Lipid and Lipoprotein Profiles in Youth With and Without Type 1 Diabetes

The SEARCH for Diabetes in Youth Case-Control Study

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OBJECTIVE — The purpose of this study was to compare the lipid profile and the prevalence of lipid abnormalities in youth with and without type 1 diabetes and explore the role of glycemic control on the hypothesized altered lipid profile in youth with type 1 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional analysis of 512 youth with type 1 diabetes (mean duration 4.22 years) and 188 healthy control subjects aged 10–22 years in Colorado and South Carolina. SEARCH for Diabetes in Youth (SEARCH) participants with type 1 diabetes and healthy control subjects recruited from primary care offices in the same geographic regions were invited to attend a research visit. Fasting lipid profiles were compared between youth with type 1 diabetes (stratified according to categories of optimal [A1C <7.5%] and suboptimal [A1C ≥7.5%] glycemic control) and healthy nondiabetic youth, using multiple linear and logistic regression.

RESULTS — Youth with type 1 diabetes and optimal A1C had lipid concentrations that were similar (total cholesterol, LDL cholesterol, and LDL particle size) or even less atherogenic (HDL cholesterol, non-HDL cholesterol, triglyceride, and triglyceride–to–HDL cholesterol ratio) than those observed in nondiabetic youth, whereas youth with suboptimal glycemic control had elevated standard lipid levels (total cholesterol, LDL cholesterol, and non-HDL cholesterol). Youth with type 1 diabetes also had significantly elevated apolipoprotein B levels and more small, dense LDL particles than nondiabetic youth, regardless of glycemic control.

CONCLUSIONS — Youth with type 1 diabetes have abnormal lipid levels and atherogenic changes in lipoprotein composition, even after a relatively short disease duration. As in adults, glycemic control is an important mediator of these abnormalities.

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Diabetes is a major risk factor for cardiovascular disease (CVD) (1). In patients with type 1 diabetes, atherosclerosis occurs earlier in life, leading to increased morbidity and mortality compared with those in the general population (2). Moreover, studies of the natural history of atherosclerosis development point to an origin of the lesions in childhood and adolescence (3).

Lipid concentrations are strongly related to the risk of CVD in adults with diabetes (4), Although lipid levels in adults with type 1 diabetes have been described as comparable to those in nondiabetic individuals (5), adults with type 1 diabetes are known to have a higher risk for atherosclerotic disease compared with that of the general population (2). The SEARCH for Diabetes in Youth (SEARCH) study recently showed that a substantial proportion of youth aged 10–22 years with type 1 diabetes had lipid levels outside the recommended targets (6). However, it is not known whether the lipid profile (lipid concentrations and lipoprotein composition) in youth with type 1 diabetes is proatherogenic compared with that in healthy nondiabetic youth. Some data suggest that, in adults with diabetes, lipoprotein composition is more atherogenic (7) and is substantially influenced by glycemic control (8). The goals of this study were to compare the lipid and lipoprotein profile, as measured by total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, non-HDL cholesterol, the triglyceride–to–HDL cholesterol ratio, apolipoprotein B (apoB), and LDL particle size and density in youth with and without type 1 diabetes, and to explore the role of glycemic control, as measured by A1C, on the hypothesized altered lipid profile in type 1 diabetic youth.

RESEARCH DESIGN AND METHODS

— Data for this analysis derive from the SEARCH Case-Control Study, an ancillary study to SEARCH (9). SEARCH is a multicenter study that conducts population-based ascertainment of nongestational cases of physician-diagnosed diabetes in youth.

SEARCH Case-Control was designed to assess selected risk factors for childhood diabetes in young individuals aged 10–22 years recruited specifically at the Colorado and South Carolina SEARCH sites. Diabetes cases were identified at both sites using a network of health care providers. All youth aged ≥10 years who participated in the SEARCH study visit between July 2003 and March 2006 in Colorado and South Carolina and were of

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Table 1—*Demographic, metabolic, and clinical characteristics of participants, according to study group*

