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Estimated Insulin Sensitivity Predicts Incident Micro- and Macrovascular Complications in Adults with Type 1 Diabetes over 6 Years: the Coronary Artery Calcification in Type 1 Diabetes Study

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Abstract

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Objective—Reduced insulin sensitivity (IS) is well documented in type 1 diabetes (T1D) and may contribute to vascular complications. We examined the association of estimated IS (eIS) with incident macro- and microvascular complications in adults with T1D in the prospective CACTI study.

Methods—Participants (N=652) were 19-56 years old at baseline and re-examined 6.2±0.6 years later. Urinary albumin excretion was measured, and categorized as microalbuminuria or greater. Diabetic retinopathy (DR) was based on self-reported history, proliferative DR (PDR) as history of laser eye therapy and coronary artery calcium (CAC) was measured using electron-beam CT. Progression of CAC was defined as a change in the square root transformed CAC volume score of ≥2.5. IS was estimated (eIS) by an equation derived from clamp studies. Predictors of each complication were examined using stepwise logistic regression and subjects with complications at

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baseline excluded. Age, T1D duration, sex, HbA1c, SBP, LDL-C, and eIS were considered for inclusion.

Results—Greater eIS at baseline predicted lower odds of developing albuminuria (OR: 0.67, 95% CI 0.51-0.88), DR (OR 0.79, 0.64-0.97), PDR (OR: 0.76, 0.57-0.99) and CACp (OR: 0.71, 0.60-0.85) in multivariable models.

Conclusions—Greater eIS conferred protection from the development of vascular complications over 6-years in T1D.

Keywords

Insulin sensitivity; insulin resistance; type 1 diabetes; microvascular complications; macrovascular complications

Introduction

The public health burden of type 1 diabetes (T1D), a disease affecting approximately 1.4 million people in the U.S. and 30 million globally, is progressively increasing largely due to the prevalence of the associated vascular complications (1-3). Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with T1D (2-5). Annually, up to 2% of young adults with T1D develop CAD (2-5). By their mid-forties, over 70% of men and 50% of women with T1D develop coronary artery calcification (CAC) (5), a marker of subclinical atherosclerotic plaque burden. Diabetic nephropathy remains the leading cause of end-stage renal disease in the United States (6), and diabetic retinopathy is the single most common cause of new-onset blindness (7).

Despite significant improvement in conventional risk factors (e.g. hypertension, glycemic control and dyslipidemia) during the past two decades, vascular complications continue to be a major concern for health providers taking care of patients with T1D (8, 9). For that reason, there is a need for improved methods of identifying people at risk of vascular complications at an early stage, as well as additional therapeutic targets to supplement conventional risk factors in preventing development and progression of these complications.

Reduced insulin sensitivity (IS) is well documented in both adolescents and adults with T1D (10-12), and is thought to contribute both to the initiation and progression of vascular complications (13-17). Measuring insulin sensitivity by hyperinsulinemic-euglycemic clamp techniques remains invasive and too cumbersome for clinical care, but newer insulin sensitivity estimation (eIS) equations, which demonstrate strong agreement with measured glucose infusion rate, offer promise in the clinical setting (18). We recently published an eIS equation using common clinical parameters, which performed better than previous equations in estimating IS in adolescents and adults with T1D (18).

The Coronary Artery Calcification in Type 1 diabetes (CACTI) study provided the opportunity to examine the association between eIS at baseline and development of both macro-defined as progression of CAC) and microvascular (defined as albuminuria, diabetic retinopathy (DR) and/or proliferative DR (PDR)) complications in a prospective cohort of adults with T1D. We hypothesized that greater eIS at baseline would independently predict

lower odds of developing both micro- and macrovascular complications over 6 years in adults with T1D.

