Albuminuria According to Status of Autoimmunity and Insulin Sensitivity Among Youth With Type 1 and Type 2 Diabetes

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OBJECTIVE—To evaluate whether etiologic diabetes type is associated with the degree of albuminuria in children with diabetes.

RESEARCH DESIGN AND METHODS—SEARCH is an observational, longitudinal study of children with diabetes. Youth with newly diagnosed diabetes were classified according to diabetes autoantibody (DAA) status and presence of insulin resistance. We defined insulin resistance as an insulin sensitivity score <25th percentile for the United States general youth population. DAA status was based on positivity for the 65-kD isoform of glutamate decarboxylase and insulinoma-associated protein 2 antigens. The four etiologic diabetes type groups were as follows: DAA$^+$/insulin-sensitive (IS) ($n = 1{,}351$); DAA$^+$/insulin-resistant (IR) ($n = 438$); DAA$^-$/IR ($n = 379$); and DAA$^-$/IS ($n = 233$). Urinary albumin:creatinine ratio (UACR) was measured from a random urine specimen. Multivariable regression analyses assessed the independent relationship between the four diabetes type groups and magnitude of UACR.

RESULTS—Adjusted UACR means across the four groups were as follows: DAA$^+$/IS = 154 μg/mg; DAA$^+$/IR = 137 μg/mg; DAA$^-$/IR = 257 μg/mg; and DAA$^-$/IS = 131 μg/mg ($P < 0.005$). Only DAA$^-$/IR was significantly different. We performed post hoc multivariable regression analysis restricted to the two IR groups to explore the contribution of DAA status and insulin sensitivity (continuous) to the difference in UACR between the IR groups. Only insulin sensitivity was significantly associated with UACR ($\beta = -0.54$; $P < 0.0001$).

CONCLUSIONS—In youth with diabetes, the DAA$^-$/IR group had a greater UACR than all other groups, possibly because of the greater magnitude of insulin resistance. Further exploration of the relationships between severity of insulin resistance, autoimmunity, and albuminuria in youth with diabetes is warranted.

Previous reports suggested that the clinical course and factors contributing to the development and progression of diabetic nephropathy did not differ by diabetes type and that diabetic nephropathy was preceded by albuminuria that worsened over time (1,2). More recent data have further elucidated the natural history of diabetic kidney disease. In the absence of albuminuria, a significant number of people with diabetes, especially type 2, still develop a decline in glomerular filtration rate (3,4). Thus, there may be identifiable differences in the natural history of nephropathy inherent to the underlying diabetes type. Multiple pediatric diabetes cohorts have found a higher prevalence of albuminuria and progressive kidney failure in youth with a clinical diagnosis of type 2 diabetes than with type 1 diabetes (5–7). Such data suggest that insulin resistance, a key component of the pathophysiology of type 2 diabetes, may be an important contributor to diabetic nephropathy in youth with diabetes.

The epidemic of overweight and obesity has made it increasingly difficult to clinically diagnose diabetes type, because insulin resistance and autoimmunity often coexist (8,9). Cohort studies of youth with type 1 diabetes have found a significant increase in microvascular and macrovascular diseases in those with concurrent insulin resistance (10–12). The

prevalence of albuminuria in insulin-resistant (IR) individuals with type 1 diabetes has not been compared with individuals with type 2 diabetes. Thus, the role of autoimmunity and insulin resistance across the spectrum of diabetes types and the risk for microvascular complications warrant investigation. Herein, we investigate the magnitude of albuminuria according to the status of autoimmunity and insulin resistance in youth with newly diagnosed type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

The SEARCH for Diabetes in Youth Study is a multicenter, observational study of youth with incident diabetes who are followed-up longitudinally. A detailed description of study methods has been published previously (13). In brief, SEARCH is an ongoing study that began in 2001 to conduct population-based ascertainment of cases of diabetes in youth younger than 20 years of age. The study protocol was reviewed and approved by local institutional review boards that had jurisdiction over the local study populations. Cases were ascertained from geographically defined populations in Ohio, Colorado, South Carolina, and Washington, among enrollees in several health plans in California and Hawaii, and Indian Health Service beneficiaries from four American Indian populations. Youth identified with incident nonsecondary diabetes were invited to a baseline study visit. Self-reported race and ethnicity were collected using the 2000 United States Census questions (14).

