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## The dose response effect of insulin sensitivity on albuminuria in children according to diabetes type

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### Abstract

**Background**—Insulin resistance is associated with microalbuminuria among youth with diabetes mellitus. We sought to determine the dose-response effect of insulin sensitivity (IS) on the magnitude of albuminuria and whether there is a threshold below which urine albumin excretion increases.

**Methods**—These analyses included participants from the SEARCH for Diabetes in Youth Study with incident diabetes who completed a baseline study visit (N = 2988). We estimated IS using a validated equation incorporating waist circumference, HbA1C and fasting serum triglycerides.

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### Ethics statement

The study protocol was reviewed and approved by local institutional review boards (IRB) that had jurisdiction over the local study populations. Consent was obtained from parents of all participants under age 18 years and assent from participants according to the specific age requirement deemed by the local IRB.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Disease

Multivariate regression analyses were performed to assess the effect of IS on urine albumin creatinine ratio (UACR), stratified by diabetes type. The IS threshold was then determined using segmented regressions within each diabetes type and incorporated into the multivariate model.

**Results**—There was an association between IS and UACR in type 2 diabetes only (beta =  $-0.39$ ;  $p < 0.001$ ). There was strong statistical evidence for a threshold effect of IS score on UACR in the group of youth with type 2 (beta =  $0.40$ ;  $p < 0.001$ ) but not type 1 diabetes ( $p = 0.3$ ).

**Conclusions**—In cross-sectional analyses, there is a negative association between IS and UACR in youth with type 2 but not type 1 diabetes, and this association likely includes a threshold effect of IS on UACR.

### Keywords

microalbuminuria; urine:albumin creatinine ratio; insulin resistance; nephropathy; metabolic syndrome

## INTRODUCTION

The rising prevalence of diabetes in adolescents and young adults poses a major public health problem, as a greater lifetime diabetes exposure in this group will translate into a greater future burden of microvascular complications [1]. Diabetic kidney disease (DKD) accounts for nearly half of end-stage kidney disease in the USA, and is a major risk factor for cardiovascular events and death [2–4]. Although the precision of microalbuminuria as a predictor for increased risk is less than initially thought, the degree of albuminuria after long diabetes duration is still the strongest available biomarker for the risk of progressive DKD [5]. Albuminuria has also been noted to occur in the presence of obesity, even in the absence of diabetes [6, 7]. Moreover, albuminuria is more prevalent in early type 2 than type 1 diabetes; and differences in body mass index (BMI) and hypertension do not completely explain this difference [8]. It is possible that insulin resistance could explain the higher levels of urinary albumin associated with obesity and type 2 diabetes.

In a previous study from SEARCH, we analyzed the urine albumin:creatinine ratio (UACR) across four etiologic diabetes sub-groups categorized according to diabetes autoantibody (DAA) status (DAA + versus -) and insulin sensitivity (IS) status. We found that the UACR levels among participants in the DAA-/insulin resistant group were significantly higher than those observed in all other groups, even after multivariable adjustment. To explore the underlying factors that accounted for the difference in UACR between the two insulin resistance groups, we performed multivariable regression analyses restricted to these two groups. Only the degree of IS was significantly associated with UACR ( $\beta = -0.54$ ;  $p < 0.0001$ ), suggesting that the difference between the insulin resistant DAA+ versus DAA- groups was due to a greater degree of insulin resistance in the DAA-group. Herein, we propose to extend these analyses to determine: 1) whether the association between IS and UACR differs by diabetes type (defined by provider diagnosis), sex or race/ethnicity, and 2) whether there is a threshold of IS below which urine albumin excretion increases.

## METHODS

### Population

The SEARCH for Diabetes in Youth Study is a multicenter, observational, population-based study of youth with diabetes. A detailed description of study methods has been published previously [9]. SEARCH investigators have conducted population-based ascertainment of incident cases of diabetes in youth aged less than 20 years old from 2002 onwards. Cases were ascertained from geographically defined populations in Ohio, Colorado, South Carolina and Washington, among enrollees in one health plan in California, and Indian Health Service participants from four American Indian populations. Youth identified with incident, non-secondary diabetes were invited for a baseline study visit. Self-reported race and ethnicity were collected using the 2000 U.S. Census questions [10].

