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Lipids and lipoprotein ratios: Contribution to carotid intima media thickness in adolescents and young adults with type 2 diabetes mellitus

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BACKGROUND: Dyslipidemia is common among adolescents with type 2 diabetes (T2D).

OBJECTIVE: To assess whether the lipoprotein ratios of low-density lipoprotein (LDL) cholesterol/high-density lipoprotein (HDL) cholesterol or triglycerides/HDL or non-HDL cholesterol are more useful than the traditional lipid panel to predict increased arterial thickness in adolescents and young adults with T2D.

METHODS: We evaluated 244 adolescents and young adults with T2D in a cross-sectional study (mean age 18 years; 56% African American; 65% female). Demographics, anthropometrics, and laboratory data were collected. Arterial thickness was assessed with carotid intima media thickness (IMT). Bivariate correlations and general linear models were used to determine the independent contributions of the various lipid parameters to carotid IMT.

RESULTS: Bivariate correlations showed LDL/HDL ratio was the strongest predictor of carotid IMT ($P < .02$). After adjustment for potential covariates LDL/HDL was no longer significant. HDL cholesterol was the only lipid to independently (negatively) contribute to carotid IMT. Other risk factors that were independently associated with carotid IMT included age, race, sex, body mass index *z* score, and hemoglobin A_{1c}. Together these cardiovascular risk factors explained <20% of the variance in carotid IMT.

CONCLUSIONS: HDL cholesterol is the only lipid to independently associate with carotid IMT. Lipoprotein ratios and non-HDL did not provide additional information. The low variance in carotid IMT explained by traditional risk factors suggests nontraditional risk factors may be important to assess to better understand the contributors to early-stage atherosclerosis in adolescents and young adults with T2D.

Dyslipidemia is common in adults with type 2 diabetes[1–3] and contributes to the increased risk to develop cardiovascular disease in the setting of type 2 diabetes.[4] Lipid abnormalities often include high plasma triglycerides (TGs), low

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levels of high-density lipoprotein (HDL) cholesterol, and increased small dense low-density lipoprotein (LDL) particles, termed diabetic dyslipidemia.[5] Recent data suggest that non-HDL cholesterol[6,7] or lipoprotein ratios, including LDL/HDL or TG/HDL,[8,9] or both may be able to better predict cardiovascular disease risk than the traditional lipid profile.

Dyslipidemia is also common in youth with type 2 diabetes.[3,10] Whether non-HDL cholesterol or lipoprotein ratios are more useful than the traditional lipid profile to predict early arterial thickness as measured by carotid intima media thickness (IMT) in adolescents and young adults with type 2 diabetes is not known.

Methods

Participants were recruited from the Diabetes Clinic at Cincinnati Children's Hospital Medical Center, local physician offices, college campuses, and health fairs as part of a cross-sectional study that was designed to evaluate cardiovascular structure and function in adolescents and young adults with type 2 diabetes, as previously described.[11]

Eligibility criteria for the study included age older than 11 years with a diagnosis of type 2 diabetes given by a health care provider. All persons had no evidence of another specific type of diabetes (type 1 diabetes) and were non-insulin dependent. For 210 participants islet cell antibody was also available and showed no evidence of glutamic acid decarboxylase, islet cell antigen 512, and insulin autoantibodies. Pregnant females were excluded from this study.

Before enrollment in the study, written informed consent was obtained from subjects $\geq$18 years or the parent or guardian with written assent for subjects $<$18 years according to the guidelines established by the Institutional Review Board at Cincinnati Children's Hospital Medical Center and in accordance with the Declaration of Helsinki.

Participants were seen by in-person study visit when demographic, anthropometric, and fasting blood ($>$10 hour) was drawn. Height and weight were obtained as previously described.[11]. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Pubertal staging (breast staging for females and testicular staging for males) was obtained from self-report data. Blood pressure (BP) was obtained manually with sphygmomanometer (Baum Desktop Model with V-Lok cuffs; Copiague, New York, NY) according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents[12] with the average of 3 measurements used in the analysis. Duration of type 2 diabetes was measured from the date of diagnosis to the date of study.

Fasting plasma lipid profiles were performed in a laboratory that is standardized by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention. The LDL cholesterol concentration was estimated with the Friedewald equation. Fasting plasma glucose was measured with a Hitachi model 704 glucose analyzer (Roche Hitachi, Indianapolis, IN). Glycosylated hemoglobin A_{1c} (hemoglobin A_{1c}) was measured in red blood cells with the use of high-performance liquid chromatography methods.

On the day of the study visit carotid ultrasound studies were performed by a single research vascular technologist. Both the right and left carotid arteries were evaluated with high-resolution B-mode ultrasonography with the use of a GE Vivid 7 ultrasound imaging system (GE Medical Systems, Wauwatosa, WI) with a 7.5-MHz high-resolution linear array transducer. For each subject, the carotid wall and segments were examined independently from continuous angles to identify the thickest carotid IMT. Three segments were identified: the common artery, the bulb (bifurcation), and the internal carotid artery with the average value from the right and left side used in the analyses.

Multiple digital image loops were digitally transmitted with the Camtronics Medical System (Hartland, WI) for offline reading. A trace technique was used to measure the maximum carotid thickness from the leading edge. All images were read by a single research-trained vascular technician. Carotid IMT was measured from the leading edge (lumen-intima) to the leading edge (medial-adventia). This technique has been found to be more reproducible than point-to-point measurements (coefficient of variation for repeat readings, 5.3%–8% for trace vs 8.4%–11.6% for point-to-point measurements for the 3 carotid segments).[13]

All analyses were performed with SAS software version 9.2 (Cary, NC). Data are mean $\pm$ standard deviation. Variance-stabilizing procedures were applied as needed, and non-normally distributed variables were log transformed (ie, TGs). Bivariate correlations were used to assess the relationship between lipid parameters (independent variable) and carotid segments (dependent variable). Specific lipids of interest included LDL cholesterol, HDL cholesterol, TGs, and non-HDL cholesterol. Non-HDL cholesterol was included because it is thought to be a more powerful predictor of coronary heart disease mortality and nonfatal coronary events than LDL cholesterol in patients with diabetes.[6,14–16] Lipoprotein ratios included TG/HDL, representing small dense LDL particles,[8] and LDL/HDL.

Next, stepwise general linear models were constructed to elucidate the independent determinants of 3 carotid segments. Initial models included lipids and were adjusted for age, race, and sex. Final models incorporated additional covariates that were found to be significantly associated ($P < .05$) with 1 or more of the carotid segments in bivariate associations and included age, race, sex, BMI z score, BP, glucose, hemoglobin A_{1c}, and duration of type 2 diabetes. P values of $< .05$ were deemed significant.

Results

The study population consisted of 244 obese (BMI, 37 $\pm$ 9) adolescents and young adults with a mean age of 18.1 $\pm$ 3.1 years (range, 10–23 years; Table 1) Less than 10% of the participants were younger than 14 years.