Sample selection, design, and measurements

This is a cross-sectional analysis exploring the association between diabetes etiologic group and the magnitude of albuminuria. Inclusion criteria included having a baseline visit during which fasting blood was drawn, urine was collected, and anthropometric measurements were taken. These were used to measure diabetes autoantibodies (DAAs) and covariates used to calculate the insulin sensitivity score (waist circumference, triglycerides [TG], hemoglobin A_{1c} [HbA$_{1c}$]) and to assess urine albumin:creatinine ratio (UACR). Individuals using ACE inhibitors or angiotensin receptor blockers were excluded from these analyses (n = 38).

The study visit included measurement of waist circumference using the National Health and Nutrition Examination Survey protocol (15), systolic blood pressure, diastolic blood pressure, height, and weight, as previously described (16). Height and weight were measured to calculate BMI (kg/m^2), which was then converted to z-scores using the standard Centers for Disease Control and Prevention approach (17).

Blood and 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. Participants excluded from analysis because of missing urine sample (n = 1,064) had similar sociodemographic characteristics as the analyzed cohort (data not shown). Specimens were processed locally and shipped within 24 h to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). Measurements of serum cholesterol, TG, and HDL cholesterol were performed using Roche reagent on a Roche Module P autoanalyzer (Roche Diagnostics, Indianapolis, IN). HbA$_{1c}$ was measured by a dedicated ion-exchange high-performance liquid chromatography instrument (TOSOH Bioscience).

Random spot urine samples were collected. Urinary creatinine was measured by the Jaffe method using Roche reagent on the Roche Modular P autoanalyzer. Two quality-control samples were analyzed in each run, and the interassay coefficient of variation was consistently <2%. Urine albumin was measured immunochemically using Siemens reagent on a Siemens BNII nephelometer. The sensitivity of the assay was also 0.2 mg/dL. The interassay coefficient of variation is <5% for the high-level and <6.5% for the low-level quality-control sample. Albuminuria was defined as a UACR ≥30 μg/mg as recommended by the American Diabetes Association guidelines (18) and National Kidney Disease Outcomes Quality Initiative (19).

Definitions of DAAs and insulin sensitivity or insulin resistance

Blood samples taken at the baseline visit were analyzed for the 65-kD isoform of glutamate decarboxylase antibodies (GADA) and insulinoma-associated protein 2 antibodies (IA-2A) using the National Institute of Diabetes and

Digestive and Kidney Diseases standardized method (20). The cutoff values for positivity were 33 units/mL for GADA and 5 units/mL for IA-2A. The specificity and sensitivity were 97 and 76%, respectively, for GADA and 99 and 64%, respectively, for IA-2A (20). DAA positivity (DAA$^+$) was defined by positive titers for either GADA or IA-2A. Because many participants were treated with insulin, analysis of insulin autoantibodies was not performed.

The insulin sensitivity score was calculated from variables measured at the study visit using the following equation:

$$Exp\{4.647252 - (0.02032 * [\text{waist, cm}]) \\ - (0.002350 * [\text{TG, mg/dL}]) \\ - (0.09779 * [\text{HbA}_{1c}, \%])\}$$

This equation was developed and validated using direct measurements of glucose disposal rate from euglycemic-hyperinsulinemic clamps conducted among 85 of the 2,401 SEARCH participants included in this report and 22 matched nondiabetic control subjects (21). As previously reported, we defined insulin resistance among SEARCH participants in this study as an insulin sensitivity score value <25th percentile for the United States general youth population (insulin sensitivity <8.15) (22).

