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Estimated insulin sensitivity predicts regression of albuminuria in Type 1 diabetes

P. Bjornstad[1], **D. M. Maahs**[1,2,3], **R. J. Johnson**[3], **M. Rewers**[1,2], and **J. K. Snell-Bergeon**[1,2]

[1]Department of Paediatrics, University of Colorado School of Medicine, Aurora, CO, USA

[2]Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO, USA

[3]Department of Nephrology, University of Colorado Denver, Aurora, CO, USA

Abstract

Aim—To test the hypothesis that greater baseline insulin sensitivity would predict regression of albuminuria over 6 years in adults with Type 1 diabetes.

Method—We enrolled 81 people aged 30–48 years with albuminuria at baseline in the present study and re-examined them 6 years later. Urinary albumin excretion rate was measured and albuminuria was defined as urinary albumin excretion rate ≥20 μg/min. Regression of albuminuria was defined as normoalbuminuria (urinary albumin excretion rate <20μg/min) at follow-up. Predictors of regression of albuminuria were examined in stepwise logistic regression. The variables age, diabetes duration, sex, serum uric acid, HbA_{1c}, systolic blood pressure, LDL cholesterol, HDL cholesterol, BMI, baseline albumin excretion rate, estimated insulin sensitivity at baseline, change in estimated insulin sensitivity from baseline to follow-up and angiotensinconverting enzyme inhibitor/angiotensin receptor blocker use were considered for inclusion in the model.

Results—Estimated insulin sensitivity was significantly higher at both baseline (4.6±1.2 vs 3.4±1.7; P=0.002) and follow-up (5.2±1.9 vs. 3.5±1.7; P<0.0001) in people who had regression of albuminuria vs those who did not. HbA_{1c} (odds ratio 0.4, 95% CI 0.2–0.8; P=0.006), estimated insulin sensitivity (odds ratio 2.5, 95% CI 1.3–4.9; P=0.006) at baseline and change in estimated insulin sensitivity from baseline to follow-up (odds ratio 2.7, 95% CI 1.4–5.3; P=0.003) were independently associated with regression of albuminuria in a multivariable stepwise model.

Conclusions—In conclusion, over 6 years, higher baseline estimated insulin sensitivity and change in estimated insulin sensitivity independently predicted regression of albuminuria. Improving insulin sensitivity in people with Type 1 diabetes is a potential therapeutic target to increase rates of regression of albuminuria.

Correspondence to: Petter Bjornstad. Petter.Bjornstad@childrenscolorado.org.

Competing interests
None declared.

Introduction

Diabetic nephropathy is one of the leading causes of mortality in Type 1 diabetes [1–3]. Microalbuminuria, the earliest clinical phenotype of diabetic nephropathy, has a cumulative lifetime incidence of ~50% in Type 1 diabetes, and develops at a rate of ~2–3% annually [4]. The paradigm of diabetic nephropathy has changed over the last decade with the demonstration that microalbuminuria does not necessarily imply progressive nephropathy, and may in fact regress to normoalbuminuria [5]. A decrease in estimated insulin sensitivity has been shown to be associated with incident microalbuminuria in adults with Type 1 diabetes [6]; however, no data exist on whether insulin sensitivity is associated with regression of albuminuria. We hypothesized, therefore, that a higher estimated insulin sensitivity at baseline would predict regression of albuminuria over 6 years in adults with Type 1 diabetes in the present prospective Coronary Artery Calcification in Type 1 Diabetes (CACTI) study.

Methods

The CACTI study enrolled 652 people with Type 1 diabetes, 19–56 years old, who were asymptomatic for cardiovascular disease at the baseline visit in 2000–2002 and who were reexamined 3 and 6 years later, as previously described [7]. In all, 129 participants with Type 1 diabetes had albuminuria at baseline, and 82 of those participants had albuminuria at both baseline and follow-up and were considered for the analysis. One participant underwent a kidney transplant and was excluded from the analysis, giving us a total of 81 participants. The participants with missing follow-up data (n=48) were not significantly different from the 81 participants included in the study with regard to age, HbA_{1c} level, estimated insulin sensitivity at baseline, LDL and HDL cholesterol levels, BMI, systolic blood pressure or serum uric acid concentration (data not shown). The study was approved by the Colorado Multiple Institutional Review Board and all participants provided written informed consent.

