Estimated Insulin Sensitivity and Cardiovascular Disease Risk Factors in Adolescents with and without Type 1 Diabetes

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Objective To test the hypothesis that cardiovascular disease (CVD) risk factors are similar in nondiabetic (non-DM) adolescents compared with those with type 1 diabetes (T1D) in the most insulin-sensitive (IS) tertile, and that CVD risk factors are more atherogenic with decreasing IS in adolescents with T1D.

Study design IS for adolescents with T1D (n = 292; age = 15.4 ± 2.1 years; duration = 8.8 ± 3.0 years, hemoglobin A1c = 8.9% ± 1.6%) and non-DM controls (n = 89; age = 15.4 ± 2.1 years) was estimated using the model: $\log_e$IS = .64725 − 0.02032 (waist [cm]) − 0.09779 (hemoglobin A1c [%]) − 0.00235 (triglycerides [mg/dL]). CVD risk factors (blood pressure, fasting total and low- and high-density lipoprotein-cholesterol (HDL-c), high sensitivity C-reactive protein, and body mass index z score) were compared between all non-DM adolescents and those with T1D in the most IS tertile, and then examined for a linear trend by IS tertile in adolescents with T1D, adjusted for sex, race/ethnicity, and Tanner stage.

Results Estimated IS was significantly lower in adolescents with T1D compared with those without (T1D = 7.8 ± 2.4, non-DM = 11.5 ± 2.9; $P < .0001$). CVD risk factors were similar for non-DM compared with the adolescents with T1D with the most IS, except for higher (HDL-c) and diastolic blood pressure in adolescents with T1D ($P < .05$). Among adolescents with T1D, all CVD risk factors except for (HDL-c), were more atherogenic across decreasing IS tertiles in linear regression analysis ($P < .05$).

Conclusion Adolescents with T1D who are the most IS have similar CVD risk factors compared with non-DM adolescents. CVD risk factors are inversely associated with IS in adolescents with T1D. IS may be an important therapeutic target for reducing CVD risk factors in adolescents with T1D. *(J Pediatr 2013;162:297-301)*.

Cardiovascular disease (CVD) is the primary cause of death in type 1 diabetes (T1D) with many risk factors recognized in early adolescence.[1] Insulin sensitivity (IS) is decreased in T1D compared with nondiabetic (non-DM) individuals. Normal-weight adolescents with T1D have lower IS than do body mass index (BMI)-matched control subjects.[2,3] Using the hyperinsulinemic-euglycemic clamp procedure, an insulin sensitivity score (ISS) was developed in conjunction with the SEARCH for Diabetes in Youth Study to estimate IS in adolescents (lower ISS = less IS). Although there are data linking decreased hyperinsulinemic-euglycemic clamp defined IS to adiposity,[4] decreased exercise capacity,[2] a more atherogenic lipid profile,[5] and a more atherogenic lipoprotein cholesterol distribution in youth[6] and adults[7] with T1D, there are little data relating decreased IS to other CVD risk factors in larger populations of youth with T1D.

Our objectives were to compare the relationship between IS and CVD risk factors in adolescents with T1D and non-DM controls. We tested the hypotheses that: (1) CVD risk factors are similar in non-DM adolescents compared with subjects with T1D in the most IS tertile; and (2) among adolescents with T1D, CVD risk factors are more atherogenic with decreasing ISS.

BMI	Body mass index
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
GDR	Glucose disposal rate
HbA1c	Hemoglobin A1c
HDL-c	High-density lipoprotein cholesterol
IS	Insulin sensitivity
ISS	Insulin sensitivity score
Non-DM	Nondiabetic
T1D	Type 1 diabetes

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Methods

The Determinants of Macrovascular Disease in Adolescents with T1D study was initiated to investigate atherosclerotic disease risk in youth with and without T1D. Enrollment began in 2008 and concluded in 2010. Subjects were 12-19 years of age. Study participants with T1D were diagnosed by islet cell antibody or by provider clinical diagnosis, had diabetes duration >5 years at entry into the study, and received care at the Barbara Davis Center for Childhood Diabetes. Non-DM control subjects were recruited from friends of the study subjects as well as from campus and community advertisements. No siblings or first-degree relatives of patients with T1D were included. Subjects were excluded for diabetes of any other type and for any history of abnormal cardiac anatomy or arrhythmia that would preclude the subject from vascular function measurements. The study was approved by the Colorado Multiple Institution Review Board, and informed consent and assent (for subjects <18 years) was obtained from all subjects.

