Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Original Article

Lipoprotein particle number and size predict vascular structure and function better than traditional lipids in adolescents and young adults

Elaine M. Urbina*, Connie E. McCoy, Zhiqian Gao, Philip R. Khoury, Amy S. Shah, Lawrence M. Dolan, Thomas R. Kimball

Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH, USA

KEYWORDS:
Carotid arteries;
Arterial stiffness;
Lipoproteins;
Dyslipidemia;
Pediatrics

BACKGROUND: In adults, dyslipidemia is associated with higher carotid thickness and arterial stiffness, predictors of cardiovascular events. In young subjects, lipid concentrations have not been consistently associated with vascular measures.

OBJECTIVE: The objective of the study was to compare nuclear magnetic resonance (NMR) measures of lipoprotein particle number (low-density lipoprotein [LDL] particle, low-density lipoprotein [HDL] particle, very low-density lipoprotein [VLDL] particle) and size (LDL size, HDL size, and VLDL size) to determine if they were associated with vascular measures more strongly than lipid concentrations (LDL cholesterol, HDL cholesterol, and triglyceride [TG]).

METHODS: We evaluated 214 lean (L), 228 obese (O), and 214 diabetic (T2DM) subjects aged 10 to 24 years (33% male and 39% Caucasian). Cardiovascular risk factors, vascular structure, and arterial stiffness were measured. General linear models were constructed including demographics, risk factors, and traditional or NMR lipid parameters. A composite vascular function score was developed as the outcome in receiver operator characteristic scores for determining which lipid parameter was superior in predicting vascular damage.

RESULTS: Risk factors worsened from L to O to T. However, LDL cholesterol was similar in O and T, whereas LDL size differentiated the 3 groups (T > O > L, $P \leq .0001$). Models demonstrated the superiority of NMR values, which entered for all but 1 vascular outcome and explained more of the variance than traditional lipid concentrations. Receiver operator characteristic curves demonstrated that NMR values were superior in predicting vascular outcomes. Models stratified by race were similar but cutpoints predicting vascular outcomes differed by race for TG, TG/HDL, and VLDL.

CONCLUSION: Lipoprotein particle number and size are more strongly related to vascular structure and function than traditional lipid values. NMR lipid measures may be a better indicator of risk for target organ damage than traditional lipid measures in adolescents and young adults.

This study was supported by NIH (NHLBI) R01 HL076269 & in part by US Public Health Service Grant #UL1 RR026314 from the National Center for Research Resources, NIH (CTSA grant).

* Corresponding author. Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 7002, Cincinnati, OH 45229, USA.
E-mail address: elaine.urbina@cchmc.org
Submitted February 14, 2017. Accepted for publication May 22, 2017.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2017.05.011

Introduction

In the late 1950s, the Framingham Heart Study established the relationship between elevated cholesterol levels and cardiovascular (CV) disease.[1] Subsequent data demonstrate that a substantial number of individuals who develop CV disease have normal low-density lipoprotein (LDL) cholesterol (LDL-C) levels.[2] Recently, direct measurement of lipoprotein particle size with nuclear magnetic resonance (NMR) has become available for clinical and research use.[3] The use of NMR allows for measurement of number and size of LDL particles, which may be better predictors of CV events[4] and early noninvasive atherosclerotic target organ damage (carotid intima media thickness [cIMT])[5] in adults than traditional cholesterol concentration.

Few studies have measured lipoprotein particle size and number in adolescents and young adults[6,7] but none have compared their usefulness in predicting target organ damage in young subjects. Therefore, we measured traditional and NMR lipid values and cIMT and arterial stiffness in adolescents and young adults. We hypothesized that NMR lipid values would be more strongly associated with target organ damage than traditional lipids even after adjusting for other CV risk factors.

Materials and methods

Population

The population consisted of 674 subjects mean aged 18 years (10–24 years, 33% male, 39% Caucasian) recruited for a study of the effects of type II diabetes mellitus (T2DM) on CV health. There were 12 Hispanics: 6 subjects who identified as White and Hispanic, 1 Black and Hispanic, 4 other Hispanic, and 1 more than 1 race Hispanic. Of the non-Hispanics, 259 were White, 394 Black, 1 American Indian, 8 more than 1 race. Because there were so few Hispanics and races other than White or Black, for analyses, the races/ethnicities were compressed into White and Black without regards to ethnicity. Subjects with T2DM were matched by age, race (Caucasian or African American), and sex to both lean and obese controls. T2DM ($T = 214$) was determined using American Diabetes Association criteria.[8] Obese controls ($O = 228$) had body mass index (BMI) ≥95th percentile by CDC criteria with normal oral glucose tolerance test. Lean subjects ($L = 214$) had BMI ≤85th percentile. Pregnant women were excluded. Written informed consent was obtained from individuals aged >18 years or the parent or guardian for individuals aged <18 years. Written assent was also obtained for individuals aged <18 years according to the guidelines established by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Laboratory

After a minimum 10-hour overnight fast, participants had questionnaire, anthropometric, blood pressure (BP), laboratory, and vascular structure and function data collected. Experienced personnel obtained 2 measures of height using a calibrated stadiometer (Veeder-Root, Elizabethtown, NC) and 2 measures of weight using a Health-O-Meter electronic scale. The average of each was used. Three measures of BP were obtained with a mercury sphygmomanometer according to published pediatric standards,[9] and the average was used. Fasting plasma glucose, insulin, glycosylated hemoglobin (HbA1c), and high sensitivity C-reactive protein were measured by standard techniques.[10] Assays of fasting plasma lipids were carried out in an NHLBI-CDC standardized laboratory. LDL-C concentration was calculated using the Friedewald equation as previously described.[10]

The lipoprotein particle analysis was performed with a 400-MHz proton NMR analyzer at LipoScience (Raleigh, NC) as previously described.[3] In brief, the number of particles of lipoprotein subclasses of different size is derived from the measured amplitudes of the distinct lipid methyl group NMR signals they emit. The intensity of each signal is proportional to the quantity of the subclass, which is converted to particle concentration units (nmol/L for LDL particle [LDL-P] and very low-density lipoprotein cholesterol particle [VLDL-P] and μmol/L for high-density lipoprotein cholesterol particle [HDL-P]).

Although this technique can separate VLDL, LDL, and HDL into 10 subclasses, average particle numbers were counted (VLDL-P, LDL-P, and HDL-P) and sizes (VLDL-S, LDL-S, and HDL-S) were computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its methyl NMR signal. NMR lipoprotein particle analyses were done on frozen samples that had been stored at −80°C. Previous studies have demonstrated that NMR lipoprotein particle analyses are unaffected by frozen storage and multiple freeze-thaw cycles.[11] Reproducibility of the NMR-measured lipoprotein particle parameters determined by replicate analyses of plasma pools found between-run coefficients of variability for low-normal concentrations were <4% for total LDL-P and HDL-P concentrations, <0.5% for LDL-S and HDL-S, <8% for large and small LDL subclasses, and <5% for large and small HDL subclasses.[11] For all NMR analyses, samples were handled in a fully blinded fashion such that investigators had no knowledge of subject characteristics.

Vascular testing

Carotid ultrasound was performed using B-mode ultrasonography with a GE Vivid 7 ultrasound imaging system (GE Medical Systems, Wauwatosa, WI) with a high-resolution linear array vascular ultrasound centered at 7.5 MHz. For each subject, the far wall of each carotid segment bilaterally was examined independently from continuous angles to identify the thickest cIMT for the right and left common, bulb (bifurcation), and internal carotid arteries. Multiple digital image loops were digitally