Variable	Type 1, A1C <7.5%	*P* value*	Control	*P* value†	Type 1, A1C ≥7.5%
n	164		188		348
Age at visit	13.9 (13.4–14.4)	0.1	14.4 (14.0–14.8)	0.02	15.0 (14.7–15.4)
Sex (% male)	57.3	0.001	39.9	0.1	46.6
Race/ethnicity (%)		<0.0001		<0.0001	
Non-Hispanic white	82.9		54.3		79.9
Hispanic	8.5		17.6		9.8
African American	8.5		28.2		10.3
A1C (%)	6.5 (6.4–6.6)	<0.001	5.1 (5.1–5.2)	<0.001	9.2 (9.0–9.4)
BMI (kg/m^2)	22.7 (22.0–23.4)	0.07	23.7 (22.8–24.7)	0.001	22.0 (21.6–22.5)
BMI *z* score	0.6 (0.4–0.8)	0.5	0.7 (0.5–0.8)	0.03	0.5 (0.4–0.6)
Waist (cm)	79.5 (77.7–81.4)	0.7	80.1 (77.9–82.3)	0.1	78.2 (77.0–79.5)
Systolic blood pressure (mmHg)	106.5 (104.8–108.2)	0.3	107.6 (106.0–109.2)	0.2	106.3 (105.0–107.6)
Diastolic blood pressure (mmHg)	69.0 (67.5–70.5)	0.3	69.9 (68.6–71.3)	0.2	68.8 (67.8–69.9)
Physical activity	4.21 (3.47–4.94)	0.01	5.41 (4.66–6.17)	0.7	5.21 (4.57–5.86)
Insulin dose (units · kg^{-1} · day^{-1})	0.54 (0.50–0.59)		N/A		0.82 (0.78–0.86)
Duration (years)	2.2 (1.7–2.8)		N/A		5.1 (4.6–5.6)

Characteristics are expressed as means (95% CI) or %. *Type 1 diabetes and A1C <7.5 versus control. †Type 1 diabetes and A1C ≥7.5 versus control. N/A, not applicable.

non-Hispanic white, African American, and Hispanic backgrounds were also invited to participate in SEARCH Case-Control. Altogether, 64% of eligible type 1 diabetic subjects participated. Control subjects were recruited from primary care offices in the same geographic areas and were confirmed by fasting glucose to be nondiabetic by American Diabetes Association (ADA) criteria (10). The study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study population.

Data collection

The clinical diabetes type assigned by the health care provider was obtained from medical records or physician reports and categorized as type 1 diabetes if the provider assignment was type 1, type 1a, or type 1b. Race/ethnicity was collected from self-reports using 2000 U.S. Census–based questions and categorized as non-Hispanic white, Hispanic, and African American. Pubertal development was self-assessed using the method described by Marshall and Tanner (11) with a standardized series of drawings with explanatory text. The Tanner stage ranged from 1 (prepuberal) to 5 (adult stage). BMI was calculated (weight in kilograms divided by the square of height in meters) and age- and sex-specific BMI *z* scores were derived based on the Centers for Disease Control and Prevention national standards (12). Physical activity was obtained by self-report using questions based on the Youth Risk Behavior Surveillance System (13) and was categorized as the average number of 30-min blocks of moderate-to-vigorous activity per day.

Laboratory samples were obtained under conditions of metabolic stability, defined as no episode of diabetic ketoacidosis during the previous month. All specimens were processed locally and shipped within 24 h to the central laboratory (University of Washington) for analysis. Measurements of plasma cholesterol, triglycerides, and HDL cholesterol were performed enzymatically on a Hitachi 917 autoanalyzer (Roche Molecular Biochemicals, Indianapolis, IN). LDL cholesterol was calculated by the Friedewald equation for individuals with a triglyceride concentration <400 mg/dl and the BetaQuantification procedure for those with triglycerides of ≥400 mg/dl (13). A1C was measured by a dedicated ion-exchange high-performance liquid chromatography instrument (TOSOH, San Francisco, CA). ApoB was measured by a nephelometric system (BNII; Behring Diagnostics, Deerfield, IL). Relative flotation number (R_f) for LDL was determined by a technique described previously (14). Cut points for elevated lipid levels (total cholesterol ≥200 mg/dl, LDL cholesterol ≥130 mg/dl, high non-HDL cholesterol ≥130 mg/dl, elevated triglycerides ≥150 mg/dl, and low HDL cholesterol ≤35 mg/dl) were taken from the Third Report of the National Cholesterol Education Program (Adult Treatment Panel III) (1) and the ADA (15).

