Glucose Control Predicts 2-Year Change in Lipid Profile in Youth with Type 1 Diabetes

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Objective To test the hypothesis that a change in glycated hemoglobin (A1c) over a follow-up interval of approximately 2 years would be associated with concomitant changes in fasting lipids in individuals with type 1 diabetes (T1D).

Study design All subjects with T1D diagnosed in 2002-2005 in the SEARCH for Diabetes in Youth study with at least 2 study visits ~12 and ~24 months after an initial visit were included (age at initial visit, 10.6 ± 4.1 years; 48% female; diabetes duration, 10 ± 7 months; 76% non-Hispanic white; A1c = 7.7% ± 1.4%). Longitudinal mixed models were fit to examine the relationship between change in A1c and change in lipid levels (total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-c], low-density lipoprotein-cholesterol [LDL-c], log triglycerides [TG], and non–HDL-c) with adjustment for possible confounders.

Results Change in A1c over time was significantly associated with changes in TC, HDL-c, LDL-c, TG, and non–HDL-c over the range of A1c values. For example, for a person with an A1c of 10% and then a 2% decrease in A1c 2 years later (to 8%), the model predicted concomitant changes in TC (−0.29 mmol/L, −11.4 mg/dL), HDL-c (0.03 mmol/L, 1.3 mg/dL), LDL-c (−0.23 mmol/L, −9.0 mg/dL), and non–HDL-c (−0.32 mmol/L, −12.4 mg/dL) and an 8.5% decrease in TG (mmol/L).

Conclusions Improved glucose control over a 2-year follow-up was associated with a more favorable lipid profile but may be insufficient to normalize lipids in dyslipidemic T1D youth needing to decrease lipids to goal. *(J Pediatr 2013;162:101-7)*.

Hyperglycemia and dyslipidemia are metabolic abnormalities commonly found in individuals with type 1 diabetes (T1D). Both increase the risk of cardiovascular disease (CVD), the leading cause of mortality in individuals with T1D.[1]

The antecedents of adult CVD, including dyslipidemia, are present in children and numerous studies demonstrate tracking of CVD risk factors into adulthood.[2-4] Furthermore, CVD risk factors in childhood are associated with both surrogate markers of atherosclerosis[4] and atherosclerotic lesions at autopsy in adults.[2,3] Due to these findings, the American Diabetes Association,[5] the American Academy of Pediatrics,[6] the International Society of Pediatric and Adolescent Diabetes,[7] and the American Heart Association[8] have all published guidelines for intervention in youth with diabetes and dyslipidemia. However, because there is a paucity of data on dyslipidemia in youth with T1D, these guidelines are based on extrapolation of data from adults and from youth without diabetes.[1]

Each of these professional organizations recommends intensification of glucose control, a healthy diet, and exercise as the initial therapy for dyslipidemia in youth with T1D. However, it is unclear to what extent improved glucose

A1c	Glycated hemoglobin
BMI	Body mass index
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
HDL-c	High-density lipoprotein-cholesterol
LDL-c	Low-density lipoprotein-cholesterol
NHW	Non-Hispanic white
SEARCH	SEARCH for Diabetes in Youth Study
T1D	Type 1 diabetes
TC	Total cholesterol
TG	Triglycerides

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control alters lipid measurements. Better understanding of the association of glucose control to dyslipidemia would inform current practice guidelines and clinical decision making about the treatment of dyslipidemia in youth with T1D.[1] Therefore, we tested the hypothesis that a change in glycated hemoglobin (A1c) over a follow-up interval of ~2 years would be associated with concomitant changes in the lipid profile in youth with T1D participating in the SEARCH for Diabetes in Youth study (SEARCH).

Methods

SEARCH is an ongoing study that began in 2001 to conduct population-based case ascertainment of youth <20 years with diabetes.[9] SEARCH has a defined protocol for incident cases to have 12- and 24-month follow-up visits after their initial study visit. This report includes information for the participants in the 2002-2005 incident cohorts and the corresponding 12- and 24-month visits for participants with at least 1 follow-up visit after the initial study visit. The study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study populations, and all participants provided informed consent and/or assent.