Materials and Methods

The CACTI Study enrolled 1416 subjects 19-56 years old, 652 with and 764 without T1D, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000-02 and then were re-examined 3 and 6 years later, as previously described (19). Participants (n=652) with T1D who had data available for eIS at baseline were included in this analysis. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated BMI in kg/m^2. Resting systolic (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the patient was seated, and the second and third measurements were averaged for subsequent analysis. After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4°C until assayed. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol was separated using dextran sulfate and LDL cholesterol was calculated using the Friedewald formula. High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant).

CACTI clamp cohort – estimated insulin sensitivity (eIS)

eIS was calculated using an equation developed in a subset of the study cohort (n=87, 40 with T1D and 47 normal controls, frequency matched for age, gender and weight) who underwent a 3 stage hyperinsulinemic-euglycemic clamp study to measure insulin sensitivity, as previously described in detail (10, 20). The model included waist circumference, daily insulin dose per kg body weight, triglycerides and diastolic blood pressure (DBP): exp(4.1075 – 0.01299*waist (cm) – 1.05819*insulin dose (daily units per kg) – 0.00354*triglycerides (mg/dl) – 0.00802*diastolic blood pressure (mm Hg)) (20). We have previously demonstrated that eIS, developed in the CACTI study, improved on the performance of former estimating equations in individuals with and without T1D (20).

Diabetic nephropathy

Diabetic nephropathy was defined as incident albuminuria. Albuminuria was defined as AER ≥ 20 μg/min if timed urine samples were obtained, or ACR ≥ 30 mg/g for spot samples if AER was unavailable. Two timed overnight urine samples were collected in duplicate and urine creatinine and albumin were measured (RIA, Diagnostic Products) and averaged. At both visits, urinary albumin excretion rate (AER) and albumin/creatinine ratio (ACR) were measured. Glomerular filtration rate (GFR) ($ml/min/1.73m^2$) was determined using CKD-EPI creatinine and CKD-EPI cystatin C equations respectively (21). Serum creatinine was measured according to package insert instructions using a Roche Mira Plus II analyzer until 2006 and then an Olympus AU400e (r=0.9999 between methodologies) traceable to the National Institutes of Standards and Technology Standard Reference Material in the University of Colorado Clinical Translational Research (CTRC) Lab. Cystatin C was measured in the University of Colorado Hospital clinical lab using the commercially

available Dade-Behring assay following package insert instructions on a BNII or Prospec instrument as previously described (22).

Diabetic retinopathy

Diagnosis of DR was based on self-reported history of diabetic retinopathy. Self-reported DR has been validated as both a sensitive and specific tool for determining DR (23).

Proliferative diabetic retinopathy

Diagnosis of PDR was based on self-reported history of proliferative retinopathy with laser eye treatment. Self-reported prior laser treatment has been validated as both a sensitive and specific tool for determining PDR (23, 24).

CAC progression

CAC measurements were obtained in duplicate using an ultrafast Imatron C-150XLP electron beam computed tomography (EBCT) scanner (Imatron, San Francisco, CA). The average of the two Agatston scores was used as the CAC score for that visit. Scans were repeated on follow-up, an average of 6.2±0.6 years after the baseline exam. Presence of CAC was defined as a CAC score > 0. Progression of CAC (CACp) was defined as an increase in the CAC volume score of ≥ 2.5 square root transformed units. This definition of progression has previously been shown to represent significant progression of atherosclerosis (9).

Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Differences between men and women were assessed using Chi-Square for categorical variables and *t*-test for continuous variables. Logistic regression was performed to evaluate the associations between variables at baseline and development of incident albuminuria, incident DR, incident PDR and CACp. We excluded subjects with albuminuria (n=129), DR (n=184) and PDR (n=145) at baseline in our analyses. For CACp we did not exclude baseline disease as we were measuring progression of disease rather than incidence.

