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Lipid and Lipoprotein Profiles in Youth with and Without Type 1 Diabetes: The SEARCH Case-Control Study

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Objective: 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: Cross-sectional analysis of 512 youth with type 1 diabetes (mean duration 4.22 years) and 188 healthy controls age 10-22 years in Colorado and South Carolina. SEARCH youth 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 non-diabetic 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-C, and LDL particle size) or even less atherogenic (HDL-C, non-HDL-C, triglyceride, triglyceride/HDL-C ratio) than those observed in non-diabetic youth, while youth with suboptimal glycemic control had elevated standard lipid levels (total, LDL-C and non-HDL-C). Youth with type 1 diabetes also had significantly elevated Apo B levels and more small/dense LDL particles than non-diabetic 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.

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 to 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 non-diabetic individuals (5), adults with type 1 diabetes are known to be at higher risk for atherosclerotic disease compared to the general population (2). The SEARCH study recently showed that a substantial proportion of youth age 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 pro-atherogenic in comparison to healthy non-diabetic youth. Some data suggest that, in adults with diabetes, lipoprotein composition is more atherogenic (7), and 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 (LDL-C), HDL-cholesterol (HDL-C), triglyceride, non-HDL-cholesterol (non-HDL-C), triglyceride/HDL-C Ratio, apolipoprotein B (Apo B), 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 hemoglobin A1c (A1c), on the hypothesized altered lipid profile in type 1 diabetes youth.

RESEARCH DESIGN AND METHODS

Data for this analysis derive from the SEARCH for Diabetes in Youth Case-Control (SEARCH CC) Study, an ancillary study to SEARCH for Diabetes in Youth (9). SEARCH is a multi-center study that conducts population-based ascertainment of non-gestational cases of physician-diagnosed diabetes in youth.

SEARCH CC was designed to assess selected risk factors for childhood diabetes in young people ages 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 age $\geq$ 10 years who participated in the SEARCH study visit between July 2003 and March 2006 in Colorado and South Carolina and were of non-Hispanic white (NHW), African-American (AA) and Hispanic background were also invited to participate in SEARCH CC. Altogether, 64% of eligible type 1 diabetes subjects participated. Control subjects were recruited from primary care offices in the same geographic areas and were confirmed by fasting glucose to be non-diabetic by ADA criteria(10). The study was reviewed and approved by the local Institutional Review Boards (IRBs) 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 US Census-based questions and categorized as non-Hispanic white (NHW), Hispanic, and African American (AA). Pubertal development was self-assessed using the method described by Tanner and Marshall (11) with a standardized series of drawings with explanatory text. The Tanner stage ranged from 1 (prepuberal) to 5 (adult stage).

Body mass index (BMI) was calculated (kg/m^2) and age- and gender-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 minute 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 hrs to the central laboratory (University of Washington) for analysis. Measurements of plasma cholesterol, triglycerides, and HDL-C were performed enzymatically on a Hitachi 917 auto analyzer (Roche Molecular Biochemicals, Indianapolis, IN). LDL-C was calculated by the Friedewald equation for individuals with a triglyceride concentration less than 400 mg/dl and the BetaQuantification procedure for those with triglycerides of 400 mg/dl or greater (13). A1c was measured by a dedicated ion exchange HPLC instrument (TOSOH, San Francisco, CA). Apo B was measured by a nephelometric system (BNII; Behring Diagnostics, Deerfield, IL). Relative flotation number (Rf) for LDL was determined by a previously described technique (14). Cut points for elevated lipid levels- total cholesterol (≥ 200 mg/dL), LDL-C (≥ 130 mg/dl), high non-HDL-C (≥130 mg/dL), elevated triglycerides (≥ 150 mg/dl) and low HDL-C (≤35 mg/dL)- were taken from the Third Report of the National Cholesterol Education Program (Adult Treatment Panel III) (1), and the American Diabetes Association (ADA) (15).