### Sample selection, design and measurements

This cross-sectional analysis explored the association between diabetes type and the magnitude of albuminuria. Inclusion criteria consisted of having an in-person visit, on average 10 months after the diagnosis of diabetes, where fasting blood was drawn, urine was collected and anthropometric measurements taken ( $n = 2988$ ). Individuals taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers were excluded from these analyses ( $n = 38$ ). Diabetes type was defined by the health care provider diagnosis. The study visit included measurement of waist circumference using the National Health and Nutrition Examination Survey protocol [11], systolic and diastolic blood pressures (SBP; DBP), height and weight, as previously described [12]. BMI ( $\text{kg}/\text{m}^2$ ) was converted to z-scores using the standard Centers for Disease Control and Prevention approach [13].

Blood and single, random urine samples were obtained under conditions of metabolic stability, defined as no episodes of diabetic ketoacidosis in the preceding month and the absence of fever and acute infections. Urine was not collected from girls who were menstruating. Specimens were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). Measurements of serum cholesterol, triglycerides (TG) and high density lipoprotein (HDL) cholesterol were performed using Roche reagent on a Roche Module P autoanalyzer (Roche Diagnostics, Indianapolis, IN). HbA1c was measured by a dedicated ion exchange high-performance liquid chromatography instrument (TOSOH Bioscience).

A random urine specimen was used for calculation of UACR. Urinary creatinine was measured on the Roche Modular P autoanalyzer by the Roche enzymatic method with calibrator values traceable to the isotope dilution mass spectroscopy reference procedure. Two quality-control samples were analyzed in each run, and the inter-assay coefficient of variation was consistently  $<2\%$ . Urine albumin was measured immunochemically using Siemens reagent on a Siemens BNII nephelometer. The inter-assay coefficient of variation was  $<5\%$  for the high and  $<6.5\%$  for the low-level quality-control sample. We defined albuminuria as a UACR  $30\ \mu\text{g}/\text{mg}$  as recommended by the American Diabetes Association guidelines [14] and the National Kidney Disease Outcomes Quality Initiative [15].

We estimated IS using a validated equation based on euglycemic hyperinsulinemic clamp data as follows:

$$IS = \exp [4.647252 - (0.02032 \times \text{waist, cm}) - (0.09779 \times \text{HbA1c, \%}) - (0.002350 \times \text{triglyceride, mg/dL})]$$

This equation was developed and validated using direct measurements of glucose disposal rate (GDR) from euglycemic-hyperinsulinemic clamps conducted among 85 SEARCH participants, and 22 matched non-diabetic control subjects [16]. As previously reported, we defined insulin resistance among SEARCH participants in this study as IS below the 25<sup>th</sup> percentile for the U.S. general youth population ( $IS < 8.15$ ) [17].

Blood samples taken at the baseline visit were analyzed for the 65-kD isoform of glutamate decarboxylase and insulinoma-associated-2 antibodies using the NIDDK standardized method [18]. The cutoff values for positivity were 33 DK units/mL for GADA and 5 DK units/mL for IA-2A. The specificity and sensitivity were 97 and 76 %, respectively for GADA, and 99 and 64 %, respectively for IA-2A [18]. Positive titers for either GADA or IA-2A were used to define DAA positivity. Because many participants were treated with insulin, analysis of insulin autoantibodies was not performed.

### Statistical analysis

We performed statistical analyses using SAS software, version 9.3 (SAS Institute, Cary, NC) and R (R Core Team, 2015) [19]. The sample sizes for youth from race/ethnic groups other than non-Hispanic white were small. Hence, all racial/ethnic groups other than non-Hispanic white were combined into a single ‘minority’ category. The means and percentages of the demographic and clinical characteristics were compared between diabetes types, based on their health care provider’s diagnosis, using chi square and Wilcoxon two-sample test, which is more robust to deviations from the assumption of normality.

Multivariate regression analyses were performed to assess the relationship between IS and UACR. The logarithm of UACR was used as the outcome. Covariates included age, sex, race/ethnicity, DAA positivity, diabetes duration and SBP z-score. A-priori, the decision was made to leave HbA1c out of the model due to the fact that HbA1c is incorporated into the calculation of IS. Measurements of body size were also left out of the model because waist circumference was also incorporated into the IS calculation, and this measure is collinear with other parameters reflecting BMI.

**Interaction analyses**—We tested interaction between diabetes type and IS within the combined cohort first, and if the interaction term was significant to  $p < 0.05$  all subsequent analyses were stratified by diabetes type. Additional IS\*sex and IS\*ethnicity interactions were also explored within each diabetes type.

