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

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Abstract

Objective—To test the hypothesis that cardiovascular disease (CVD) risk factors are similar in adolescents with and without diabetes (T1D) in the most insulin sensitive (IS) tertile and CVD risk factors are more atherogenic with decreasing IS in adolescents with T1D.

Study design—Adolescents with IS T1D (n=292; age=15.4±2.1 years; duration=8.8±3.0 years, HbA1c=8.9±1.6%) and non-diabetic (non-DM) controls (n=89; age=15.4±2.1 years) was estimated using the model: $\log_e IS = 4.64725 - 0.02032(\text{waist, cm}) - 0.09779(\text{HbA1c, \%}) - 0.00235(\text{triglycerides, mg/dl})$. CVD risk factors (blood pressure, fasting total, LDL and HDL-cholesterol, hs-CRP, and BMI 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; $p<0.0001$). CVD risk factors were similar for non-DM compared with the adolescents with most IS T1D, except for higher HDL-c and DBP in adolescents with T1D ($p<0.05$). Among adolescents with T1D, all CVD risk factors except for HDL-c, were more atherogenic across decreasing IS tertiles in linear regression analysis ($p<0.05$).

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 adolescents with IS T1D. IS may be an important therapeutic target for reducing CVD risk factors in adolescents with T1D.

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

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T1D as compared with non-diabetic (non-DM) individuals. Normal weight adolescents with T1D have lower IS than BMI-matched controls (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 insulin sensitive). 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 as 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.

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 (BDC). 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 BDC was assessed by a pediatric endocrinologist. Non-DM subjects were requested to have Tanner Stage assessed with a physical exam by a pediatric endocrinologist with the option of self-assessment if the subject refused a physical exam. Medical history was obtained with standardized questionnaires including last menses for females, average daily insulin use, methods of insulin administration (number of injections /day or if on an insulin pump boluses/day), other medication use (including ACE 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, Inc., San Diego, CA) 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. Waist circumference was measured at the navel on bare skin using the Figure Finder Tape Measure by Novel Products, Inc (Rockton, IL), which provides consistent and repeatable 4 oz. of tension and accuracy to 3/32 inch.

Laboratory Assays

HbA1c was measured on the DCA Advantage by Siemens at the Children's Hospital Colorado main clinical lab. Total cholesterol (TC), HDL-cholesterol (HDL-c), and triglycerides (TG) were performed in the Clinical Translational Research Core (CTRC) lab using an Olympus AU400e Chemistry. LDL-cholesterol (LDL-c) was calculated using the

Friedwald formula. hs-CRP was measured at the Children's Hospital Colorado CTSC core lab utilizing a multiplex assay platform Siemens (formally Dade Behring) BNII Nephelometer.

Insulin sensitivity score

The ISS for adolescents ages 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: $\log_e \text{IS} = 4.64725 - 0.02032(\text{waist, cm}) - 0.09779(\text{HbA1c, \%}) - 0.00235(\text{TG, mg/dl})$ ($R^2=0.74$ 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 adjusted for sex, race/ethnicity and Tanner Stage. We 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 square means $\pm$ SE for CVD risk factors are presented adjusted for sex, race/ethnicity and Tanner Stage differences between all 4 groups. P-values <0.05 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.

Results

In the cohort, there were no differences in sex distribution among the non-DM adolescents and those with T1D by ISS tertiles ($p=0.39$), but there were differences for race/ethnicity ($p=0.004$ comparing NHW to all other races) and for Tanner Stage ($p<0.0001$). Because sex, race/ethnicity, and Tanner Stage are all important determinants of IS, we present the descriptive data (least square means $\pm$ 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 ; $p<0.0001$).