Variables considered for inclusion in the multivariable models were based on *a priori* criteria: significance in previous work, significant contribution to the model (p-value of <0.1), or confounding between the main variable of interest and the outcome by >10%. The following variables were considered for inclusion in the models: eIS, HDL-C, LDL-C, systolic blood pressure, antihypertensive medications, HbA1c, T1D duration and age. Stepwise logistic regression was used to determine which variables remained in multivariable models predicting DR, PDR, albuminuria and CACp, respectively. Only variables with p-value<0.1 in stepwise selection were included in the models. Odds ratios (OR) represent the odds of developing incident DR, incident PDR and incident albuminuria, or experiencing CACp for every unit increase in the independent variable, and are reported with 95% CI. Significance was based on an α-level of 0.05.

Results

Over 6 years 9.6% of men and 6.1% of women developed incident albuminuria, 11.3% of men and 6.0% of women developed incident PDR, 23.2% of men and 14.3% of women developed incident DR and 52.5% of men and 34.0% of women experienced CACp as previously described (15). Baseline subject characteristics stratified by gender are shown in Table 1.

Each standard deviation (SD) increase in eIS at baseline was associated with lower odds of incident albuminuria, DR, PDR and CACp (Figure 1). Furthermore, in stepwise multivariable logistic regression models examining shared risk factors of vascular complications, each SD increase in eIS at baseline was independently associated with lower odds of incident albuminuria (OR: 0.52, 95% CI 0.35-0.83, p=0.005), incident DR (OR: 0.69, 95% CI 0.50-0.95, p=0.02), PDR (OR: 0.65, 95% CI 0.42-0.99, p=0.049) and CACp (OR: 0.59, 95% CI 0.46-0.77, p<0.0001), Table 2). HbA1c predicted increased odds of developing DR, PDR and CACp in multivariable models (Table 2). Diabetes duration and male sex predicted DR, PDR and CACp (Table 2). Moreover, age predicted CACp (Table 2).

To further test the independence of the associations between eIS and the vascular complications, we also adjusted for antihypertensive medication, and the associations remained significant between eIS and albuminuria (OR: 0.56, 95% CI 0.37-0.87, p=0.009), DR (OR: 0.71, 95% 0.52-0.98, p=0.03) and CACp (OR: 0.53, 95% CI 0.41-0.68, p<0.0001), but was attenuated in PDR (OR: 0.69, 95% 0.45-1.08, p=0.10).

Discussion

Greater eIS at baseline independently predicted lower odds of developing albuminuria, DR, PDR and CACp in a contemporary cohort of adults with T1D. A major challenge in preventing vascular complications of T1D is the difficulty in accurately identifying high risk patients and the need for additional targets to supplement the conventional therapies. There are clinical trials underway exploring the role of metformin in preventing cardiorenal complications of T1D (REMOVAL [NCT01483560] and EMERALD [NCT01808690]), but insulin sensitivity may prove to be an equally important target in the prevention of DR and PDR.

The American Diabetes Association recommends that most adults with T1D should achieve a HbA1C <7.0% (<53 mmol/mol), BP <130/80 mm Hg, and LDL-C <100 mg/dL (25). We have previously reported that only 6% of adults with T1D in CACTI achieved all three ABC goals (26), and not a single subject met the American Heart Association's 7 metrics for ideal cardiovascular health (ICH) (27). The suboptimal ABC and ICH control may be reflective of unattainable goals for subjects with T1D or the lack of sufficiently effective strategies to achieve these goals. While there is strong evidence showing the benefits of ABC and ICH control in reducing vascular complications in T1D (1, 27), optimal control does not abolish the risk for complications. For these reasons there is a call for novel therapeutic targets to supplement conventional therapies.

