Higher Prevalence of Elevated Albumin Excretion in Youth With Type 2 Than Type 1 Diabetes

The SEARCH for Diabetes in Youth Study

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OBJECTIVE — To estimate the prevalence of an elevated albumin-to-creatinine ratio (ACR) (≥30 μg/mg) among youth with type 1 or type 2 diabetes and to identify factors associated with elevated ACR and their effect on the relationship between elevated ACR and type of diabetes.

RESEARCH DESIGN AND METHODS — Cross-sectional data were analyzed from 3,259 participants with onset of diabetes at <20 years of age in the SEARCH for Diabetes in Youth, a multicenter observational study of diabetes in youth. Multiple logistic regression was used to explore determinants of elevated ACR and factors accounting for differences in this prevalence between type 2 and type 1 diabetes.

RESULTS — The prevalence of elevated ACR was 9.2% in type 1 and 22.2% in type 2 diabetes (prevalence ratio 2.4 [95% CI 1.9–3.0]; $P < 0.0001$). In multiple logistic regression analysis, female sex, A1C and triglyceride values, hypertension, and type of diabetes (type 2 versus type 1) were significantly associated with elevated ACR. Adjustment for variables related to insulin resistance (obesity, hypertension, dyslipidemia, and inflammation) attenuated, but did not completely explain, the association of diabetes type with elevated ACR.

CONCLUSIONS — Youth with type 2 diabetes have a higher prevalence of elevated ACR than youth with type 1 diabetes, in an association that apparently does not completely depend on age, duration of diabetes, race/ethnicity, sex, level of glycemic control, or features of insulin resistance.

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Abbreviations: ACR, albumin-to-creatinine ratio; CRP, C-reactive protein; IQR, interquartile range.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Reports of type 1 and type 2 diabetes are becoming more common in youth (1,2), but little is known about whether the burden and risk factors for diabetes-related complications differ by type of diabetes in youth. An abnormal concentration of albumin in the urine is one of the earliest forms of clinical evidence of nephropathy, and microalbuminuria predicts progression to diabetic nephropathy (3) and cardiovascular disease (4). Current recommendations of the American Diabetes Association are to screen for microalbuminuria once a child is 10 years old and has had type 1 diabetes for 5 years and to screen children with type 2 diabetes at diagnosis and annually thereafter. Two of three values must be abnormal before the clinical diagnosis can be made, due to variability in albumin excretion rates (5). A spot urine early in the morning measuring the albumin-to-creatinine ratio (ACR) is one such screening method (5), and repeated abnormalities are required to clinically diagnose albuminuria.

While an extensive literature exists on microalbuminuria and elevated ACR in children and adolescents with type 1 diabetes (6–15), and diabetic nephropathy is well described in adults with type 2 diabetes (16), little data exist in youth with type 2 diabetes (17–20). Recently, clinical features of insulin resistance were found to be predictive of incident microalbuminuria among youth with type 1 diabetes (21). In adults, microalbuminuria is a component of the World Health Organization's definition of the metabolic syndrome (22) and is associated with insulin resistance measured with the clamp technique (23,24).

The SEARCH for Diabetes in Youth Study (SEARCH) is a multicenter, population-based study of youth with diabetes (25). (A complete list of SEARCH investigators is included in the online appendix [available at http://dx.doi.org/10.2337/dc07-0450].) The aim of this report on 3,259 youth participating in the SEARCH study is to identify factors associated with

elevated ACR in youth with diabetes and study their effect on the relationship between elevated ACR and type of diabetes.

RESEARCH DESIGN AND METHODS

— A detailed description of the study methods in SEARCH has been published (25). In brief, SEARCH is an ongoing study that began in 2001 to conduct population-based ascertainment of cases of diabetes in youth aged <20 years. Cases were identified *1*) in geographically defined populations in Ohio, Washington, South Carolina, and Colorado; *2*) among health plan enrollees in Hawaii (Hawaii Medical Service Association, Med-Quest, and Kaiser Permanente Hawaii) and in southern California; (Kaiser Permanente); and *3*) among young people listed on rolls of health service beneficiaries in three American Indian populations in Arizona and New Mexico and among participants in the National Institute of Diabetes and Digestive and Kidney Diseases Pima Indian study in Arizona (26). The study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study populations.

During the study visit, survey information was collected and blood was drawn for measurement of A1C, fasting glucose, C-peptide, lipids, fibrinogen, high-sensitivity C-reactive protein (CRP), and diabetes autoantibodies, and an examination was performed to measure systolic and diastolic blood pressure, height, weight, and waist circumference, as previously described (27). The average of two weight (electronic scale) and two height measurements (stadiometer) was used to calculate BMI (kg/m^2). Overweight was defined as a BMI ≥95th percentile for age and sex, based on the 2000 Centers for Disease Control and Prevention growth charts. Waist circumference was measured using the National Health and Nutrition Examination Survey protocol (28). High blood pressure was defined as *1*) antihypertensive medication use (although it is possible that alternately these medications could have been started for albuminuria or renal prophylaxis); *2*) systolic or diastolic blood pressure >95th percentile for age, sex, and height in participants ≤17 years; or *3*) systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in participants aged ≥18 years (29).

