Serum Lipids and Glucose Control

The SEARCH for Diabetes in Youth Study

Diana B. Petitti, MD, MPH; Giuseppina Imperatore, MD, PhD; Shana L. Palla, MS; Stephen R. Daniels, MD, PhD; Lawrence M. Dolan, MD; Ann K. Kershnar, MD; Santica Marcovina, PhD, ScD; David J. Pettitt, MD; Catherine Phoker, MD; for the SEARCH for Diabetes in Youth Study Group

Objective: To assess the relationship of serum lipid concentrations with glucose control in youth with diabetes mellitus.

Design: Cross-sectional analyses of data from the SEARCH for Diabetes in Youth study.

Setting: Multicenter study of youth with diabetes onset at younger than 20 years.

Patients/Participants: Nineteen hundred seventy-three SEARCH participants aged 10 years or older with hemoglobin A1c and fasting total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride measured at the SEARCH study examination.

Main Exposure: Hemoglobin A1c.

Outcome Measure: Lipid concentrations.

Results: There were significant trends of higher levels of TC, LDL-C, triglyceride, and non–HDL-C (but not HDL-C) with higher hemoglobin A1c concentrations for both diabetes types. The slopes of TC increase were 7.8 mg/dL (0.20 mmol/L) per unit increase in hemoglobin A1c for type 1 and 8.1 mg/dL (0.21 mmol/L) for type 2. Levels of TC, LDL-C, triglyceride, and non–HDL-C were all significantly higher (all P values <.001) in type 2 than in type 1 diabetes (mean differences in milligrams per deciliter [millimoles per liter], +13.6 [+0.35] for TC; +8.3 [+0.22] for LDL-C; +66.3 [+0.75] for triglyceride; +25.5 [+0.66] for non–HDL-C). Levels of HDL-C were lower in youth with type 2 diabetes (mean difference, −11.9 mg/dL [−0.31 mmol/L]). Among those with type 1 diabetes in poor glycemic control, 35%, 27%, and 12% had high concentrations of TC (≥200 mg/dL [5.17 mmol/L]), LDL-C (≥130 mg/dL [3.36 mmol/L]), and triglyceride (≥200 mg/dL [2.26 mmol/L]), respectively. In youth with type 2 diabetes in poor glycemic control, percentages with high levels of TC, LDL-C, and triglycerides were 65%, 43%, and 40%, respectively.

Conclusions: Glycemic control and lipid levels are independently associated in youth with both type 1 and type 2 diabetes.

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Author Affiliations: Kaiser Permanente Southern California, Pasadena (Drs Petitti, Kershnar, and Pettitt); Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Imperatore); Department of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, NC (Ms Palla); Children’s Hospital Medical Center, Cincinnati, Ohio (Drs Daniels and Dolan); Northwest Research Laboratory, Seattle, Wash (Dr Marcovina); Children’s Hospital and Regional Medical Center, Seattle (Dr Phoker).

In adults with diabetes, the risk of atherosclerotic cardiovascular disease morbidity and mortality is greatly increased. Diabetes mellitus also increases the risk of microangiopathy, which manifests itself as renal failure, retinopathy, and neuropathy. In non-diabetic youth, atherosclerosis is known to begin during childhood and adolescence.1-5 Many studies show that the microvascular changes and the precursors of atherosclerosis can be observed in young patients early in the course of type 1 diabetes.6-10