During the study visit, survey information, including medication use, was collected, an examination was performed to measure systolic and diastolic blood pressures, height, weight, body mass index (BMI), and waist circumference, as previously described,[9] and blood samples were obtained under conditions of metabolic stability after at least 8 hours of fasting. Specimens were processed locally at the sites and within 24 hours shipped to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, Washington), where they were analyzed for measurement of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), and triglycerides (TG). Measurements of TC, HDL-c, and TG were performed enzymatically using Roche reagent on a Hitachi Modular P autoanalyzer (Roche Diagnostics, Indianapolis, Indiana). Low-density lipoprotein-cholesterol (LDL-c) levels were calculated by the Friedewald equation for individuals with TG levels <4.52 mmol/L and by Lipid Research Clinics Beta Quantification for those with TG levels ≥4.52 mmol/L. Non–HDL-c concentration was computed as TC minus HDL-c. A1c levels were measured by ion-exchange high-performance liquid chromatography (TOSOH G7; TOSOH Biosciences Inc, South San Francisco, California).

The diabetes type was categorized as type 1 or type 2, based on the health care provider diagnosis.[9] Race/ethnicity was self-reported using the 2000 census questionnaire format. Five categories were created (Hispanic, American Indian, non-Hispanic black, Asian/Pacific Islander, non-Hispanic white [NHW]).

The study population consisted of all SEARCH participants with T1D who were diagnosed from 2002 through 2005 and had at least 2 study visits where fasting lipids and A1c were measured simultaneously. Subjects reporting use of lipid-lowering medications (n = 7) were excluded. Of the 1193 participants included in these analyses, fasting lipids were measured in all twice, and in 563 they were measured 3 times over a ~24-month period. Subjects were invited to a SEARCH visit only after diabetes has been diagnosed and no patients in diabetic ketoacidosis were included in the analyses.

Statistical Analyses

The mean and SD (or median and Quartile 1, Quartile 3) for each variable of interest were calculated based on data collected at the initial visit. Longitudinal mixed models using all data from the initial and subsequent visits were fit to examine the relationship between A1c (initial value and time-varying values) and time-varying lipid levels (TC, HDL-c, LDL-c, TG, and non–HDL-c) included as the outcome in each model. As a marker of time for each participant, we included duration of diabetes (number of months since diabetes diagnosis) in these mixed models. Because this study is observational, all assessments of the lipid measures (baseline and follow-up) are contained in our statistical models as part of the outcome.

Multivariable modeling focused on the effects of the initial A1c (measured at the first SEARCH study visit) and the time-varying effects of A1c measured at the 12- and/or 24-month follow-up visits. In addition, we explored any interaction of the main effects. Each model also included several participant-level characteristics that were measured at the initial visit as covariates. These effects included participant age (included as age and age^2 to allow for nonlinear relationships), race/ethnicity (NHW versus other groups), sex, site, season of the year when measurements were performed (autumn versus each other season), and baseline BMI z score (BMI value represented as a z score that adjusts for age and sex for each participant). Because Tanner staging was not available for all participants due to institutional review board restrictions at some centers, we examined the correlation between Tanner staging (where available) and participant age. We found these 2 measures were highly correlated (r = .84, $P < .0001$); thus, the inclusion of age in the above models was also considered a surrogate for pubertal stage.

For multivariable models, the β coefficient and 95% CIs for the association of time-varying A1c (to determine the association of change in A1c with change in lipid) adjusted for initial A1c and diabetes duration are reported (adjusted for age, age^2, race/ethnicity, sex, site, season of the year, and baseline BMI z score). Additionally, an interaction term (initial A1c × time-varying A1c) was included in this model to determine whether the association of change in A1c with changes in lipids was different depending on the initial A1c value. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

The clinical characteristics of 1193 individuals at the initial visit are described in Table I (age = 10.6 ± 4.1 years, 48% female, T1D duration = 10 ± 7 months, 76% NHW, A1c = 7.7% ± 1.4%). Mean and SD for fasting lipid measures at