Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

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

Petter Bjornstad [a,b,*], David M. Maahs [a,b,c], Lindsey M. Duca [b,d], Laura Pyle [a], Marian Rewers [a,b], Richard J. Johnson [c], Janet K. Snell-Bergeon [a,b]

[a] Department of Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, CO
[b] Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO
[c] Department of Nephrology, University of Colorado Denver, Aurora, CO
[d] Colorado School of Public Health, University of Colorado Denver, Aurora, CO

ARTICLE INFO

Article history:
Received 19 January 2016
Received in revised form 8 February 2016
Accepted 9 February 2016
Available online xxxx

Keywords:
Insulin sensitivity
Insulin resistance
Type 1 diabetes
Microvascular complications
Macrovascular complications

ABSTRACT

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 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.

1. 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 (de Ferranti et al., 2014; Libby et al., 2005; Stark Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013). Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with T1D (de Ferranti et al., 2014; Krolewski et al., 1987; Libby et al., 2005; Olson, Edmundowicz, Becker, Kuller, & Orchard, 2000). Annually, up to 2% of young adults with T1D develop CAD (de Ferranti et al., 2014; Krolewski et al., 1987; Libby et al., 2005; Olson et al., 2000). By their mid-forties, over 70% of men and 50% of women with T1D develop coronary artery calcification (CAC) (Olson et al., 2000), a marker of subclinical atherosclerotic plaque burden. Diabetic nephropathy remains the leading cause of end-stage renal disease in the United States (Collins et al., 2011), and diabetic retinopathy is the single most common cause of new-onset blindness (Fong et al., 2003).

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 (Orchard, Secrest, Miller, & Costacou, 2010; Snell-Bergeon et al., 2003). 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 (Nadeau et al., 2010; Schauer et al., 2011; Westreich & Mottl, 2015), and is thought to contribute both to

Duality of interest: Drs. Bjornstad, Snell-Bergeon, Johnson, Rewers, Pyle and Maahs, and Ms. Duca have no conflict of interest to disclose.

* Corresponding author at: Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, 1775 Aurora Court, Aurora, CO, 80045. Tel.: +1 720 777 4659; fax: +1 720 777 7301.
E-mail address: Petter.Bjornstad@childrenscolorado.org (P. Bjornstad).

http://dx.doi.org/10.1016/j.jdiacomp.2016.02.011
1056-8727/

the initiation and progression of vascular complications (Bjornstad, Cherney, & Maahs, 2014; Bjornstad, Maahs, Cherney, et al., 2014; Bjornstad, Maahs, Rivard, et al., 2014; Bjornstad, Snell-Bergeon, McFann, et al., 2014; Cleland, Fisher, Colhoun, Sattar, & Petrie, 2013). 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 (Duca et al., 2016). 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 (Duca et al., 2016).

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.

2. 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 (Maahs et al., 2005). 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).

2.1. 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 (Duca et al., 2016; Schauer et al., 2011). 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)) (Duca et al., 2016). 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 (Duca et al., 2016).

2.2. 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/1.73 m^2) was determined using CKD-EPI creatinine and CKD-EPI cystatin C equations respectively (Inker et al., 2012). 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 (Maahs, Jalal, McFann, Rewers, & Snell-Bergeon, 2011).

2.3. 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 (Grassi et al., 2013).

2.4. 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 (Grassi et al., 2009; Grassi et al., 2013).

2.5. 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 (Snell-Bergeon et al., 2003).

3. 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

Please cite this article as: Bjornstad, P., et al., Estimated insulin sensitivity predicts incident micro- and macrovascular complications in adults with type 1 diabetes over 6 years..., *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.02.011