The Diabetes Control and Complications Trial (DCCT) reported in 1993 that aggressive glycemic control decreases the likelihood of microvascular complications in type 1 diabetes11 and later showed that glycemic control reduces the likelihood of subclinical and clinical macrovascular disease.12,13 In the DCCT, the benefits of stringent glycemic control extended to adolescents with type 1 diabetes.14 The benefits were long-lasting.13,15 Glycemic control also reduces the likelihood of microvascular complications in adults with type 2 diabetes.16 Lipid concentrations are strongly related to the risk of macrovascular disease (coronary heart disease, stroke, and peripheral vascular disease) in adults with diabetes. Treatment with HMG-glutaryl CoA enzyme reductase inhibitors (statins), which lower low-density lipoprotein cholesterol (LDL-C) levels, prevents primary and secondary coronary events in adults with type 1 and type 2 diabetes.17-19 Recent evidence suggests that lipid and lipoprotein concentrations are related to nephropathy, retinopathy, and neuropathy in type 1 diabetes.20-23 In an animal model of diabetes, statin treatment prevented diabetic microangiopathy.24
Studies of the effects on cardiovascular disease outcomes of early intervention to reduce dyslipidemia in youth with either type 1 or type 2 diabetes have not been done. It also is not known whether pharmacologic intervention to manage lipid concentrations in adolescents and young adults with diabetes has a favorable benefit-to-risk ratio. These questions assume considerable importance in light of the high prevalence of lipid abnormalities in youth with type 1 and type 2 diabetes found by SEARCH investigators in a large, ethnically diverse population being managed under a variety of medical care models. SEARCH also noted a high prevalence of poor glycemic control among youth with diabetes. Data on the association between glycemic control and lipid concentrations in children and adolescents with diabetes, especially type 2 diabetes, are few. In the present analysis, SEARCH used cross-sectional data to assess the association of glycemic control with concentrations of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, and non–HDL-C in youth aged 10 to 22 years with either type 1 or type 2 diabetes.

METHODS

Data for this analysis derive from the cross-sectional component of the SEARCH for Diabetes in Youth Study. The study protocol was reviewed and approved by the local institutional review boards that had jurisdiction. All centers complied with the privacy requirements of the Health Insurance Portability and Accountability Act. Written informed consent for the study visit was obtained according to the local institutional review board requirements from patients aged 18 years or older or from a subject’s parent or guardian if the subject was younger than 18 years. Written assent was also obtained from patients younger than 18 years as governed by local institutional review board instructions.

PARTICIPANTS

A detailed description of SEARCH study methods has been published elsewhere. In brief, SEARCH is a multicenter study that began conducting population-based ascertainment of cases of diabetes in patients younger than 20 years in 2001 at 6 centers in Ohio, Colorado, Washington, South Carolina, Hawaii, and southern California. SEARCH sought to identify all existing (prevalent) cases of nongestational diabetes in patients younger than 20 years in 2001 and all newly diagnosed (incident) cases of nongestational diabetes in the same age group in subsequent calendar years. Networks of reporting providers are the primary source of identification of incident diabetes cases. To identify 2001 prevalent cases, centers used databases and data sources that were sometimes common to all centers (eg, hospital discharge records) and sometimes unique to a specific center (eg, laboratory data on performance of hemoglobin A1c [HbA1c] tests) as well as reporting providers.

Youth with diabetes who completed the study survey, except those whose diabetes was secondary diabetes (defined as diabetes due to a chronic illness, congenital anomaly, or drug), were invited to a study visit. During the study visit, additional survey information was collected on medication use; blood was drawn for measurement of TC, LDL-C, HDL-C, triglyceride, and HbA1c; and an examination was done to measure height and weight.

Diabetes cases were considered valid if diagnosed by a health care provider. In this analysis, diabetes type is based on the clinical diagnosis made by a health care provider. This information was collected either from the health providers at the time of the diabetes case report to SEARCH or from medical records. Eligible for this analysis were patients from the 2001 prevalent cases and 2002 incident cases who were aged 10 years or older at the time they participated in a SEARCH examination, who had their blood drawn while fasting, and whose fasting lipid measurement was completed by December 1, 2004. Cases classified clinically by a health care provider as type 1, type 1A, or type 1B were combined in a single type 1 category. Cases with another or an unknown clinical classification (13 unknown and 3 hybrid) were excluded. The 3 cases clinically classified as maturity onset diabetes of youth were analyzed with the type 2 cases because the clinical classification was not confirmed.

DATA COLLECTION

Blood samples were obtained under conditions of metabolic stability, defined as having had no episode of diabetic ketoacidosis during the previous month and having fasted for at least 8 hours. Specimens were processed locally at the sites and then shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle) where they were analyzed. Measurements of TC, HDL-C, and triglyceride were performed enzymatically on a Hitachi 917 autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, Ind). Low-density lipoprotein cholesterol was calculated by the Friedewald equation for individuals with triglyceride concentrations of less than 400 mg/dL (4.52 mmol/L) and by Lipid Research Clinics Beta Quantification for those with triglyceride concentrations of at least 400 mg/dL (4.52 mmol/L). Non–HDL-C was calculated as TC minus HDL-C. Hemoglobin A1c was measured by ion exchange, high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, Calif).