Participants were assigned to one of four diabetes etiologic groups, according to the status of autoimmunity and insulin resistance at their baseline visit. These four groups were as follows: DAA$^+$/insulin-sensitive (IS); DAA$^+$/IR; DAA$^-$/IR; and DAA$^-$/IS.

Statistical analyses

Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC) and S-PLUS software version 6.0 (Insightful, Seattle, WA). Each minority group was limited in sample size; hence, for the present report, all racial/ethnic groups other than non-Hispanic white were combined into a single "ethnic minority" category. The distribution of each potential covariate was evaluated and, when necessary, logarithmically transformed for normalization of the distribution. The means and percents of covariates were compared across the four etiologic groups using χ^2 and ANOVA tests when appropriate. Multivariable regression analyses assessed the relationship between the four etiologic groups and the magnitude of UACR. Both the

Shapiro–Wilk test and Kolmogorov–Smirnov test indicated that the residuals did not deviate significantly from a normal distribution. A plot of residuals against the predicted values of the outcome variable found no evidence that the variance of the residuals changed across the range of predicted values. Covariates included in the model were age at visit, sex, race/ethnicity, parental education and insurance type, clinic site, diabetes duration, HbA_{1c}, systolic blood pressure z-score, and BMI z-score. Results were considered significant if $P < 0.05$.

RESULTS—The sociodemographic and clinical characteristics of the 2,401 participants, according to the four etiologic groups, are depicted in Table 1. The ethnic minority group comprised of 323 Hispanics, 312 non-Hispanic blacks, 99 Asians/Pacific Islanders, and 23 Native Americans/Alaska Natives. There were significant differences across the four etiologic groups for all covariates. The largest differences were in the DAA⁻/IR group, which, in comparison with the other three groups, demonstrated a preponderance of ethnic minorities and elevated systolic blood pressure, diastolic blood pressure, and TG levels. Elevated UACR (≥30 μg/mg) was prevalent in 16% of the DAA⁻/IR group, which was significantly higher than that of all other groups ($P = 0.0007$).

Multivariable analysis suggested that the etiologic groups significantly contributed to the variability of UACR ($P = 0.004$). The adjusted mean UACR for the DAA⁻/IR group was significantly higher than those of the other three groups (Table 2). All other pairwise comparisons were nonsignificant (data not shown).

To explore reasons for the difference in UACR between the two IR groups, we performed a post hoc t test on the means of the insulin sensitivity scores and found them to be significantly different ($P < 0.0001$). We then assessed the contribution of DAA status and insulin sensitivity to the difference in UACR between the two IR groups by performing a post hoc multivariable analysis restricted to the IR participants. The regression equation used the original model but incorporated DAA status and insulin sensitivity (continuous) in place of the four etiologic diabetes type groups. DAA status was not statistically significant ($\beta = 0.18$; $P = 0.08$), whereas insulin sensitivity was significantly and inversely associated with UACR ($\beta = -0.54$; $P < 0.0001$).

CONCLUSIONS—This is the first study to compare the magnitude of albuminuria in youth with diabetes classified according to markers of the underlying etiology of diabetes using measures of autoimmunity and insulin resistance. We found that in youth with recently diagnosed autoimmune-mediated diabetes, there was no difference in UACR between those who were IS compared with IR. There was, however, a significantly higher UACR in youth without autoimmunity but with IR over all other subgroups. There were significant difference in covariates that could be confounders or mediators of the effect of etiologic subgroup; however, we statistically controlled for this issue in our multivariable analysis. We hypothesized that the difference in albuminuria between the two IR groups could be attributable to a greater severity of insulin resistance in the DAA⁻/IR group. Post hoc analyses showed insulin sensitivity to be significantly associated with UACR in the IR groups.