Statistical analysis: Statistical analyses were performed using SAS for Windows software version 9.2 (SAS Institute Inc, Cary, NC). Demographic characteristics were described with means and standard deviations for continuous variables and frequencies for categorical variables. The natural logarithmic transformations of total cholesterol, LDL-C, 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 sub-optimal (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 vs. control and type 1 diabetes sub-optimal A1c vs. control) as the primary independent variable, adjusting for age (as a second order polynomial), sex, race/ethnicity and BMI. Mixed effects models were utilized to allow for unequal variances by diabetes status. Mixed model analysis results are expressed as adjusted means and 95% confidence intervals, adjusted to the mean age, BMI, and observed race/ethnicity and gender proportions for the type 1 diabetes group. Adjusted prevalence estimates of abnormal lipid concentrations (and 95% confidence intervals) were obtained with logistic regression by calculating the predicted prevalence for type 1 diabetes and controls at the mean age and observed race/ethnicity and gender proportions for the type 1 diabetes group.

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 sub-optimal A1c values, and 188 healthy controls with complete data on main variables of interest. Compared with control youth, patients with type 1 diabetes and optimal A1c values were more likely to be male, non-Hispanic white, tended to be slightly younger and less physically active. Compared with

control youth, patients with type 1 diabetes and sub-optimal A1c values were older, more likely to be non-Hispanic white, and to have lower BMI. Waist circumference, blood pressure levels and Tanner stage were not different between the three groups. As expected, mean A1c levels were higher in both sub-groups 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 diabetes sub-groups in terms of disease duration, physical activity and daily insulin dose. Separate analyses to assess the potential influence of these differences between the two diabetes sub-groups on various lipid parameters were also conducted.

Table 2 compares the mean lipid levels among controls, youth with type 1 diabetes with optimal A1c levels (<7.5%), and with sub-optimal values for A1c (≥7.5%), after adjustment for age, sex, race/ethnicity and BMI. Compared with controls, youth with optimal A1c levels had similar mean levels of total cholesterol, LDL-C, non-HDL-C, and LDL particle size (LDL Rf), lower levels of triglyceride, higher HDL-C levels, and a lower triglyceride/HDL-C ratio. However, mean Apo B concentrations were higher, despite no differences in LDL-C levels. Focusing now on type 1 diabetes youth with sub-optimal levels of A1c, they had a more atherogenic lipid and lipoprotein pattern, such that mean values were significantly higher than in controls for total cholesterol, LDL-C, non-HDL-C, and ApoB, and significantly lower for LDL particle size. Nevertheless, even youth with sub-optimal A1c had higher HDL-c levels than controls. 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 sub-optimal A1c, respectively). Additional adjustment for minor differences in physical activity patterns did not influence the observed differences HDL-C cholesterol. Adjustment for different daily insulin doses only slightly attenuated the difference in triglyceride levels between the two diabetes sub-groups (62.7 vs. 71.5 mg/dl in type 1 diabetes with optimal and sub-optimal 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 diabetes group with the healthy control group. Similar to the findings regarding mean lipid levels, the prevalence of abnormal standard lipid concentrations (total cholesterol, LDL-C, HDL-C) was similar in youth with type 1 diabetes and optimal A1c levels versus non-diabetic youth. Type 1 diabetes with optimal glycemic control also had the lowest prevalence of elevated triglyceride of all three groups. The type 1 diabetes youth with sub-optimal glycemic control had higher prevalence of abnormal standard lipid factors than controls, reaching statistical significance for elevated total cholesterol. The proportion of youth with elevated non-traditional lipid factors, high ApoB, and small dense LDL particles was significantly higher in type 1 diabetes patients with both optimal and sub-optimal A1c levels, compared with healthy controls. There was a gradient of increasing prevalence of elevated Apo B levels with increasing A1c.

CONCLUSION

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-C), or even less atherogenic (HDL-C, triglyceride, Triglyceride/HDL ratio), than

those observed in non-diabetic youth. In contrast, youth with type 1 diabetes and suboptimal glycemic control have higher standard lipid levels and prevalence of lipid abnormalities (total, LDL-C and non-HDL-C) than non-diabetic youth. Moreover, youth with type 1 diabetes have significantly elevated Apo B levels and more small/dense LDL particles than non-diabetic youth, regardless of glycemic control. We also found that the most frequent lipid abnormalities in youth with type 1 diabetes compared with non-diabetic controls are elevated Apo B 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-C levels, agrees with previous data in adults (16). In general, lipid concentrations were shown to be anti-atherogenic 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 poorly controlled adults with 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 to normal subjects. Under normal circumstances, triglyceride-rich particles are rapidly hydrolyzed by Lipoprotein Lipase (LPL). 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 on youth with T1D versus healthy controls.