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The Centers for Disease Control and Prevention standards were used to estimate BMI percentile for age. In the analyses that categorized lipids concentrations, the cut points for elevated lipid concentration were adapted from those published by the National Cholesterol Education Program and the American Heart Association. In some analyses, HbA1c was categorized in 4 groups. The lower cut point used to define the first group (<6.7%, near normal) was chosen to reflect near-normal glycemia. The upper cut point of the second group (<8.0%, good) was chosen to encompass the recommendation from the American Diabetes Association for age-specific HbA1c values in youth with type 1 diabetes (<8.0% at ages 6-12 years; <7.5% at ages 13-19 years; <7.0% at ages ≥20 years) for all ages of the SEARCH subjects included in this analysis. The lower cut point for the fourth group (<9.5%, poor) was chosen to reflect unacceptable glucose levels. Values of HbA1c between 8.0% and 9.5% (intermediate) comprised the third group.

ANALYSIS

All statistical analyses were conducted using SAS for Windows version 8.2 (SAS Institute Inc, Cary, NC). Descriptive characteristics of the SEARCH participants in the analysis were calculated separately for type 1 and type 2 diabetes. Means and standard deviations were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. Analyses were performed first considering each of the lipid values and HbA1c measured on a continuous scale and then repeated where the lipids and HbA1c were considered as ordered categories. For the analyses using continuous measures, we used general linear models (linear regression) with the lipids mea-
To examine whether increasing values of HbA1c predict different lipid values. The Cochran-Mantel-Haenszel test was used to examine whether the HbA1c and lipid relationship remained significant after controlling for diabetes type. The Breslow-Day test was done to assess whether the HbA1c–lipid relationship was the same for type 1 and type 2 diabetes, that is, testing for interaction.

Methods that analyze continuous data in categories are generally less powerful statistically than methods based on linear models. The categorical analyses did not, however, lead to different conclusions about association, trend, or interaction for any lipid examined. The descriptive data from the categorical analysis are presented because the categories are clinically relevant and because the data permit conclusions about the prevalence of lipid concentration abnormalities in youth with diabetes at various HbA1c levels.

RESULTS

Of 7539 individuals with diabetes identified by SEARCH in 2001 and 2002 and invited for a study visit, 3215 (43%) had a study visit. Of these, 2469 were aged 10 years or older at the time of the SEARCH study examination; the 1973 youth who had data on fasting lipid concentrations, diabetes type, and HbA1c are included in this analysis. Of the youth aged 10 years or older included in this analysis, 1680 were type 1 and 283 were type 2.

Table 1 lists demographic and clinical characteristics by diabetes type. Of youth with type 1 diabetes, 39% (95% confidence interval, 37% to 41%) had HbA1c concentrations less than 8% compared with 54% of youth with type 2 diabetes (95% confidence interval, 48% to 60%). Of youth with type 1 diabetes, 39% (95% confidence interval, 48% to 60%). Of youth with type 1 diabetes, 39% (95% confidence interval, 25% to 33%) had HbA1c concentrations of 9.5% or more compared with 31% (95% confidence interval, 26% to 37%) of those with type 2 diabetes. There were statistically significant differences in virtually all of these characteristics comparing type 1 and type 2 diabetes.

Table 2 lists the means for the lipid and HbA1c concentrations by diabetes type. The mean (SD) concentration of HbA1c was 8.6% (1.7%) in type 1 diabetes and 8.3% (2.7%) in type 2 diabetes.
Type 1: Slope = 0.09,

The estimated mean differences between type 1 and type 2 diabetes holding HbA1c constant were +13.6 mg/dL (+0.35 mmol/L) for TC; +8.3 mg/dL (+0.22 mmol/L) for LDL-C; +86.3 mg/dL (+0.75 mmol/L) for triglyceride; and +25.5 mg/dL (+0.66 mmol/L) for non–HDL-C (all P values < .001). Youth with type 2 diabetes had a lower concentration of HDL-C than those with type 1 diabetes (estimated mean difference, −11.9 mg/dL [−0.31 mmol/L], P < .001). After adjustment for age, sex, duration of diabetes, BMI percentile for age and sex, and race/ethnicity, the associations of higher HbA1c concentrations with higher TC, LDL-C, triglyceride, and non–HDL-C concentrations remained statistically significant for both type 1 and type 2 (Table 3). After adjustment, there was no association of higher HbA1c concentration with lower HDL-C concentration.