We measured height and weight, and calculated BMI in kg/m^2. Resting systolic and fifth-phase diastolic blood pressure were measured three times while the patient was seated, and the second and third measurements were averaged. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was combined for analyses. Physical activity was estimated in kilocalories expended per week based on sports and recreation reported in the preceding week as previously described [8,9].

After an overnight fast, blood was collected, centrifuged and separated, as previously described [6]. Serum uric acid concentrations were measured via a clinical analyser using a uricase-based commercial kit. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol was separated using dextran sulphate and LDL cholesterol was calculated using the Friedewald formula. High-performance liquid chromatography was used to measure HbA_{1c} (BioRad Variant; Bio-Rad, Hercules, CA, USA), and the assay was Diabetes Control and Complications Trial-aligned

Albuminuria

We defined albuminuria as a mean urinary albumin excretion rate ≥20 μg/min on two timed overnight urine samples which were collected two nights in a row in duplicate and albumin were measured (radioimmunoassay kit; Diagnostic Products Corp., Los Angeles, CA, USA) and averaged. Subjects with only one measurement, or only with spot urines available, were excluded from the analyses. Glomerular filtration rate (ml/min/1.73m^2) was determined using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation [10]. Cystatin C was measured using the commercially available Dade–Behring assay as previously described [11].

Estimated insulin sensitivity

Estimated insulin sensitivity was calculated using an equation developed in a subset of the entire study cohort (*n*=77) who underwent a hyperinsulinaemic-euglycaemic clamp study to measure insulin sensitivity. The model included waist circumference, daily insulin dose per kg body weight, triglycerides and diastolic blood pressure: 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 (mmHg)], and explained 63% of the variance in the glucose disposal rate in the hyperinsulinaemic-euglycaemic clamp studies [12–15].

Statistical analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC, USA). The distribution of albumin excretion rate was skewed, and natural log transformations were applied (e.g. natural log albumin excretion rate). Differences between subjects who developed regression of albuminuria and those who did not were assessed using a chi-squared test for categorical variables and a *t*-test for continuous variables. Multivariable stepwise logistic regression was performed to evaluate the associations between variables and regression of albuminuria. Variables considered for inclusion in the multivariable models included: age, sex, diabetes duration, serum uric acid concentration, HbA_{1c}, LDL and HDL cholesterol levels, systolic blood pressure, BMI, baseline natural log albumin excretion rate, estimated insulin sensitivity at baseline, change in estimated insulin sensitivity (from baseline to follow-up), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker usage and current smoking. These variables were the same reported/considered by Perkins *et al*. [5] with the addition of serum uric acid concentration and estimated insulin sensitivity. We further examined the associations between estimated insulin sensitivity at baseline with continuous improvement in albumin excretion rate over time by linear regression, and with a 25% reduction in albumin excretion rate over 6 years by logistic regression. Significance was based on an α level of 0.05.

Results

The characteristics of the study participants at baseline and follow-up, stratified by persistence or regression of albuminuria, are shown in Table 1. Over a mean ±SD of 6.1±0.5 years, 38% (31/81) of the participants with albuminuria at baseline experienced regression to normoalbuminuria. Participants who developed regression of albuminuria tended to be women and to have lower HbA_{1c}, lower LDL cholesterol and higher HDL cholesterol levels,

lower diastolic blood pressure, higher estimated glomerular filtration rate based on cystatin C at follow-up and higher estimated insulin sensitivity at baseline (Table 1). Estimated insulin sensitivity also significantly increased over time in the participants who experienced regression at 6 years [0.8 vs 0.1 mg/kg per min; P=0.04 (Table 1)]. There was no difference in angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use between participants with and without regression of albuminuria, probably because most participants with albuminuria at baseline were receiving these medications (72%). There was also no significant difference in smoking, insulin dose and reported physical activity among those with and without persistent albuminuria (Table 1).