Our finding that there was no difference in UACR between youth with autoimmune-mediated diabetes who were IS compared with IR was unexpected. The hypothesis that insulin resistance in addition to autoimmunity could increase the risk of microvascular complications of diabetes was proposed 20 years ago (23). Several studies have since identified increases in both microvascular and macrovascular complications in persons with type 1 diabetes with versus without insulin resistance (11,12,24,25). It is difficult to compare these studies with ours because of differences in study population and methodologies, especially our pediatric cohort with newly diagnosed diabetes and estimation of insulin resistance.

Table 1—*Sociodemographic and clinical characteristics of 2,401 youth with type 1 or type 2 diabetes according to etiologic group: SEARCH for Diabetes in Youth Study*

Variable*	DAA⁺/IS $n = 1,351$	DAA⁺/IR $n = 438$	DAA⁻/IR $n = 379$	DAA⁻/IS $n = 233$	P†
Age at diagnosis, years	9.3 (3.7)	12.9 (2.8)	13.8 (2.6)	9.3 (4.0)	<0.0001
Age at visit, years	10.3 (3.7)	14.1 (2.9)	14.9 (2.7)	10.4 (4.0)	<0.0001
Male, n (%)	729 (54)	221 (50)	145 (38)	137 (59)	<0.0001
Ethnicity, NHW n (%)	1,044 (77)	310 (71)	105 (28)	177 (76)	<0.0001
Diabetes duration, months	9.1 (5.8)	11.2 (6.7)	11.1 (6.9)	9.7 (6.2)	<0.0001‡
HbA_{1c}, %	7.4 (1.2)	8.6 (2.1)	7.7 (2.3)	7.2 (1.4)	<0.0001‡
BMI z-score	0.3 (0.9)	1.2 (0.9)	2.0 (0.8)	0.2 (0.9)	<0.0001
Insulin sensitivity score	11.7 (1.2)	5.9 (1.4)	3.8 (1.9)	11.9 (1.3)	<0.0001‡
SBP z-score	−0.6 (0.9)	−0.4 (0.9)	0.4 (1.1)	−0.5 (0.9)	<0.0001
DBP z-score	0.1 (0.8)	0.2 (0.8)	0.5 (0.9)	0.1 (0.7)	<0.0001
Total cholesterol, mg/dL	158 (27)	168 (34)	175 (43)	157 (27)	<0.0001‡
TG, mg/dL (median [25th, 75th])	52 (41, 66)	82 (60, 113)	122 (83, 189)	53 (43, 69)	<0.0001‡
HDL, mg/dL	56 (13)	51 (13)	42 (11)	55 (13)	<0.0001
LDL, mg/dL	90 (23)	98 (26)	104 (36)	90 (22)	<0.0001‡
UACR, μg/mg (median [25th, 75th])	7 (5, 13)	6 (4, 13)	8 (5, 17)	7 (5, 12)	0.0146‡
UACR >30 μg/mg, n (%)	123 (9)	53 (12)	59 (16)	17 (7)	0.0007

DBP, diastolic blood pressure; NHW, non-Hispanic white; SBP, systolic blood pressure. *Mean (SD) unless otherwise noted. †P value across all four categories using χ^2 test or ANOVA when appropriate. ‡Using log distribution for association tests.

Table 2—UACR least-square means and pairwise comparisons with DAA⁻/IR group in the SEARCH population

Diabetes subcategory	LS mean for UACR	P
DAA⁺/IS	154 μg/mg	0.01
DAA⁺/IR	137 μg/mg	0.0005
DAA⁻/IR	257 μg/mg	Referent
DAA⁻/IS	130 μg/mg	0.005

LS, least square. All other pairwise comparisons were nonsignificant. Covariates included in the multivariable analysis were age at visit, sex, race/ethnicity, parental education and insurance type, clinic site, diabetes duration, HbA$_{1c}$, systolic blood pressure z-score, and BMI z-score.