Table 4 lists the proportions of youth in lipid categories by glycemic control category. Because lipid

Figure. Plots of lipid value by hemoglobin A1c (HbA1c) concentration and fitted regression lines by diabetes type. A, Total cholesterol concentration by HbA1c concentration. B, Low-density lipoprotein (LDL) cholesterol concentration by HbA1c concentration. C, High-density lipoprotein (HDL) cholesterol concentration by HbA1c concentration. D, Triglyceride concentration by HbA1c concentration. E, Non-HDL cholesterol concentration by HbA1c concentration. Values come from the SEARCH for Diabetes in Youth Study with patients aged 10 years or older from cases in 2001 and 2002. Slope is the increase in lipid concentration in milligrams per deciliter for each 1.0 unit increase in HbA1c concentration.
levels increase with increasing values of HbA1c, a very high percentage of youth are classified as having “high” TC, LDL-C, and triglyceride concentrations in the category “poor glycemic control” for both type 1 and type 2 diabetes. Among those with type 1 diabetes who were in poor glycemic control, 35%, 27%, and 12% had high concentrations of TC (≥200 mg/dL [5.17 mmol/L]), LDL-C (≥130 mg/dL [3.36 mmol/L]), and triglyceride (≥200 mg/dL [2.26 mmol/L]), respectively. In youth with type 2 diabetes who were in poor glycemic control, percentages with high TC, LDL-C, and triglyceride concentrations were 65%, 43%, and 40%, respectively.

**COMMENT**

In 1992, the DCCT reported a positive correlation between glycemic control and the concentrations of TC, LDL-C, and triglycerides at screening in 1569 patients with type 1 diabetes aged 13 to 40 years (mean age, 25.8 years for women and 27.2 years for men), but only 20% were younger than 18 years of age. All had type 1 diabetes, and the overwhelming majority were non-Hispanic and white. The data from the SEARCH study are important because they show that the association between poor glycemic control and higher concentrations of TC, LDL-C, and triglyceride extends to children and youth aged 10 to 22 years in all major ethnic/racial groups in the United States and characterizes both type 1 and type 2 diabetes in this age group.

Table 3. Results of Multiple Linear Regression Analyses: Amount of Change in Lipid in Milligrams per Deciliter for Each 1.0 Unit Increase in Hemoglobin A1c, Adjusting for Age, Sex, Race/Ethnicity, Diabetes Duration, and BMI Percentile for Age and Sex

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Type 1 (95% CI)</th>
<th>Type 2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>7.7 (6.7 to 8.8)</td>
<td>7.4 (5.3 to 9.4)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>5.1 (4.3 to 6.0)</td>
<td>3.9 (2.1 to 5.7)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.2 (−0.2 to 0.6)</td>
<td>−0.1 (−0.6 to 0.5)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.11 (0.1 to 0.1)</td>
<td>0.09 (0.1 to 0.1)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>7.6 (6.6 to 8.6)</td>
<td>7.4 (5.4 to 9.5)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Change in lipid in milligrams per deciliter for each 1.0 increase in hemoglobin A1c.

Table 4. Percentage Distributions of Lipid Concentration in Categories by Hemoglobin A1c Category According to Clinically Diagnosed Diabetes Type

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.7 (n = 105)</td>
<td>6.7-7.9 (n = 509)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>52</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Some percentage distributions may not sum to 100 because of rounding.
concentrations were independent of BMI for age, as well as sex, duration of diabetes, and age at diagnosis, for both types of diabetes. In SEARCH, poorer glycemic control was not associated with HDL-C concentration in type 1 or type 2 diabetes. However, youth with type 2 diabetes had a lower mean concentration of HDL-C at all values of glycemic control. The DCCT analysis also reported no association of glycemic control with HDL-C in subjects with type 1 diabetes. In SEARCH, the lack of association of poorer glycemic control with HDL-C remained despite the inclusion of BMI percentile for age and other variables in a multivariate analysis for subjects with type 1 or with type 2 diabetes.