All subjects fasted overnight (≥8 hours). Tanner stage for all patients with T1D was assessed by a pediatric endocrinologist. Non-DM subjects were requested to have Tanner stage assessed with a physical examination by a pediatric endocrinologist with the option of self-assessment if the subject refused a physical examination. Medical history was obtained with standardized questionnaires including last menses for females, average daily insulin use, methods of insulin administration (number of injections per day, or if on an insulin pump, boluses per day), other medication use (including angiotensin-converting enzyme inhibitors, other blood pressure–lowering medications, and lipid-lowering medications), tobacco use, physical activity, and family history (including diabetes, coronary artery disease, stroke, hypertension, and dyslipidemia). After subjects had been laying supine for a minimum of 5 minutes, blood pressure measurements were obtained using a Dynapulse 5200A (Pulse Metric, San Diego, California), and 3 measurements were averaged. Height was measured to the nearest 0.1 cm with shoes removed using a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg using a Detecto scale (Detecto, Webb City, Missouri). Waist circumference was measured at the navel on bare skin using the Figure Finder Tape Measure by Novel Products (Rockton, Illinois), which provides consistent and repeatable oz of tension and accuracy to 3/32 inch.

Laboratory Assays

Hemoglobin (Hb)A1c was measured on the DCA Advantage by Siemens (Princeton, New Jersey) at the Children's Hospital Colorado main clinical lab. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides were performed in the Clinical Translational Research Core lab using an Olympus AU400e Chemistry (Olympus, Brea, California). Low-density lipoprotein cholesterol was calculated using the Friedwald formula. High-sensitivity C-reactive protein was measured at the Children's Hospital Colorado Clinical Translational Research Core lab using a multiplex assay platform Siemens (formally Dade Behring) BNII Nephelometer.

ISS

The ISS for adolescents aged 12-19 years with T1D (n = 292; age 15.4 ± 2.1 years; duration 8.8 ± 3.0 years) and non-DM controls (n = 89; age 15.4 ± 2.1 years) was determined using the SEARCH ISS model: $\log_e$IS = 4.64725 − 0.02032 (waist [cm]) − 0.09779 (HbA1c [%]) − 0.00235 (TG [mg/dL]) (R^2 = 0.74 in the initial SEARCH model).[4] The ISS for the adolescents with T1D in the current study was then divided into tertiles (ISS ≤6.84, ISS 6.84-8.64, and ISS ≥8.64).

Statistical Analyses

CVD risk factors were compared between all non-DM adolescents and those with T1D in the most ISS tertile using PROC GLM (SAS Institute, Cary, North Carolina) adjusted for sex, race/ethnicity, and Tanner stage. The authors tested for a linear trend for more atherogenic CVD risk factors by ISS tertile within adolescents with T1D, adjusted for sex, race/ethnicity, and Tanner stage. Least-squares mean ± SE values for CVD risk factors are presented adjusted for sex, race/ethnicity, and Tanner stage differences between all 4 groups. P values <.05 were considered statistically significant. Categorical data (sex, race/ethnicity, and Tanner stage) by ISS category are presented in the **Table** and were then adjusted for in statistical analyses to avoid their confounding effect on the association of ISS with CVD risk factors, as these are all important determinants of IS and CVD risk factors. There were 19 subjects who were not included in these analyses due to missing data. Analyses were performed using SAS version 9.2 (SAS Institute).

Results

In the cohort, there were no differences in sex distribution among the non-DM adolescents and those with T1D by ISS tertiles (P = .39), but there were differences for race/ethnicity (P = .004 comparing non-Hispanic whites to all other races) and for Tanner stage (P < .0001). Because sex, race/ethnicity, and Tanner stage are all important determinants of IS, we present the descriptive data (least squares mean ± SE) in the **Table** adjusted for these variables. The ISS was significantly higher in non-DM compared with adolescents with T1D (non-DM = 11.5 ± 2.9, T1D = 7.8 ± 2.4; P < .0001).

Adolescents with IS T1D and Those without T1D

CVD risk factors (adjusted for sex, race/ethnicity, and Tanner stage) were similar for non-DM compared with adolescents with the most IS T1D except for higher diastolic blood pressure (non-DM: 64 ± 1 vs 66 ± 1 mm Hg in most IS T1D, P < .01) and higher HDL-c (non-DM: 51 ± 2 vs 55 ± 2 mg/dL in most IS T1D, P < .004) in the most IS T1D group (**Table**).