Orchard et al. demonstrated that estimated glucose disposal rate (eGDR) predicted overt nephropathy in adults with T1D in the EDC cohort (28) over a decade ago. We have also previously demonstrated a cross-sectional association between measured insulin sensitivity and CAC in a small subset of subjects with T1D in CACTI who underwent hyperinsulinemic-euglycemic clamp studies (10). In support of this finding, we here report a strong independent association between eIS at baseline and CACp over 6 years in the full T1D cohort. Furthermore, we report for the first time that eIS at baseline also predicts lower odds of developing DR and PDR independent of other established risk factors. Diabetic retinopathy (DR) remains the most common cause of new onset blindness in adults (7). The prevalence of PDR and DR in CACTI at baseline were 27% and 33% of men and 19% and 26% of women respectively which is consistent with the prevalence reported by several population-based studies (29).

Reduced insulin sensitivity as a unified risk factor for the development of both micro-and macrovascular complications does not necessarily imply causation, but there is increasing evidence implicating reduced insulin sensitivity in the pathogenesis of vascular complications in T1D (30). The exact mechanism of reduced insulin sensitivity in T1D remains unclear. Several factors have been implicated including prolonged exposure to supraphysiologic levels of exogenous insulin, weight gain caused by intensive insulin therapy and perhaps most importantly similar genetic and environmental factors that lead to type 2 diabetes (13, 31). Another possible mechanistic pathway linking reduced insulin sensitivity to vascular complications in T1D is via insulin's effects on overall non-essential fatty acid exposure and lipotoxicity in development of macro- and microangiopathy. There are robust data demonstrating that subjects with T1D with insulin resistance and/or family history of type 2 diabetes are at greater risk of micro- and macrovascular complications (32). Furthermore, high prevalence of metabolic syndrome (38% in men and 40% in women) has been reported in subjects with T1D (33). Insulin sensitivity holds promise as an independent therapeutic target to reduce vascular complications in T1D, with both lifestyle changes (diet and exercise) and drugs such as metformin (34). The REducing With MetfOrmin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL, NCT01483560) (35) and Effects of Metformin on Cardiovascular Function in Adolescents With Type 1 Diabetes (EMERALD, NCT01808690) are ongoing double-blind randomized clinical trials with metformin to improve insulin sensitivity in subjects with T1D in an attempt to prevent vascular complications.

There are limitations of this study worth mentioning, including the limited number of observations for incident albuminuria and incident PDR. DR and PDR were also self-reported and could have been affected by poor recall, but self-reporting of DR has recently been validated for subjects with T1D with sensitivity and specificity greater than 90% (23, 24). Moreover, we did not have data on diabetic neuropathy, another important microvascular complication in T1D. Our study utilizes the eIS equation derived from the largest euglycemic-hyperinsulinemic clamp study in adults both with and without T1D (20) and improved on the performance of previous eIS equations in individuals with and without T1D (18, 28) . Additionally, a direct measure of insulin sensitivity would have been too cumbersome for use in a large-scale clinical study like CACTI. More importantly our main goal was to explore the utility of eIS in predicting vascular complications in adults with

T1D. We adjusted for a variety of important confounding variables, but cannot rule out the presence of unknown risk factors that may have biased or confounded the present analyses. Results from this study may not be generalizable to significantly younger or older subjects with T1D. We also acknowledge that microalbuminuria as a proxy for diabetic nephropathy is not without controversy (36). We have previously reported an association between eIS, albuminuria and rapid GFR decline (34), but this paper is novel in that it explores the associations between eIS and CACp, DR and PDR.

In summary, greater eIS at baseline appears to be protective against the development and progression of both micro- and macrovascular complications of T1D. For that reason, estimated insulin sensitivity may supplement conventional risk factors in identifying people at risk of vascular complications in clinical care. Despite the BARI-2D study (37) showing no benefit of insulin sensitizing strategy on nephropathy in older adults with established coronary artery disease with type 2 diabetes, modification of insulin sensitivity holds promise as a novel target to reduce vascular complications in T1D. Translation of insulin sensitivity into clinical practice as a therapeutic target requires investment in adequately powered clinical trials to capture important long-term vascular outcomes.