Adolescents with IS T1D and those without T1D

CVD risk factors (adjusted for sex, race/ethnicity, and Tanner Stage) were similar for non-DM as compared with adolescents with the most IS T1D except for higher diastolic blood pressure (DBP) (non-DM: 64 ± 1 v 66 ± 1 mmHg in most IS T1D, $p<0.01$) and higher HDL-c (non-DM: 51 ± 2 v 55 ± 2 mg/dl in most IS T1D, $p<0.004$) in the most IS T1D group (Table). This was despite the non-DM group being slightly older (15.1 ± 0.2 v 14.5 ± 0.3 years, $p<0.006$), having a higher ISS (11.2 ± 0.3 v 9.6 ± 0.3 ; $p<0.0001$), and as expected, a lower HbA1c ($5.4 \pm 0.2\%$ v $8.0 \pm 0.2\%$, $p<0.0001$) (Table).

Linear Trend by ISS Tertile

CVD risk factors were tested for a linear trend and were more atherogenic in adolescents with T1D in decreasing ISS tertiles (Table). The only CVD risk factor that did not show a linear trend in increasing atherogenicity as IS decreased was HDL-c (T1D most IS= 55 ± 2 mg/dl, T1D middle IS= 55 ± 2 mg/dl, T1D Least IS= 53 ± 2 mg/dl; $p>0.05$). All other CVD risk factors that were examined for a linear trend (BMI z-score, TC, LDL-c, SBP, DBP, and hs-CRP) were more atherogenic as IS decreased ($p<0.0001$). Results were obtained for the

Table with additional adjustment for BMI z-score (data not shown) and for waist circumference (with the exception of SBP with p-values of 0.04 and 0.058 for the comparison of non-DM controls with adolescents with the most IS T1D and for the linear trend by ISS tertile, respectively, and for linear trend for BMI z-score [$p=0.68$]).

Discussion

Our data show that as IS decreases in adolescents with T1D, CVD risk factors become more atherogenic. Reduced IS is well-accepted as a CVD risk factor in other populations (8), but the role of insulin resistance in T1D is less appreciated, in part due to the difficulty of estimating IS in people with T1D (3;8–10). Our data are significant in that monitoring and controlling IS may be an important therapeutic target to reduce CVD risk in T1D, especially given that both potential lifestyle (diet (11) and exercise (12)) and pharmacologic options (such as metformin (13)) are available to improve IS.

There have been previous studies in adults, but not in adolescents, focusing on estimates of IS as determined by glucose disposal rate (GDR) from hyperinsulinemic-euglycemic clamps. Williams et al generated an estimated GDR based on hyperinsulinemic-euglycemic clamps in T1D in a study with 24 adults (14), which has been applied in a number of studies of adults with T1D. For example, Chillaron et al applied this estimate to 91 adults with T1D and showed a link between vascular complications and decreased IS (15). Data from the DCCT as reported by Kilpatrick found that quantifying insulin resistance via estimated GDR using the Williams equation identified adults with T1D at higher risk to develop both microvascular and macrovascular complications (16). Expanding upon these studies of adults, our study shows the link between decreased IS and CVD risk earlier in the physiologic pathway and with shorter duration of diabetes, in a relatively large cohort of adolescents with T1D and those without. Although there have been related studies of estimated GDR in adult cohorts, this study is the first study of its kind to apply a pediatric specific estimated GDR to adolescents with T1D to characterize the association of IS with CVD risk factors.

It is well established that IS is impaired in T1D and associated with vascular risk with the original description of this phenomenon being published over 40 years ago (17). DeFronzo (18), Yki-Jarvinen (19), Amiel (20) and Arslanian (21) all described decreased IS historically in people with T1D, but mean glycemia was higher, as they were performed prior to the DCCT results leading to recommendations to lower target HbA1c, and insulin regimens differed from those typically used today (22). More recently, hyperinsulinemic-euglycemic clamp studies continue to demonstrate significant insulin resistance in both adolescents (mean HbA1c=8.7±1.6%) (2) and adults (mean HbA1c=7.5±0.9%) (3) with T1D as compared with age, sex, pubertal stage, habitual level of physical activity, and BMI similar non-DM controls, despite lower HbA1c than pre-DCCT studies. These data also demonstrate that although IS decreases with increasing obesity, IS is decreased in both adolescents and adults with T1D as compared with non-DM controls at similar BMI. Moreover, the CACTI study showed that directly measured IS was associated with coronary artery calcification (3), a surrogate marker of coronary artery disease predictive of future cardiovascular disease outcomes, and adolescent studies show that decreased IS is the strongest predictor of reduced exercise capacity (2), a cardiovascular functional marker and predictor of mortality. Because cardiovascular disease is the leading cause of death in T1D with earlier mortality, such data are important for health outcomes for people with T1D and potentially can help provide insights into the pathogenesis of CVD in T1D.

