluation of different aspects of the vessel wall and the atherosclerotic process. On the other hand, our data may not be applicable to other populations. Another weakness is the cross-sectional nature of the analysis, which precludes establishment of cause and effect. Furthermore, although the analyses have been adjusted for gender, a separate analysis for men and women was not possible due to the sample size.

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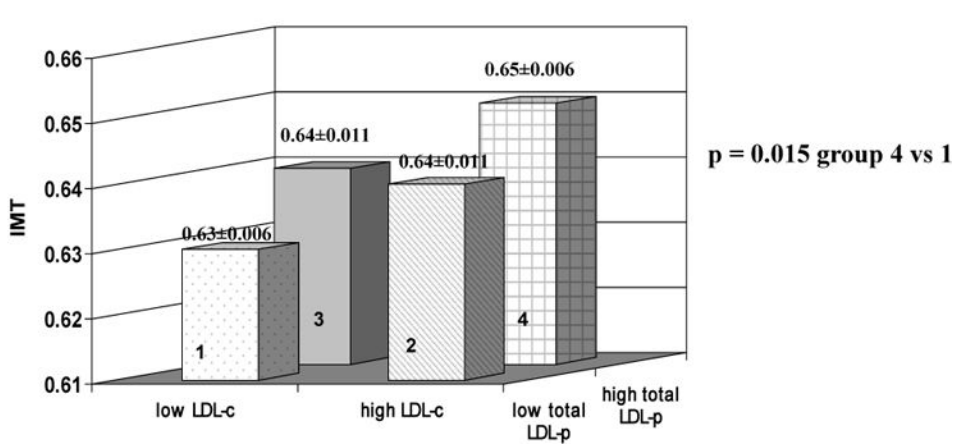


Figure 1.

Additive role of total LDL cholesterol and LDL particle concentration in early atherosclerosis as measured by intimal medial thickness

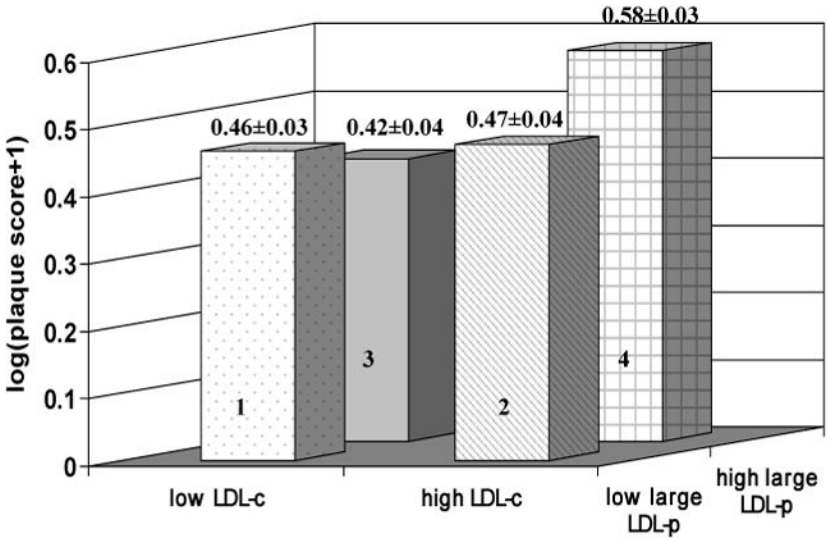
Group 1 = low LDL cholesterol and low LDL particle concentration, n = 248.

Group 2 = high LDL cholesterol and low LDL particle concentration, n = 80.

Group 3 = low LDL cholesterol and high LDL particle concentration, n = 81.

Group 4 = high LDL cholesterol and high LDL particle concentration, n = 247.

Abbreviations. IMT = intimal medial thickness; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle number.



p = 0.006 group 4 vs 1

Figure 2.

Additive role of large LDL cholesterol and LDL particle concentration in later atherosclerosis as measured by plaque score

Group 1 = low LDL cholesterol and low large LDL particle concentration), n = 221.

Group 2 = high LDL cholesterol and low large LDL particle concentration, n = 107.

Group 3 = low LDL cholesterol and high large LDL particle concentration, n = 108.

Group 4 = high LDL cholesterol and high large LDL particle, n = 220.

Abbreviations. LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle number.

Table 1

General characteristics of the study population (n = 656)

Variable	Mean	Range
Age (years)	50	35–92
Women	55%	
Body mass index (kg/m^2)	27.4	16.7–52.7
Waist circumference (cm)	88.1	50.8–139.7
Systolic blood pressure (mmHg)	120	84–175
Diastolic blood pressure (mmHg)	77	52–107
Fasting plasma glucose (mmol/l)	5.1	3.9–6.9
(mg/dL)	92.7	71–124
Plasma cholesterol (mmol/l)	5.5	3.2–10.1
(mg/dL)	213.7	122–389
Plasma triglyceride (mmol/l)	1.4	0.36–10.1
(mg/dL)	126.4	32–891
LDL cholesterol (mmol/l)	3.3	1.2–7.1
(mg/dL)	125.6	48–275
HDL cholesterol (mmol/l)	1.6	0.6–4.4
(mg/dL)	63.3	24–170
Apolipoprotein A1 (mg/dL)	163.3	57–296
Apolipoprotein B (mg/dL)	104.0	35–196
Current smoker	58.4%	
Use of antihypertensive drugs	13.4%	
Intimal medial thickness (mm)	0.64	0.34–1.10
Median plaque score (number of segments)	0	0–7
Persons with at least 1 plaque	45.9%	