Statistical analysis

Statistical analyses were performed using SAS for Windows (version 9.2; SAS Institute, Cary, NC). Demographic characteristics were described with means and 95% confidence intervals (CIs) for continuous variables and frequencies for categorical variables. The natural logarithmic transformations of total cholesterol, LDL cholesterol, triglyceride, non-HDL cholesterol, and apoB were used to improve normality of the residuals. Youth with type 1 diabetes were categorized according to glycemic control as optimal (A1C <7.5%) or suboptimal (A1C ≥7.5%), and each category was compared with the referent control group. Lipid levels were compared by mixed-effects models using A1C status (type 1 diabetes optimal A1C versus control and type 1 diabetes suboptimal A1C versus control) as the primary independent variable, with adjustments for age (as a second-order polynomial), sex, race/ethnicity, and BMI. Mixed-effects models were used to allow for unequal variances by diabetes status. Mixed-model analysis results are expressed as adjusted means (95% CI), adjusted to the mean age, BMI, and observed race/ethnicity and sex proportions for the type 1 diabetic group. Adjusted prevalence estimates of abnormal lipid concentrations (95% CIs) were obtained with logistic regression by calculating the predicted prevalence for type 1 diabetic and control subjects at the mean age, observed race/ethnicity, and sex proportions for the type 1 diabetic group.

Table 2—*Lipid levels in nondiabetic control youth and youth with type 1 diabetes with optimal (A1C <7.5%) and suboptimal (A1C ≥7.5%) glycemic control*

Variable	Type 1, A1C <7.5%	*P* value*	Control	*P* value†	Type 1, A1C ≥7.5%
	164		188		348
Cholesterol (mg/dl)	155.6 (151.0–160.3)	0.8	156.2 (152.0–160.5)	<0.0001	169.8 (165.8–174.0)
LDL cholesterol (mg/dl)	91.2 (87.3–95.3)	0.7	91.9 (88.3–95.6)	0.0003	100.1 (96.9–103.5)
Triglyceride (mg/dl)	62.8 (58.5–67.3)	<0.0001	81.2 (75.5–87.4	0.2	76.6 (71.8–81.7)
HDL cholesterol (mg/dl)	50.6 (48.7–52.5)	<0.0001	46.1 (44.4–47.7)	<0.0001	52.3 (50.8–53.8)
Non–HDL cholesterol (mg/dl)	104.5 (100.4–108.8)	0.07	109.4 (105.4–113.5)	0.006	116.5 (112.7–120.4)
Triglyceride-to–HDL cholesterol ratio	1.45 (1.29–1.60)	<0.0001	2.10 (1.89–2.31)	0.9	2.14 (1.73–2.55)
ApoB (mg/dl)	69.1 (65.9–72.5)	<0.0001	54.3 (52.0–56.7)	<0.0001	76.9 (74.1–79.9)
LDL (R_f)	0.283 (0.280–0.286)	0.4	0.282 (0.279–0.285)	<0.001	0.275 (0.272–0.278)

Data are adjusted means (95% CI). *Type 1 diabetes and A1C <7.5 versus control. †Type 1 diabetes and A1C ≥7.5 versus control.

RESULTS — Table 1 summarizes the demographic, metabolic, and clinical characteristics of participants, according to study category. There were 164 youth with type 1 diabetes and optimal A1C values, 348 youth with suboptimal A1C values, and 188 healthy control subjects with complete data on the main variables of interest. Compared with control youth, patients with type 1 diabetes and optimal A1C values were more likely to be male and non-Hispanic white and tended to be slightly younger and less physically active. Compared with control youth, patients with type 1 diabetes and suboptimal A1C values were older and subwere more likely to be non-Hispanic white and to have lower BMI. Waist circumference, blood pressure levels, and Tanner stage were not different among the three groups. As expected, mean A1C levels were higher in both subgroups with type 1 diabetes than in control youth. Given these differences, lipid levels explored in Table 2 were adjusted for age, sex, race/ethnicity, and BMI. There were significant differences between the two type 1 diabetic subgroups in terms of disease duration, physical activity, and daily insulin dose. Separate analyses to assess the potential influence of these differences between the two diabetic subgroups on various lipid parameters were also conducted.

Table 2 compares the mean lipid levels among control subjects, youth with type 1 diabetes with optimal A1C levels (<7.5%), and youth with suboptimal values for A1C (≥7.5%) after adjustment for age, sex, race/ethnicity, and BMI. Compared with control subjects, youth with optimal A1C levels had similar mean levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, and LDL particle size (LDL R_f); lower levels of triglyceride; higher HDL cholesterol levels; and a lower triglyceride–to–HDL cholesterol ratio. However, mean apoB concentrations were higher, despite no differences in LDL cholesterol levels. Type 1 diabetic youth with suboptimal levels of A1C had a more atherogenic lipid and lipoprotein pattern, such that mean values were significantly higher than those in control subjects for total cholesterol, LDL cholesterol, non-HDL cholesterol, and apoB and significantly lower for LDL particle size. Nevertheless, even youth with suboptimal A1C had higher HDL cholesterol levels than control subjects. These patterns were virtually unchanged with additional adjustment for differences in duration of diabetes between the two groups of youth with type 1 diabetes (2.2 vs. 5.1 years in youth with type 1 diabetes with optimal and suboptimal A1C, respectively). Additional adjustment for minor differences in physical activity patterns did not influence the observed differences in HDL cholesterol. Adjustment for different daily insulin doses only slightly attenuated the difference in triglyceride levels between the two diabetes subgroups (62.7 vs. 71.5 mg/dl in type 1 diabetes with optimal and suboptimal A1C, respectively).