**Threshold analyses**—We performed threshold estimation using a segmented regression approach. Segmented regressions were fitted using the ‘segmented’ package in R [20]. This package implements an iterative procedure that starts with an initial threshold value, which is repeatedly updated until convergence is reached.

## RESULTS

The final sample for these analyses included 2,950 participants. Participants excluded from analysis due to missing urine sample (N = 527 type 1; N = 85 type 2 participants) had a few dissimilarities to those included in the analysis (Supplemental Table 1). The most significant differences were among the participants with type 1 diabetes. Those with a urine sample had lower fasting glucose (165 versus 187 mg/dl, <0.001) and shorter diabetes duration (9.3 versus 10.3 months,  $p < 0.001$ ), than those without a urine sample.

Socio-demographic and clinical characteristics were significantly different between type 1 and type 2 participants (Table 1). Participants with type 2 diabetes were older, predominantly female and from racial/ethnic minority groups. They had a lower IS score and HbA1c, but higher BMI, BP and lipid levels. Although microalbuminuria was more common in the type 2 participants, there was no statistically significant difference in the distribution of UACR by diabetes type, despite a numeric trend toward more elevated levels in type 2.

The interaction between IS and diabetes type was statistically significant ( $p < 0.001$ ) and therefore, all other analyses were stratified. IS was significantly associated with UACR in participants with type 2 diabetes ( $p < 0.001$ ), but not type 1 diabetes ( $p = 0.25$ ). Interactions between IS and sex and IS and ethnicity on UACR were not statistically significant within either diabetes type.

Using a segmented regression approach, a threshold for the relationship between IS and UACR was detected at IS = 6.7 and IS = 4.7 for participants with type 1 and type 2 diabetes, respectively (Figure 1). There was clear statistical evidence for a threshold effect of IS on UACR in participants with type 2 ( $p < 0.001$ ), but not type 1 diabetes ( $p = 0.09$ ). Output from these multivariate regression analyses are displayed in Table 2. These data indicate that in participants with type 2 diabetes there is an inverse relationship between IS and UACR, and below the IS threshold of 4.7 the relationship becomes even stronger. The performance of the models including versus omitting the threshold value are available in Supplemental Table 2.

## DISCUSSION

Type 2 diabetes in adolescents and young adults is a growing pandemic, making it imperative to better understand the potential causative factors for DKD in this inadequately studied population. Our findings provide novel evidence that early in the course of type 2 diabetes in youth, the degree of albuminuria is strongly and inversely associated with the IS score, a validated estimate of insulin sensitivity. Moreover, the nature of this relationship in type 2 diabetes likely includes a threshold effect, below which the association becomes even stronger. In youth with type 1 diabetes, the UACR was not significantly associated with the IS score.

The association of IS and albuminuria in diabetes has been noted previously [21–27], however several aspects of our study are novel. This is the first time the association between IS and albuminuria has been directly compared across diabetes types. Moreover, this is the

only investigation of IS and albuminuria in an inception cohort of diabetes, giving insight into IS as a potential pathogenic factor early in the natural history of albuminuria.

The association of albuminuria and low IS, or a surrogate abdominal adiposity, has been recognized in type 2 diabetes [24–30], in type 1 diabetes [21, 23, 31–35] and in populations without diabetes [7, 36, 37]. The few negative studies have been from populations with distinct characteristics such as hypertensive individuals or those without significant representation of overweight [25, 29]. The basis for a lack of association between albuminuria and IS in our youth with type 1 diabetes can only be speculated about, but it may be due, in part, to a relative lower prevalence of obesity, insulin resistance and albuminuria at this early stage of type 1 diabetes (Table 1). As shown in Figure 1, the association of IS and albuminuria in type 2 diabetes is most significant in the lowest portion of IS, and very few participants with type 1 diabetes were within this range. Previous SEARCH data have indicated that, although the prevalence of overweight is higher in youth with type 1 diabetes than in non-diabetic youth, the prevalence of obesity is actually somewhat lower [38]. The Epidemiology of Diabetes Interventions and Complications Study documented weight gain and increased abdominal adiposity in type 1 patients over time, as well as its association with increased vascular disease [39]. Studies of adult type 1 diabetic populations have clearly shown low IS to be predictive of subsequent micro- and macroalbuminuria [21, 23, 31–35]. Similarly, higher levels of IS in older type 1 diabetic populations predicted regression of microalbuminuria [40]. These studies were conducted in populations with type 1 diabetes with a duration of 10 – 20 years, mean BMI of 25 – 30 and a prevalence of microalbuminuria of 18 – 44 %; all characteristics very distinct from our population [23, 31, 32].