In stepwise logistic regression models considering age, sex, diabetes duration, HbA_{1c}, systolic blood pressure, LDL cholesterol, BMI, serum uric acid, baseline natural log albumin excretion rate, estimated insulin sensitivity at baseline, change in estimated insulin sensitivity from baseline to follow-up and angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker use for inclusion, the variables that remained in the model independently predicting regression of albuminuria were HbA_{1c}, natural log albumin excretion rate, estimated insulin sensitivity at baseline and change in estimated insulin sensitivity (Table 2). When also considering HDL cholesterol in the fully adjusted model, change in estimated insulin sensitivity, but not estimated insulin sensitivity at baseline entered the model, probably as a result of a strong correlation between estimated insulin sensitivity at baseline and HDL cholesterol (r=0.42; P<0.0001). To further test the longitudinal association between estimated insulin sensitivity and albumin excretion rate, we ran a linear regression model, which showed that estimated insulin sensitivity at baseline was associated with improvement in continuous albumin excretion rate over 6 years ($\beta \pm_{SE}$: 5.10±2.34; P=0.03). We also found that estimated insulin sensitivity at baseline was associated with greater odds of experiencing a 25% reduction in albumin excretion rate over 6 years, and this association remained significant after adjusting for age, sex, HbA_{1c}, LDL cholesterol, HDL cholesterol and BMI (odds ratio 1.33, 95% CI 1.01–1.76; P=0.04, per 1 $_{SD}$).

We also examined which factors led to improved estimated insulin sensitivity over time in the participants who experienced regression of albuminuria; baseline estimated insulin sensitivity ($\beta \pm_{SE}$ 0.50±0.16; P=0.005) and decrease in BMI ($\beta \pm_{SE}$ 0.29±0.13; P=0.048) were found to be significant determinants. For the participants who did not experience regression of albuminuria, HbA_{1c} level ($\beta \pm_{SE}$ 0.44±0.14; P=0.004) and estimated insulin sensitivity at baseline ($\beta \pm_{SE}$ −0.16±0.05; P=0.002) were significant risk factors for a worsening of estimated insulin sensitivity over time.

Discussion

In the present study, we found that adults with Type 1 diabetes and albuminuria who regressed to normoalbuminuria after 6 years of follow-up were significantly more insulinsensitive than those who had persistent albuminuria. The association of estimated insulin sensitivity with regression of albuminuria expands on the findings of Perkins *et al*. [5]. Similarly, we also observed a significant difference in HbA_{1c} and triglyceride levels and no significant difference in proportion of participants who were current smokers or

angiotensinconverting enzyme inhibitor/angiotensin receptor blocker use among those with and without persistent albuminuria [5]. A major challenge in preventing diabetic nephropathy is the difficulty in accurately identifying people who are at high risk and the need for additional therapeutic targets. The findings of the present study suggest that estimated insulin sensitivity is an important modifiable factor for regression of albuminuria in Type 1 diabetes.

The association between insulin sensitivity and diabetic nephropathy is increasingly recognized in people with Type 1 diabetes, but it is not a recent discovery. In 1993, Yip *et al.* [16] found reduced insulin sensitivity in a small group with microalbuminuria, while Orchard *et al.* [17] later found that estimated insulin sensitivity predicted overt nephropathy in participants with Type 1 diabetes in their EDC cohort. More recently, we have reported that estimated insulin sensitivity predicts incident microalbuminuria and a rapid decline in glomerular filtration rate in adults with Type 1 diabetes [12].

The present study has some limitations, including its observational design, the small number of subjects with baseline albuminuria, and the inclusion of only two urine albumin excretion measures at each time point and no direct measure of insulin sensitivity. We used an insulin sensitivity estimate, however, which strongly correlates with glucose disposal rate measured by the 'gold standard' method in the CACTI clamp study, thereby suggesting that it may be a true reflection of insulin sensitivity. Another limitation is that the results of the present study may not be generalizable to significantly younger or older subjects with Type 1 diabetes.

Diabetic nephropathy remains the most common cause of end-stage renal disease in the western world [18], and current treatment and risk stratification methods are inadequate. This report extends the evidence of regression of albuminuria in Type 1 diabetes as previously described by Perkins *et al*. [5] by identifying estimated insulin sensitivity as a novel clinical risk factor that predicts the regression of albuminuria. Despite the findings of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study [19], which showed no benefit of insulin-sensitizing strategy on nephropathy in older adults with Type 2 diabetes and coronary artery disease, the modification of insulin sensitivity may hold promise for reducing diabetic nephropathy in people with Type 1 diabetes.

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What's new?

- Insulin sensitivity is an increasingly recognized risk factor for diabetic nephropathy in adults with Type 1 diabetes.
- The paradigm of diabetic nephropathy has changed with the demonstration that microalbuminuria does not necessarily imply progressive nephropathy, and may in fact regress to normoalbuminuria.
- This brief report extends the evidence of regression of albuminuria in Type 1 diabetes by identifying estimated insulin sensitivity as a novel clinical risk factor predicting this regression.