We did not directly perform a hyperinsulinemic-euglycemic clamp in this study, the means of determining IS clinically via the ISS was validated by the hyperinsulinemic-euglycemic

clamp procedure, which is considered a gold-standard measure of IS (explained 74% of the variance in GDR) (4). Estimation of insulin sensitivity among patients with insulin-treated diabetes is problematic, as fasting levels of glucose and insulin reflect insulin treatment rather than underlying insulin and glucose metabolism, and so are unreliable indicators of insulin sensitivity. Moreover, insulin deficient patients with T1D are unable to produce insulin in response to glucose challenges in oral or intravenous glucose tolerance tests. In non-DM individuals, fasting levels of both insulin and glucose reflect insulin sensitivity, and methods have been developed to estimate IS based on these values, including the homeostasis model (HOMA) (23) and the Quantitative Insulin Sensitivity Check Index (Quicki) equation (24).

In summary, decreased IS is common in T1D and has a significant association to more atherogenic CVD risk factors. However, adolescents with T1D who are the most IS have similar CVD risk factors as non-DM adolescents, whereas decreased IS is associated with more atherogenic CVD risk factors. This finding suggests that decreased IS might be a modifiable therapeutic target for lowering CVD risk in adolescents with T1D.

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Reference List

1. Wadwa RP. Cardiovascular disease risk in youth with diabetes mellitus. *Rev Endocr Metab Disord*. 2006; 7(3):197–204. [PubMed: 17160723]
2. Nadeau KJ, Regensteiner JG, Bauer TA, et al. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. *J Clin Endocrinol Metab*. 2010; 95(2):513–521. [PubMed: 19915016]
3. Schauer IE, Snell-Bergeon JK, Bergman BC, et al. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: The CACTI study. *diab*. 2011; 60(1):306–314.
4. Dabelea D, D'Agostino RB Jr, Mason CC, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study. *diabetol*. 2011; 54(1):78–86.
5. Maahs DM, Nadeau K, Snell-Bergeon JK, et al. Association of insulin sensitivity to lipids across the lifespan in people with Type 1 diabetes. *Diabet Med*. 2011; 28(2):148–155. [PubMed: 21219421]
6. Maahs DM, Ferland A, Kinney G, Wang H, West A, Hokanson J, Eckel R, Nadeau K. More Atherogenic High Density Lipoprotein Profile in Insulin Resistant Adolescents with Type 1 Diabetes. *Circulation*. 2011 Ref Type: Abstract.
7. Maahs DM, Hokanson JE, Wang H, et al. Lipoprotein subfraction cholesterol distribution is proatherogenic in women with type 1 diabetes and insulin resistance. *diab*. 2010; 59(7):1771–1779.
8. Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest*. 2000; 106(4):453–458. [PubMed: 10953019]
9. Haffner SM. Epidemiological studies on the effects of hyperglycemia and improvement of glycemic control on macrovascular events in type 2 diabetes. *Diab care*. 1999; 22 (Suppl 3):C54–C56.

10. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators [see comments]. *Circulation*. 1996; 93(10): 1809–1817. [PubMed: 8635260]
11. Armeno ML, Krochik AG, Mazza CS. Evaluation of two dietary treatments in obese hyperinsulinemic adolescents. *J Pediatr Endocrinol Metab*. 2011; 24(9–10):715–722. [PubMed: 22145462]
12. Koivisto VA, Yki-Jarvinen H, DeFronzo RA. Physical training and insulin sensitivity. *Diabetes Metab Rev*. 1986; 1(4):445–481. [PubMed: 3522140]
13. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. *diabetol*. 2010; 53(5):809–820.
14. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *diab*. 2000; 49(4):626–632.
15. Chillaron JJ, Goday A, Flores-Le-Roux JA, et al. Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascular complications in patients with type 1 diabetes. *J Clin Endocrinol Metab*. 2009; 94(9):3530–3534. [PubMed: 19584183]
16. Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: “double diabetes” in the Diabetes Control and Complications Trial. *Diab care*. 2007; 30(3):707–712.
17. Martin FI, Stocks AE. Insulin sensitivity and vascular disease in insulin-dependent diabetics. *Br Med J*. 1968; 2:81–82. [PubMed: 5646096]
18. DeFronzo RA, Hendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. *diab*. 1982; 31(9):795–801.
19. Yki-Jarvinen H, Koivisto VA. Natural course of insulin resistance in type I diabetes. *N Engl J Med*. 1986; 315(4):224–230. [PubMed: 3523247]
20. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med*. 1986; 315(4):215–219. [PubMed: 3523245]
21. Arslanian S, Nixon PA, Becker D, Drash AL. Impact of physical fitness and glycemic control on in vivo insulin action in adolescents with IDDM. *Diab care*. 1990; 13(1):9–15.
22. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329(14):977–986. [PubMed: 8366922]
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *diabetol*. 1985; 28(7):412–419.
24. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000; 85(7):2402–2410. [PubMed: 10902785]

Table

Baseline Characteristics, by Insulin Sensitivity Score (ISS) tertiles in subjects with T1D

Variable	Non-DM N=89	T1D most IS (ISS N=100	T1D middle IS (ISS 6.84 – 8.64) N=95	T1D least IS (ISS 8.64) N=97
Sex, % male	46%	53%	54%	44%
Race/Ethnicity, % NHW ^a	65%	86%	82%	74%
Tanner Stage, n, % ^a				
I	4, 4%	5, 5%	3, 3%	0, 0%
II	8, 9%	19, 19%	2, 2%	1, 1%
III	12, 13%	14, 14%	7, 7%	7, 7%
IV	24, 27%	34, 34%	28, 29%	19, 20%
V	39, 44%	28, 28%	55, 58%	70, 72%
ISS ^{1,2}	11.1±0.3	9.5±0.3	7.5±0.3	5.1±0.3
Age, y ^{1,2}	15.1±0.2	14.5±0.3	15.3±0.3	15.1±0.3
T1D Duration, y	NA	8.5±0.4	8.1±0.4	7.8±0.5
HbA1c, % ^{1,2}	5.4±0.2	8.0±0.2	9.2±0.2	10.3±0.2
BMI, kg/m ² : ^{1,2}	21.8±0.5	20.8±0.5	22.3±0.6	24.8±0.6
BMI Z-score ²	0.33±0.12	0.37±0.13	0.57±0.13	1.08±0.14
Waist circumference, cm ^{1,2}	75.2±1.3	71.2±1.4	75.6±1.4	84.7±1.5
Total cholesterol, mg/dl ²	154±5	156±5	159±5	181±5
Triglycerides [*] , mg/dl ^{1,2}	87 (34–212)	70 (28–119)	83 (28–153)	123 (40–394)
HDL-c, mg/dl ¹	51±2	55±2	55±2	53±2
LDL-c, mg/dl ²	83±4	85±4	86±4	100±4
SBP, mmHg ²	108±1	109±1	111±1	114±1
DBP, mmHg ^{1,2}	64±1	66±1	68±1	71±1
CRP [*] , mg/dl ²	0.54 (0.0–9.1)	0.54 (0.0–8.9)	0.90 (0.1–7.7)	1.59 (0.1–22.0)

^{*} geometric mean (range)

NHW = non-Hispanic White

^a p<0.05, chi-square

Non-categorical data adjusted for sex, race-ethnicity, Tanner Stage and least square means±SE

¹
p<0.05 for non-DM vs. T1D most ISS tertile

²
p<0.05 for linear trend within T1D by ISS tertiles

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