Another potential explanation for our findings is the difference in age of onset and consequent pubertal diabetes duration. The vast majority of SEARCH participants with type 2 diabetes were in the peri- or post-pubertal phase at examination (age >12 years), whereas the minority of participants with type 1 diabetes had reached puberty. Data regarding the effect of puberty on diabetic complications has mostly emanated from studies of type 1 diabetes [41]. Several older studies suggested that pre-pubertal diabetes conferred protection against diabetic complications. Moreover, the pubertal phase may exacerbate complications due to changes in the hormonal balance and increasing adiposity and insulin resistance seen in puberty. While we did adjust our analyses for age and diabetes duration, we did not specifically address pubertal phase. We intend to explore this issue further with subsequent longitudinal data, when more participants have passed the pubertal phase.

The association between IS and albuminuria is likely multifactorial. Hypotheses include increased inflammatory mediators produced in visceral adipocytes, increased circulating levels of insulin and impaired insulin signaling within the podocyte [42–45]. Decreasing IS results in aberrations in adipocytokines, including decreased adiponectin and increased leptin and resistin concentrations [42]. Low levels of adiponectin found in obese states have been linked to increased reactive oxygen species, podocyte foot process effacement, endothelial cell dysfunction and albuminuria [43]. Leptin levels rise with insulin resistance, even independent of BMI, and have been found to result in increased TGF- $\beta$  and collagen deposition [42, 44].

Insulin infusion has been cited to induce transient albuminuria, and its overproduction has been hypothesized as a mechanism by which albuminuria occurs in the insulin resistant state. Insulin stimulates the renin-angiotensin system, growth factors and reactive oxygen species [46]. Alternatively, aberrant insulin signaling has direct implications on the function of the podocyte which, in its normal state, is an insulin responsive cell type [45]. Supportive of this notion that aberrant insulin signaling in the kidney may mediate the association between IS and albuminuria, are numerous small studies in animals and humans showing insulin sensitizers to reduce urinary albumin excretion [47].

Our study has several limitations. Most importantly, only a single, random UACR was available for analysis. Random urine samples carry a higher inter-individual variability than first morning samples, and multiple urine samples are required to maximize precision in quantifying albuminuria [48, 49]. This is not likely to have affected our conclusions, as the variability in UACR is not dependent upon diabetes type or insulin sensitivity. This was also a cross-sectional study design and hence only associations, rather than causality, can be inferred from the results.

Strengths of our study include the large sample size and the ethnic and geographic diversity of the SEARCH study. SEARCH participants were enrolled soon after diagnosis of diabetes, allowing insight into the early natural history of both IS and albuminuria. Moreover, to our knowledge, this is the only study to examine and compare the relationships between IS and albuminuria in type 1 and type 2 diabetes. Our equation estimating IS was developed and validated in a subset of 85 SEARCH participants and 22 nondiabetic controls undergoing euglycemic clamps, and explained 74 % of variance of the glucose disposal rate [16]. This is superior to other currently available glucose disposal rate estimating equations [21, 23]. Although the euglycemic-hyperinsulinemic clamp study is the gold standard for measurement of IS, such an invasive, costly and time-consuming method is impractical for use in large, epidemiologic studies such as the full SEARCH study.