Table 1

Baseline characteristics of participants in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study

	Persistence of albuminuria (*n*=50)	Regression of albuminuria (*n*=31)	*P*
Sex, % men	72	42	0.007
Mean ±SD age at baseline, years	38 ± 8	40 ± 8	0.28
Mean ±SD diabetes duration, years	24 ± 8	26 ± 11	0.28
Mean ±SD HbA_{1c} **mmol/mol** **%**	70.5 ± 10.8 8.6 ± 1.2	60.7 ± 9.7 7.7 ± 1.1	0.0007
Mean ±SD LDL cholesterol, mg/dl	107 ± 26	94 ± 24	0.03
Mean ±SD HDL cholesterol, mg/dl	50 ± 15	58 ± 15	0.03
Median (25^{th} – 75^{th} %) triglycerides, mg/dl	106 (74–154)	76 (56–99)	0.007
Mean ±SD systolic blood pressure, mmHg	124 ± 13	118 ± 15	0.05
Mean ±SD diastolic blood pressure, mmHg	82 ± 10	76 ± 9	0.005
Mean ±SD serum uric acid, mg/dl	5.8 ± 1.2	5.5± 1.3	0.61
Median (25^{th} – 75^{th} percentile) albumin excretion rate, μg/min	138 (54–434)	27 (21–50)	<0.0001
Median (25^{th} – 75^{th} percentile) albumin excretion rate at follow-up, μg/min	135 (42–335)	9 (5–14)	<0.0001
Mean ±SD eGFR based on cystatin C at baseline, ml/min/1.73m^2	90 ± 29	100 ± 18	0.11
Mean ±SD eGFR based on cystatin C at year 6, ml/min/1.73m^2	75 ± 34	92 ± 21	0.01
Mean ±SD insulin dose, units/kg/day	0.67 ± 0.23	0.65 ± 0.19	0.29
Mean ±SD estimated insulin sensitivity, mg/kg per min	3.4 ± 1.7	4.5 ± 1.2	0.003
Mean ±SD estimated insulin sensitivity at follow-up, mg/kg per min	3.5 ± 1.7	5.2 ± 1.9	0.0001
Receiving ACE inhibitors/angiotensin receptor blockers at baseline, %	74	68	0.54
Receiving ACE inhibitors/angiotensin receptor blockers at follow-up, %	80	81	0.94
Current smoker, %	10	14	0.63
Mean ±SD BMI, kg/m^2 **Sex-adjusted mean** ±SE*	27.1 ± 4.5 26.9 ± 0.6	25.5 ± 3.2 25.7 ± 0.6	0.10 0.15
Mean ±SD waist circumference, cm **Sex-adjusted mean** ±SE*	91.1 ± 13.7 90.6 ± 1.6	85.2 ± 10.4 85.5 ± 2.0	0.04 0.047
Median (25^{th} – 75^{th} percentile) exercise, kcal/week **Sex-adjusted geometric mean** ±SE*	1760 (897–3896) 1697.5 ± 1.2	1261 (590–4060) 1277.4 ± 1.2	0.49 0.24

eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Least-squares means ± SE.

Table 2

Stepwise multivariable models predicting regression of albuminuria

Variable (units)	Regression of albuminuria (*n*=31) Odds ratio (95% CI); *P*
Age (per 10 years)	–
Diabetes duration (per 10 years)	–
Male sex (yes/no)	–
HbA_{1c} (per 1%)	**0.4** (0.2–0.8)**; 0.008**
Serum uric acid (per 1 mg/dl)	–
Systolic blood pressure (per 10 mmHg)	–
LDL cholesterol (per 10 mg/dl)	–
Baseline natural log albumin excretion rate (per SD [1.40])	**0.3** (0.1–0.7); **0.003**
ACE inhibitor/ARB (yes/no)	–
Current smoking (yes/no)	–
BMI (per 1 kg/m^2)	–
Estimated insulin sensitivity (per SD [1.64 mg/kg^{-1} min^{-1}])	**2.3** (1.1–4.7); **0.003**
Change in estimated insulin sensitivity from baseline to follow-up (per SD [1.25 mg/kg per min])	**3.3** (1.5–7.4); **0.003**

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Odds ratios represent the odds of developing regression of albuminuria for every unit(s) increase in the independent variable. Dashes indicate that variables did not enter the model.