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Drs. Petter Bjornstad, Laura Pyle and Janet K. Snell-Bergeon are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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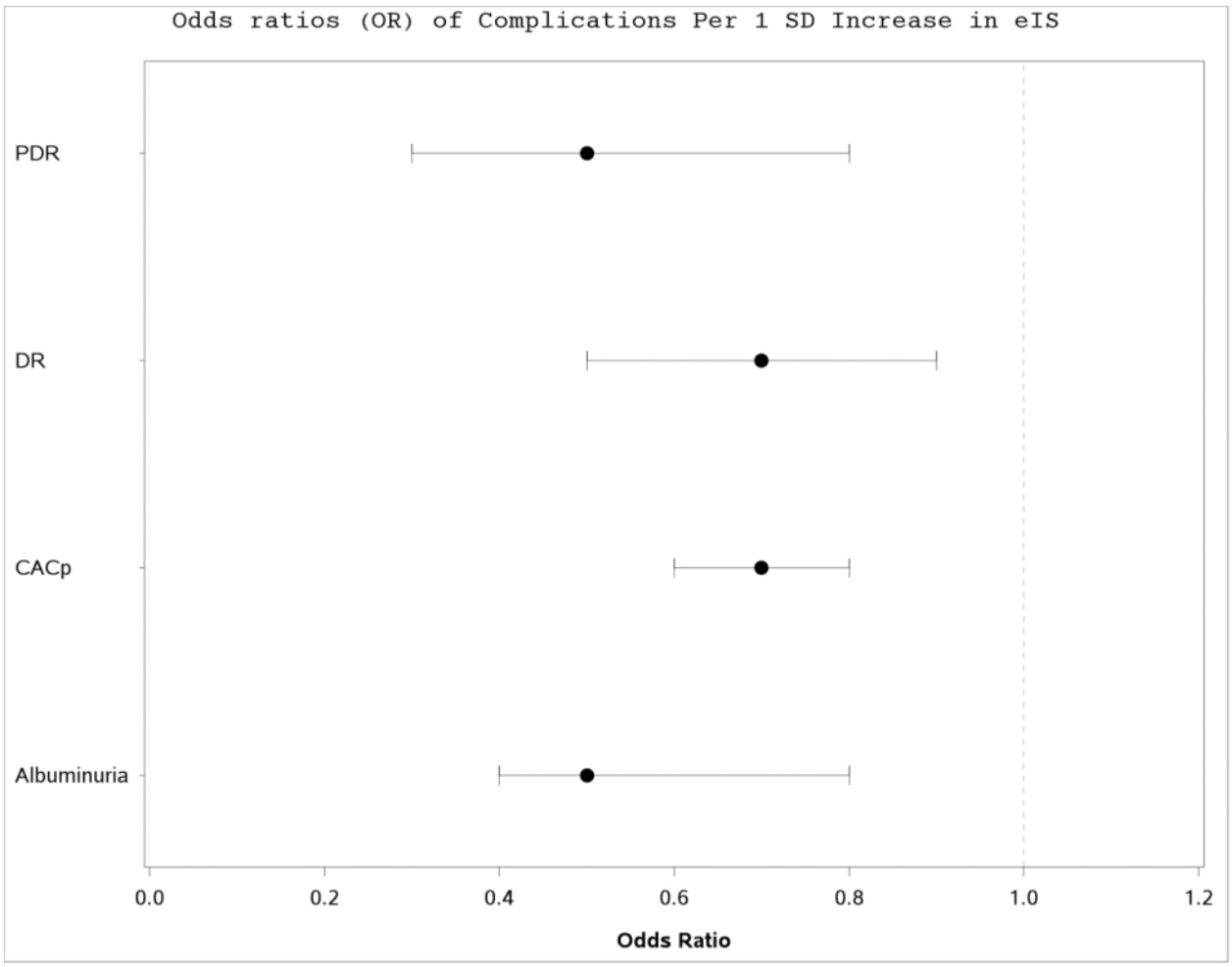