Figure 1 shows the age-, sex- and race/ethnicity-adjusted prevalence estimates of abnormal lipid concentrations in each study group, with *P* values comparing each type 1 diabetic group with the healthy control group. Similar to the findings regarding mean lipid levels, the prevalence of abnormal standard lipid

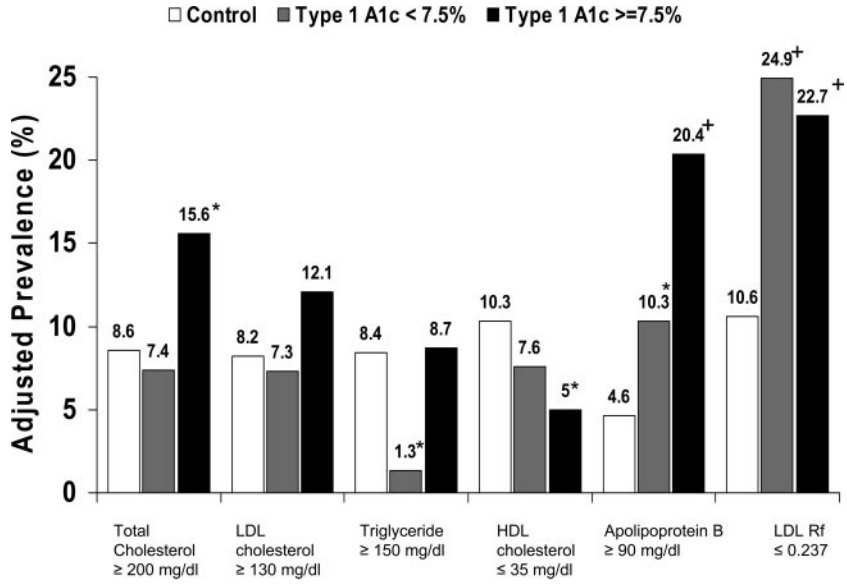

Figure 1—*Prevalence of abnormal lipid concentrations, adjusted for age, sex, and race/ethnicity in nondiabetic youth, youth with type 1 diabetes in optimal (A1C <7.5%), and suboptimal (A1C ≥7.5%) glycemic control.* *P < *0.05, type 1 diabetes with optimal or suboptimal A1C versus healthy youth.* +P < *0.01, type 1 diabetes with optimal or suboptimal A1C versus healthy youth.*

concentrations (total cholesterol, LDL cholesterol, and HDL cholesterol) was similar in youth with type 1 diabetes and optimal A1C levels versus nondiabetic youth. Youth with type 1 diabetes with optimal glycemic control also had the lowest prevalence of elevated triglyceride of all three groups. The type 1 diabetic youth with suboptimal glycemic control had a higher prevalence of abnormal standard lipid factors than control subjects, reaching statistical significance for elevated total cholesterol. The proportion of youth with elevated nontraditional lipid factors, high apoB, and small, dense LDL particles was significantly higher in type 1 diabetic patients with both optimal and suboptimal A1C levels compared with healthy control subjects. There was a gradient of increasing prevalence of elevated apoB levels with increasing A1C.

CONCLUSIONS — We found that in youth with type 1 diabetes and relatively short disease duration (mean 4.2 years) mean lipid levels and prevalence of lipid abnormalities are substantially influenced by glycemic control. Youth with type 1 diabetes and optimal A1C levels have lipid profiles that are similar (total and LDL cholesterol) or even less atherogenic (HDL cholesterol, triglyceride, and triglyceride-to-HDL ratio) than those observed in nondiabetic youth. In contrast, youth with type 1 diabetes and suboptimal glycemic control have higher standard lipid levels and prevalence of lipid abnormalities (total cholesterol, LDL cholesterol, and non-HDL cholesterol) than nondiabetic youth. Moreover, youth with type 1 diabetes have significantly elevated apoB levels and more small, dense LDL particles than nondiabetic youth, regardless of glycemic control. We also found that the most frequent lipid abnormalities in youth with type 1 diabetes compared with nondiabetic control subjects are elevated apoB levels and an increased proportion with small, dense LDL particles.