The significant difference in UACR between the DAA⁺/IR and DAA⁻/IR groups also was unexpected. Post hoc analysis restricted to the two IR groups indicated that differences in the degree of IS between the two groups was associated with the higher UACR in the DAA⁻/IR group. This finding, along with the lack of difference in UACR between the DAA⁺/IR and the two IS groups, suggest a threshold effect of IR on the magnitude of albuminuria. Our study design imposes a logical yet arbitrary cutpoint for IR to define the four diabetes etiologic groups. Future studies exploring the shape of the relationship between insulin sensitivity and UACR are needed to clarify their relationship.

We are not the first to find an association between the degree of insulin resistance and the degree of albuminuria (26–28). The components of metabolic syndrome have long been identified as risk factors for albuminuria, even in the absence of diabetes (27,29). Recently, several theories have been proposed regarding the mechanisms with which insulin resistance could lead to albuminuria as well as other microvascular and macrovascular complications (30–32). Visceral adipose tissue is unique in its ability to function as a metabolic and endocrinologic organ (32). Macrophage infiltration and adipokine production result in an inflammatory and hormonal cascade that has been found to have direct effects on endothelial and podocyte functions within the glomerulus (30,31,33). Moreover, in the presence of adipokines, podocytes have been noted to develop altered insulin signaling that renders them more susceptible to apoptosis, leading to albuminuria (30,31). It is also important to consider that the relationships of diabetic nephropathy lesions and albuminuria are more complex in type 2 versus type 1 diabetes. A substantial subset of microalbuminuric type 2 patients may

have glomerular structural parameters in the normal range, whereas this is rare among type 1 patients (34). Thus, the prognostic significance of the albuminuria findings in the current study will require long-term follow-up.

There are several limitations to our study. Most importantly, we collected only a single random urine specimen. Orthostatic proteinuria is fairly common in children, as is intraindividual variation in UACR (35,36). However, both of these situations would result in nondifferential misclassification, which would bias the results toward the null hypothesis. Another limitation is the use of only two antibodies, IA-2A and GADA, for identification of autoimmune-mediated diabetes. Recently, autoantibodies to zinc transporter 8 have been identified in the pathogenesis of type 1 diabetes (37). Although there are plans to measure this autoantibody in SEARCH, it is not yet available. This could have resulted in misclassification in the DAA⁻/IR group; however, again, this would bias our results toward the null hypothesis. In addition, we estimated insulin sensitivity rather than measuring it with the euglycemic-hyperinsulinemic clamp. Euglycemic-hyperinsulinemic clamp studies are impractical for use in a large cohort of children because of the invasiveness and high cost. Our estimating equation was developed and validated in a subset of 85 SEARCH participants and 22 nondiabetic controls who underwent euglycemic-hyperinsulinemic clamp study and was found to explain 74% of the variance of glucose disposal rate (21). This is superior to a previously published estimating equation that used only 24 participants and found their equation to explain 57% of the variance in glucose disposal rate (38). We defined insulin resistance using an arbitrary cutpoint of the 25th percentile in the insulin sensitivity score in nondiabetic children. Previously, we performed sensitivity analyses using

higher and lower cutpoints of the IS score and found the groups to be extremely similar (22).

Strengths of our study include the large sample size and ethnic and geographic diversity of the SEARCH cohort, which make our findings very generalizable. Moreover, SEARCH is a unique and valuable resource because it includes youth with newly diagnosed type 1 and type 2 diabetes. No other study has had the capability to explore the impact of insulin resistance on microvascular complications across the diabetes etiologic spectrum in a pediatric population.

In summary, using a novel approach to etiologic classification of diabetes type, we have been able to explore the association of diabetes etiologic subgroups with the severity of albuminuria in newly diagnosed youth with diabetes. Our results suggest that rather than the presence of diabetes autoimmunity, it may be the severity of insulin resistance that more strongly associates with albuminuria. This finding increases the urgency for investigators to determine the pathogenesis and prognostic significance of albuminuria in these young diabetic patients, and for clinicians and public health experts to address the overweight and obesity epidemic in youth. Further analyses of the spectrum of insulin resistance and thresholds that may increase the risk for diabetic kidney disease are warranted.

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