The cross-sectional design does not permit us to conclude that poor glycemic control caused high concentrations of TC, LDL-C, triglycerides, and non–HDL-C. It is possible that both glycemic control and lipid concentration are markers for the quality of diabetes care either at the individual level or the level of the health care system. For example, youth with limited access to health care may be those more likely to have poor glycemic control and, at the same time, may be less likely to be tested and treated for lipid abnormalities. However, other evidence suggests strongly that glycemic control affects the concentrations of TC, LDL-C, and triglycerides. Thus, data from the DCCT trial showed that intensive glucose control significantly decreased the concentrations of TC, LDL-C, and triglycerides in patients aged 13 to 40 years with type 1 diabetes. Similar results have been reported in studies in adults with type 2 diabetes.

Because of the trend of higher concentrations of TC, LDL-C, and triglycerides with higher HbA1c values, a very high percentage of the SEARCH participants had HbA1c concentrations in the “poor” glycemic category. In addition, if the participants were adults, their TC, LDL-C, and triglyceride concentrations would have qualified them for pharmacologic intervention. The high prevalence of lipid abnormalities in diabetic youth with poor glycemic control underscores the importance of aggressive glucose control in children and youth with diabetes.

The American Diabetes Association has recommended pharmacologic therapy for youth with type 1 diabetes if the LDL-C level is greater than 160 mg/dL (4.14 mmol/L) and no other risk factors are present and consideration of pharmacologic therapy if the LDL-C level is between 130 and 159 mg/dL (3.36-4.11 mmol/L) based on presence of other cardiovascular risk factors. For adults with type 2 diabetes who are younger than 40 years, a group that encompasses some SEARCH youth, the American Diabetes Association recommends consideration of pharmacologic treatment based on risk factors if LDL-C is not optimal (LDL-C < 100 mg/dL [2.59 mmol/L]). We have reported that very few (<1%) of the SEARCH participants were taking a lipid-lowering drug.

Our study has important limitations. Less than half (43%) of youth with diabetes who were eligible participated in the SEARCH study visit. Nonresponse is unlikely to affect the association between glycemic control and lipid concentration. However, an unrepresentative sample would affect estimates of the prevalence of dyslipidemia and poor glycemic control if our results were generalized to all youth with diabetes. To attempt to estimate the magnitude and direction of possible bias in our prevalence estimates, we did an analysis of data on lipid and HbA1c testing and results at a SEARCH center that had access to computer-stored data on routine clinical testing, including both attendees and nonattendees at the SEARCH study examination. At this center, 1209 of 1390 youth with diabetes identified by SEARCH in 2001 or 2002 (87%) had a clinical HbA1c test in 2001 or 2002. Only 37% (n = 516) of the youth had TC and 13% (n = 185) LDL-C measured clinically in 2001 or 2002. Among those with a clinical HbA1c measurement, the mean (SD) level of HbA1c was significantly lower among participants in the study examination (8.9% [1.9%]) than among nonparticipants (9.5% [2.4%]; P < .05). Among those with a clinical TC or LDL-C measurement, there was no significant difference in mean concentration of TC or LDL-C between participants and nonparticipants in the study examination (both P values >.05). Analysis of nonresponse in the entire SEARCH study population showed a strong relationship between attendance at the study visit and age. Higher rates of nonresponse in older youth would lead to an underestimate of the problem both of poor glycemic control and of lipid abnormalities because both were related to older age in SEARCH.

Over the last decade, great progress has been made in our understanding of the link between glycemic control and better outcomes in type 1 and type 2 diabetes. The central role of dyslipidemia in causing progression of atherosclerosis in adults with diabetes has been elucidated. Randomized trials have shown that lipid-lowering therapy is important in the primary and secondary prevention of coronary events in adults with type 1 and type 2 diabetes. Knowledge about how best to manage cases of children and youth with diabetes has not kept pace with knowledge about diabetes management in adults. The quality of care for children and youth with diabetes has not been measured systematically. The SEARCH study results suggest that a substantial proportion of youth with diabetes are not managed optimally with regard to 2 key drivers of outcome in diabetes: glycemic control and lipids. Research on how to improve the care of children and youth with diabetes should be done in concert with further research to understand the mechanisms by which lipid concentrations are altered by diabetes.

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Correspondence: Diana B. Petitti, MD, MPH, Department of Research and Evaluation, Kaiser Permanente Southern California, 393 E Walnut St, Pasadena, CA 91188 (diana.b.petitti@kp.org).

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