Blood samples were obtained fasting, under conditions of metabolic stability, in the absence of fever and acute infections. Specimens were processed locally and shipped within 24 h to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). A spot urine sample was collected in the morning after an overnight rest. Urine was not collected in girls who were menstruating. Urinary creatinine was measured by the Jaffe method using Roche Diagnostics reagent on the Hitachi 917 autoanalyzer. Two quality-control samples were analyzed in each run, and the interassay coefficient of variation was consistently <2%. Urine creatinine is present at high concentration, and therefore the sensitivity of the assay (0.2 mg/dl)

Table 1—*Prevalence of elevated ACR among SEARCH participants with type 1 and type 2 diabetes by age, sex, diabetes duration, race/ethnicity, BMI, and A1C category**

	Type 1 diabetes		Type 2 diabetes	
	n (%)	*P* value†	*n* (%)	*P* value†
Overall	265/2,885 (9.2)		83/374 (22.2)	
Age (years)				
<12	89/1,291 (6.9)	<0.0001	2/19 (10.5)	0.27
≥12	176/1,593 (11.1)		81/355 (22.8)	
Sex				
Male	109/1,480 (7.4)	0.0005	29/140 (20.7)	0.59
Female	156/1,405 (11.1)		54/234 (23.1)	
Diabetes duration (months)				
0 to <12	51/515 (9.9)	0.0041	15/92 (16.3)	0.0004
12 to <60	94/1,291 (7.3)		44/225 (19.6)	
≥60	120/1,074 (11.2)		24/57 (42)	
Race/ethnicity				
Non-Hispanic white	198/2,199 (9.0)	Ref.	9/71 (12.7)	Ref.
African American	19/197 (9.6)	0.76	18/110 (16.4)	0.50
Hispanic	32/310 (10.3)	0.45	15/64 (23.4)	0.10
Asian/Pacific Islander	6/53 (11.3)	0.47	6/25 (24.0)	0.21
American Indian	2/19 (10.5)	0.69	33/92 (35.9)	0.0008
Multiple/other	8/107 (7.5)	0.59	2/11 (18.2)	0.64
BMI (kg/m^2)				
<85	191/1,867 (10.2)	0.0069	12/49 (24.5)	0.82
85 to <95	49/620 (7.9)		13/53 (24.5)	
≥95	18/341 (5.3)		57/266 (21.4)	
A1C (%)				
<7.6	60/866 (6.9)	<0.0001	19/190 (10.0)	<0.0001
7.6 to <8.7	71/963 (7.4)		10/35 (28.6)	
≥8.7	128/945 (13.5)		53/139 (38.1)	

*Different sample sizes reflect completeness of data: age, 3,258; sex, 3,259; diabetes duration, 3,254; race/ethnicity, 3,258; BMI, 3,196; and A1C, 3,138. †*P* values are for association with elevated ACR.

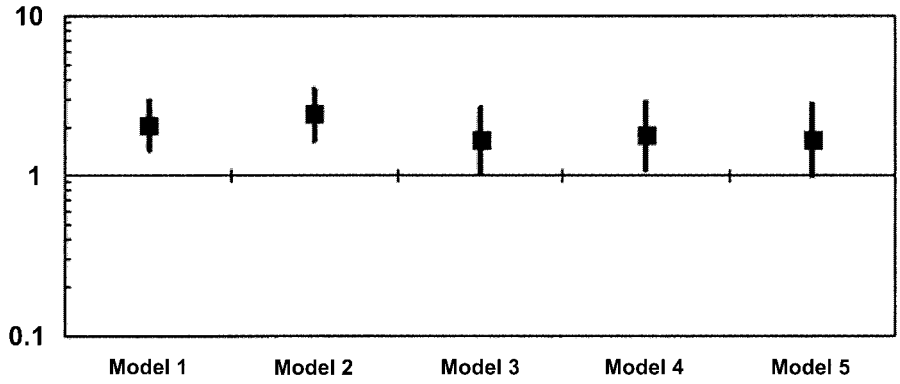

Figure 1—*Adjusted ORs and 95% CIs for the association between diabetes type (type 2 vs. type 1) and elevated ACR. Model 1 = adjusted for age, sex, race, duration; OR for diabetes type (type 2 vs. type 1) is 2.08 (95% CI 1.47–2.95),* P *< 0.0001. Model 2 = model 1 plus A1C; OR for diabetes type (type 2 vs. type 1) is 2.42 (1.68–3.49),* P *< 0.0001. Model 3 = model 1 plus hypertension, BMI, waist circumference, HDL and LDL cholesterol, and triglycerides; OR for diabetes type (type 2 vs. type 1) is 1.68 (1.05–2.67),* P *= 0.030. Model 4 = all; OR for diabetes type (type 2 vs. type 1) is 1.79 (1.11–2.88),* P *= 0.017. Model 5 (subset of 2,561 participants with measurements of fibrinogen and CRP) = model 4 plus fibrinogen and CRP; OR for diabetes type (type 2 vs. type 1) is 1.68 (1.00–2.81),* P *= 0.048.*