In conclusion, we report that in cross-sectional analyses, insulin sensitivity is significantly associated with albuminuria in children and adolescents with type 2 but not type 1 diabetes of short duration. There is likely a threshold effect of IS on UACR in type 2 diabetic adolescents and young adults, below which the association between IS and urine albumin excretion is stronger. Whether this threshold also portends an increased risk for subsequent micro- and macrovascular complications longitudinally, is a direction for future study.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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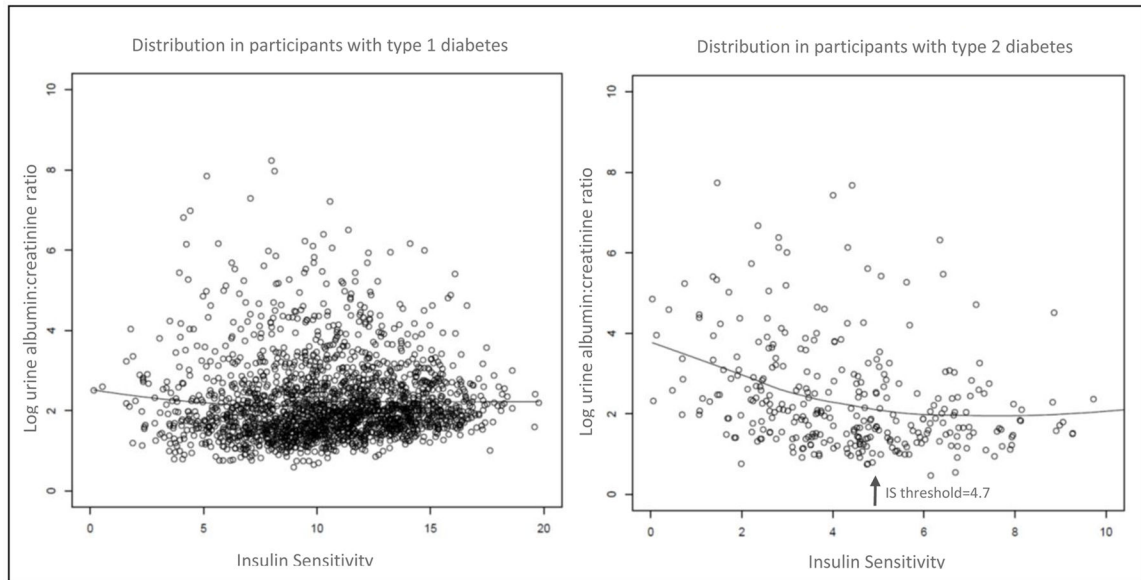
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**Figure 1.**

The relationship between urine albumin:creatinine ratio and insulin sensitivity (IS) in type 1 versus type 2 diabetic participants in the SEARCH cohort. The threshold detected in the type 2 participants is noted by the arrow, and represents the point at which further decreases in insulin sensitivity are associated with even greater degrees of albuminuria.

**Table 1**

Baseline characteristics of 2,950 participants in the SEARCH for Diabetes in Youth cohort, stratified by diabetes type.

Baseline characteristics	Type 1 mean (SD) n=2551	Type 2 mean (SD) n=399	p-value
Age at exam, years	11 (4)	15 (3)	<0.001
Male, n (%)	1352 (53)	160 (40)	<0.001
Non-Hispanic White, n (%)	1938 (76)	96 (24)	<0.001
Time from diabetes diagnosis, months	10 (6)	11 (7)	0.001
Insulin sensitivity score	10.5 (3.3)	4.4 (2.2)	<0.001
UACR, $\mu\text{g}/\text{mg}$ (median, IQR)	7.0 (7.9)	7.4 (14.1)	0.6
Albuminuria, n (%)	202 (10)	53 (17)	<0.001
HbA1c, %	7.7 (1.6)	7.2 (2.1)	<0.001
Body mass index z-score	0.53 (1.02)	2.13 (0.69)	<0.001
Overweight, n (%)	816 (32)	371 (93)	<0.0001
SBP z-score, mmHg	-0.5 (0.9)	0.39 (1.09)	<0.001
DBP z-score, mmHg	0.12 (0.81)	0.52 (0.48)	<0.001
Total cholesterol, mg/dl	160 (30)	171 (30)	<0.001
Triglycerides, mg/dl	67 (55)	161 (182)	<0.001
HDL, mg/dl	55 (13)	41 (10)	<0.001
LDL, mg/dl	92 (24)	102 (30)	<0.001

UACR = urine albumin:creatinine ratio; Albuminuria = UACR  $\geq 30 \mu\text{g}/\text{mg}$ ; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein

**Table 2**

Output from multivariate linear regression ‘segmented regression threshold model’ analysis of type 2 diabetic participants.

Covariate	Type 1 Diabetes		Type 2 Diabetes	
	Beta Coefficient	p-value	Beta Coefficient	p-value
Intercept	2.366	<0.001	4.051	<0.001
Threshold	0.063	0.09	0.397	<0.001
Insulin sensitivity score	-0.038	0.25	-0.385	<0.001
Age at diagnosis	0.012	0.1	-0.023	0.5
Male gender	-0.341	<0.001	0.010	0.9
NonHispanic White Ethnicity	-0.020	0.7	-0.1545	0.3
Diabetes autoantibodies	0.007	0.9	0.194	0.4
Systolic blood pressure Z-score	-0.002	0.9	0.009	0.9
Diabetes Duration	0.004	0.9	0.007	0.5