Notes. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2

Lipoprotein subfractions concentration and size (mean and standard deviation) in the GOCADAN participants (n = 656)

VLDL (nmol/l)	±
Total particles	64.4 (29.0)
Large	1.6 (2.1)
Intermediate	17.1 (12.4)
Small	45.7 (20.0)
Size (nm)	44.3 (8.7)
LDL (nmol/l)	±
Total particles	1119 (319)
Large	570 (181)
Small	525 (339)
Size (nm)	21.6 (0.63)
HDL (μmol/l)	±
Total particles	29.0 (6.5)
Large	6.7 (4.0)
Intermediate	1.7 (2.7)
Small	20.6 (5.2)
Size (nm)	9.2 (0.5)

Notes. HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein. Mean values in this table are the arithmetic mean from raw data and were not back transformed

Table 3

Standard plasma lipids and apolipoproteins according to tertiles of intimal medial thickness and plaque score groups

	Triglycerides (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Apolipoprotein A1 (mg/dL)	Apoolipoprotein B (mg/dL)
Intimal medial thickness					
Tertile 1	114.7±1.0	121.6±2.6	62.9±1.3	162.7±2.20	101.1±1.77
Tertile 2	113.7±1.0	124.3±2.4	64.8±1.2	163.2±2.00	104.7±1.61
Tertile 3	108.0±1.0	130.9±2.8 *	62.1±1.4	164.1±2.36	106.4±1.90
P for trend	0.26	0.03	0.69	0.70	0.07
Plaque score					
Group 1	116.1±1.0	120.82.1	62.9±1.0	162.6±1.75	101.6±1.40
Group 2	114.5±1.0	131.13.2 **	62.3±1.6	161.5±2.72	108.1±2.19 *
Group 3	103.1±1.0 *§	131.2±3.0 **	64.6±1.5	164.7±2.55	106.2±2.05
P for trend	0.02	0.01	0.42	0.66	0.09

Notes. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Intimal medial thickness tertile 1: 0.335–0.565, n = 219; tertile 2: 0.570–0.665, n = 221; tertile 3: 0.670–1.100, n = 216.

Plaque score group 1: plaque score 0, n = 355; group 2: plaque score 1, n = 119; group 3: plaque score 2–7, n = 182.

Data are expressed as LSMEANS ± SE.

Data are adjusted for age, gender, body mass index, systolic blood pressure, and current smoking.

* $p < 0.05$ vs tertile 1;

** $p < 0.01$ vs tertile 1;

§ $p < 0.05$ vs tertile 2.

Table 4

Association of intimal medial thickness and plaque score with very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein particle concentration and size

	VLDL concentration (nmol/l)				VLDL Size (nm)	LDL concentration (nmol/l)			LDL Size (nm)	HDL concentration (μmol/l)				HDL Size (nm)
	Total**	Large**	Intermediate**	Small		Total	Large	Small		Total	Large	Intermediate**	Small	
Intimal Medial Thickness Tertile														
Tertile 1	57.5±1.04	0.6±1.1	12.7±1.10	45.0±1.49	44.9±0.06	1080±23	553±13	501±23	21.6±0.04	28.9±0.47	6.71±0.28	0.22±1.16	20.3±0.38	9.19±0.03
Tertile 2	56.3±1.04	0.4±1.1	10.6±1.08	45.9±1.36	44.4±0.58	1120±20	573±12	524±21	21.6±0.04	29.2±0.43	7.01±0.25	0.28±1.27	20.4±0.35	9.23±0.03
Tertile 3	56.5±1.05	0.5±1.1	10.6±1.60	46.2±1.60	43.7±0.69	1156±24*	587±14	547±25	21.6±0.05	28.8±0.51	6.42±0.30	0.17±1.25	21.1±0.41	9.14±0.03
§ p for trend	0.812	0.266	0.198	0.615	0.266	0.037	0.113	0.226	0.492	0.851	0.514	0.423	0.212	0.445
Plaque Score Group														
Group 1	57.3±1.03	0.5±1.12	12.3±1.07	45.2±1.18	45.1±0.51	1103±18	546±10	534±18	21.6±0.03	29.4±0.37	6.90±0.22	0.24±1.21	20.7±0.30	9.20±0.03
Group 2	60.2±1.05	0.5±1.20	10.9±1.11	48.8±1.84	44.3±0.79	1151±28	592±16*	535±29	21.6±0.05	29.0±0.59	6.29±0.34	0.20±1.19	21.0±0.48	9.14±0.04
Group 3	53.5±1.05	0.3±1.18*	9.67±1.10	44.7±1.72	42.9±0.73	1130±26	606±15*	499±27	21.7±0.05	28.3±0.55	6.74±0.32	0.19±1.23	20.1±0.44	9.20±0.04
§ p for trend	0.304	0.038	0.069	0.846	0.03	0.432	0.003	0.333	0.201	0.124	0.703	0.376	0.268	0.912

Notes. HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

Intimal medial thickness tertile 1: 0.335–0.565, n = 219; tertile 2: 0.570–0.665, n = 221; tertile 3: 0.670–1.100, n = 216.

Plaque score group 1: plaque score 0, n = 355; group 2: plaque score 1, n = 119; group 3: plaque score 2–7, n = 182.

Data are expressed as LSMEANS ± SE.

Data are adjusted for age, gender, BMI, systolic blood pressure, and current smoking.

* $p < 0.05$ vs tertile 1.

** Values for total VLDL, large VLDL, intermediate VLDL, and intermediate HDL are back log-transformed.