Figure 1. Forest plot for incident micro- and macrovascular complications

Data is presented as OR and 95% CI. OR represent the increase in odds of developing albuminuria, DR, PDR and CACp for every 1 SD increase in the eIS (1.58 mg/kg^{-1} min^{-1})

Table 1
Baseline Characteristics for Study Population with T1D

	Men (n=298)	Women (n=354)	P-value
Age (years)	37 ± 9	36 ± 9	0.07
Diabetes duration (years)	24 ± 9	23 ± 9	0.29
HbA1c (%)	8.0 ± 1.2	8.0 ± 1.3	0.88
HbA1c (mmol/mol)	64 ± 13	64 ± 14	0.88
LDL-C (mg/dl)	104 ± 30	98 ± 28	0.006
HDL-C (mg/dl)	51 ± 14	60 ± 17	<0.0001
Triglycerides (mg/dl)	80 (61-113)	77 (61-104)	0.23
Systolic BP (mm Hg)	121 ± 14	114 ± 14	<0.0001
Diastolic BP (mm Hg)	80 ± 9	75 ± 8	<0.0001
BMI (kg/m^2)	26.5 ± 3.9	26.0 ± 4.7	0.09
Waist circumference (cm)	90.3 ± 11.7	80.8 ± 12.0	<0.0001
AER (μg/min)	7.4 (4.5-23.8)	5.8 (3.8-11.8)	<0.0001
$eGFR_{CREASTININE}$ at baseline ($mL/min/1.73m^2$)	100 ± 27	105 ± 28	0.02
$eGFR_{CREATININE}$ at year 6 ($mL/min/1.73m^2$)	97 ± 22	99 ± 21	0.36
$eGFR_{CYSTATIN\ C}$ at baseline ($mL/min/1.73m^2$)	107 ± 23	106 ± 20	0.68
$eGFR_{CYSTATIN\ C}$ at year 6 ($mL/min/1.73m^2$)	102 ± 23	102 ± 20	0.96
eIS ($mg/kg^{-1}\ min^{-1}$)	3.8 ± 1.4	4.8 ± 1.6	<0.0001
On antihypertensive medications (%)	41%	35%	0.08
Ever smoker (% yes)	18%	22%	0.20
Albuminuria (% yes)	27%	17%	0.005
PDR (% yes)	27%	19%	0.02
Retinopathy (% yes)	33%	26%	0.07

Data are means ± SD, % or median (25^{th} – 75^{th} %)

Table 2
Multivariable models predicting incident micro- and macrovascular complications

	Albuminuria (n=26)	DR (n=62)	PDR (n=31)	CACp (n=185)
Age (per 10 years)	–	–	–	1.99 (1.43-2.75) P<0.0001
Diabetes duration (per 10 years)	–	2.04 (1.43-2.91) P<0.0001	1.85 (1.15-3.00) P=0.01	2.24 (1.62-3.10) P<0.0001
Male sex	–	2.08 (1.13-3.84) P=0.02	2.40 (1.04-5.52) P=0.04	1.73 (1.08-2.77) P=0.02
HbA1c (per 1%)	–	1.41 (1.10-1.79) P=0.006	1.71 (1.28-2.28) P=0.0003	1.25 (1.03-1.52) P=0.03
SBP (per 10 mmHg)	–	–	–	1.20 (1.00-1.44) P=0.049
LDL-C (per 10 mg/dL)	–	0.88 (0.79-0.98) P=0.02	–	–
eIS (per SD [1.58 mg/kg^{-1} min^{-1}])	0.54 (0.35-0.83) P=0.005	0.69 (0.50-0.95) P=0.02	0.65 (0.42-0.99) P=0.049	0.59 (0.46-0.77) P<0.0001

Data is presented as OR and 95% CI. OR represent the increase in odds of developing albuminuria, DR, PDR and CACp for every unit increase in the independent variable. These are stepwise models so only variables which entered the models are presented.