Our findings that youth with sub-optimal glycemic control have increased concentrations and higher prevalence of abnormal standard lipids, as well as more small dense LDL particles and higher Apo B levels also agrees with the previous literature in adults (18). Similarly, among SEARCH youth with type 1 diabetes, total and LDL-C, triglyceride, and non-HDL-C levels (19), but also dense LDL and Apo B concentrations (14), each increased with increasing A1c.

The measurement of ApoB and dense LDL in people with diabetes has been sparse, particularly in children and adolescents. The higher proportion of youth with type 1 diabetes with elevated ApoB versus healthy controls 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 level had elevated Apo B and an increased proportion of small/dense LDL particles, relative to non-diabetic controls, suggesting that even mild hyperglycemia may be associated with atherogenic compositional lipoprotein changes, even if concentrations of standard lipid are unaffected.

Both Apo B and small dense LDL particles have been shown to be strong and independent predictors of CVD. Apo B has been shown to be a better predictor of incident CVD than LDL-C and non-HDL-C (20). 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-C, HDL-C, and triglycerides within specific targets (15). Our data suggest that Apo B and small dense LDL particles may also represent important targets, since they appear to be elevated even among well controlled patients with type 1 diabetes, and because CVD risk relates more closely to the level of ApoB than to cholesterol indices.

This study has several potential limitations. First, it is cross-sectional, and thus limited at describing observed associations. Half of the patients with type 1 diabetes in this study had a disease duration of less than two 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/ethnic-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 non-diabetic control group.

In summary, our study present novel information on characteristics of dyslipidemia in youth with type 1 diabetes compared with non-diabetic controls. 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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Table 1: Demographic, metabolic and clinical characteristics of participants, according to study group

Variable	Type 1, HbA1c< 7.5		Control		Type 1, HbA1c ≥ 7.5
	N=164	P^a	N=188	P^b	N=348
Age at visit (s.d.)	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		<.0001	
NHW	82.9		54.3		79.9
Hispanic	8.5		17.6		9.8
AA	8.5		28.2		10.3
HbA1c (%)	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 BP (mmHg)	106.5 (104.8- 108.2)	0.3	107.6 (106.0-109.2)	0.2	106.3(105.0-107.6)
Diastolic BP (mm Hg)	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 (u/kg/day)	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 and 95% Confidence Intervals or Percentages
P^a : Type 1 diabetes and A1c < 7.5 vs control;
P^b : Type 1 diabetes and A1c ≥ 7.5 vs control

Table 2: Adjusted Mean Lipid Levels (and 95% Confidence Intervals) in Non-Diabetic Control Youth and Youth with Type 1 Diabetes with Optimal (HbA1c < 7.5%) and Suboptimal (HbA1c ≥ 7.5%) Glycemic Control

Variable	Type 1, HbA1c< 7.5		Control		Type 1, HbA1c ≥ 7.5
	N=164	P^a	N=188	P^b	N=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-C (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-C (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-C (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/HDL-C 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 (Rf)	0.283 (0.280-0.286)	0.4	0.282 (0.279-0.285)	<0.001	0.275 (0.272-0.278)

P^a : Type 1 diabetes and HbA1c < 7.5 vs control;
P^b : Type 1 diabetes and HbA1c ≥ 7.5 vs control

Figure 1 Legend:

Prevalence of Abnormal Lipid Concentrations, adjusted for Age, Sex, and Race/Ethnicity in Non-Diabetic Youth, Youth with Type 1 Diabetes in Optimal (HbA1c < 7.5%) and Suboptimal (HbA1c ≥ 7.5%) Glycemic Control

*<0.05 type 1 diabetes with optimal or sub-optimal A1c versus healthy youth
†<0.01 type 1 diabetes with optimal or sub-optimal A1c versus healthy youth