Data on lipid and lipoprotein factors in youth with type 1 diabetes are scarce; studies are relatively small and often do not include a control group. Most data are based on adults with childhood-onset diabetes. Our observation that youth with type 1 diabetes and optimal glycemic control have a less atherogenic standard lipid profile, especially with respect to triglyceride and HDL cholesterol levels, agrees with previous data in adults (16). In general, lipid concentrations were shown to be antiatherogenic in adults with type 1 diabetes who had optimal glycemic control or intensive insulin treatment (16). However, the lack of abnormal lipid levels does not exclude the possibility of compositional changes that may be atherogenic, especially among those with poor glycemic control. James and Pometta (17) found that in adults with poorly controlled type 1 diabetes, triglyceride-rich lipoprotein particles are increased; LDL subclass distribution shifts to relative excess of small, dense LDL; and LDL particles are more triglyceride rich compared with those of normal subjects. Under normal circumstances, triglyceride-rich particles are rapidly hydrolyzed by lipoprotein lipase. The enzyme is induced in adipose tissue by insulin, and thus, intensive insulin therapy is typically associated with a marked fall of triglyceride-rich particles (17). This may be one explanation for lower triglyceride and higher HDL cholesterol concentrations in youth with type 1 diabetes versus healthy control subjects.

Our findings that youth with suboptimal glycemic control have increased concentrations and a higher prevalence of abnormal standard lipid levels, as well as more small, dense LDL particles and higher apoB levels, also agree with the previous literature in adults (18). Similarly, among SEARCH youth with type 1 diabetes, total and LDL cholesterol, triglyceride, and non-HDL cholesterol levels (19) and also dense LDL and apoB concentrations (14) increased with increasing A1C.

The measurement of apoB and dense LDL in individuals with diabetes has been sparse, particularly in children and adolescents. The higher proportion of youth with type 1 diabetes with elevated apoB versus healthy control subjects can be explained by the increased concentration of triglyceride-rich apoB-containing lipoproteins and by the presence of dense LDL that is enriched in apoB relative to its cholesterol content. In our study, even youth with optimal A1C levels had elevated apoB and an increased proportion of small, dense LDL particles relative to those in nondiabetic control subjects, suggesting that even mild hyperglycemia may be associated with atherogenic compositional lipoprotein changes even if concentrations of standard lipid are unaffected.

Both apoB and small, dense LDL particles have been shown to be strong and independent predictors of CVD. ApoB has been shown to be a better predictor of incident CVD than LDL cholesterol and non-HDL cholesterol (20). The dense LDL particle subclass is associated with increased risk of ischemic heart disease events (21) and narrowing of an existing cardiac stenosis in adults (22). Thus, elevated apoB and/or dense LDL particles in youth with type 1 diabetes may contribute substantially to increased cardiovascular morbidity and mortality in adulthood. Currently, the ADA guidelines for managing dyslipidemia in children and adolescents with diabetes advise optimizing glycemic control, improving diet, and keeping LDL cholesterol, HDL cholesterol, and triglycerides within specific targets (15). Our data suggest that apoB and small, dense LDL particles may also represent important targets because they appear to be elevated even among patients with well-controlled type 1 diabetes and because CVD risk relates more closely to the level of apoB than to cholesterol indexes.

This study has several potential limitations. First, it is cross-sectional and thus is limited to describing observed associations. Half of the patients with type 1 diabetes in this study had a disease duration of <2 years, thus limiting the generalizability of our findings to the larger population of youth with type 1 diabetes. We had limited power to conduct race/ethnicity-specific analyses; however, similar patterns were noted across all racial/ethnic groups. Major strengths of our study include a relatively large sample of youth with type 1 diabetes, with a range of A1C levels, a detailed examination of lipid and lipoprotein profiles, and, importantly, a nondiabetic control group.

In summary, our study presents novel information on characteristics of dyslipidemia in youth with type 1 diabetes compared with nondiabetic control subjects. Youth with type 1 diabetes present with abnormal lipid levels and atherogenic changes in lipoprotein composition, even after a relatively short disease duration. As in adults, glycemic control seems to be an important mediator of these abnormalities. Further research is needed to fully understand the mechanisms by which type 1 diabetes contributes to altered lipid profiles and increased cardiovascular risk.

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