is not a factor. Urine albumin was measured immunochemically using Dade-Behring reagent on the BNII nephelometer. The sensitivity of that assay is also 0.2 mg/dl. The interassay coefficient of variation is <5% for the high-level quality-control sample and <6.5% for the low-level quality-control sample.

ACRs were categorized according to American Diabetes Association guidelines (4): normal, <30 μg/mg; microalbuminuria, 30–299 μg/mg; and macroalbuminuria, ≥300 μg/mg. Given the small number of participants with macroalbuminuria (*n* = 51/3,259 [1.6%]), micro- and macroalbuminuria were combined to define elevated ACR (≥30 μg/mg). The clinical diabetes type was categorized as type 1 (reported type 1a, type 1, or type 1b) and type 2. Race/ethnicity was based on self-report and included data collected using the format for the 2000 census questionnaire. Five specific categories were created (Hispanic, American Indian only, African American only, Asian/Pacific Islander only, and non-Hispanic white only) along with a sixth category of multiple/other/unknown race. Because of limitations in the size of samples, for most analyses all racial/ethnic groups other than non-Hispanic white were combined into a single category. This analysis includes participants from the 2001–2003 SEARCH study cohorts.

Statistical methods

The prevalence of elevated ACR (≥30 μg/mg) was calculated and stratified according to diabetes type and age, sex, diabetes duration, race/ethnicity, and BMI category. Multiple logistic regression analysis was used to examine the adjusted odds ratios (ORs) of having an elevated ACR (≥30 vs. <30 μg/mg) in patients with type 2 versus type 1 diabetes. The covariates entered in sequential models were as follows: model 1, type of diabetes, demographic factors, and duration of disease; model 2, model 1 covariates plus hyperglycemia; model 3, model 1 covariates plus factors related to insulin resistance with different distributions by type of diabetes; model 4, all of the covariates from models 1–3; and model 5, in a subset of 2,561 participants with measurements of fibrinogen and CRP available, these markers of inflammation were added to model 4 covariates. In these models, we examined whether the hypothesized association between type of diabetes (type 2 versus type 1) and elevated ACR was explained by the addition of a particular set of metabolic risk factors. In addition, in model 4 we examined which of the above variables were independently associated with elevated ACR. We considered several two-way interactions that were not significant (diabetes type times sex and type times duration), as well as an interaction between diabetes type and BMI, which was found to be significant. *P* values ≤0.05 were considered significant. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC) and S-PLUS software, version 6.0 (Insightful, Seattle, WA).

RESULTS — Of 8,768 patients with diabetes identified by SEARCH in 2001–2003, 3,950 (45%) had a study visit. Of this group, 3,259 contributed data to the analysis, as patients without an ACR measurement and patients with a diabetes type coded as Other/Unknown/MODY were excluded. Of the final group, 2,885 had type 1 and 374 type 2 diabetes.

Participants with type 1 diabetes had a mean age at registration of 11.9 years (interquartile range [IQR] 8.7–15.4), a disease duration of 3.7 years (0.5–5.7), and included 49% female and 76% non-Hispanic white individuals. Participants with type 2 diabetes were, on average, aged 16.2 years (14.0–18.6), had a disease duration of 1.9 years (0.4–3.2), and included 63% female and 19% non-Hispanic white subjects. The prevalence of elevated ACR was 2.3 times as high in youth with type 2 diabetes (22.2% [95% CI 18.3–26.7]) as in those with type 1 diabetes (9.2% [8.2–10.3]), and it was slightly higher in female (12.8% [10.7–15.0]) than in male (10.6% [8.3–12.9]) subjects. Table 1 shows that among subjects with type 1 diabetes, the prevalence of elevated ACR was higher in adolescents than in younger children ($P < 0.0001$) and in female than in male subjects ($P = 0.0005$). Neither was statistically significantly different in type 2 diabetes. The prevalence tended to increase with duration of diabetes, especially if it was longer than 60 months (overall $P = 0.004$ for type 1 diabetes; $P = 0.0004$ for type 2 diabetes). For youth with type 1 diabetes, the percentage having an elevated ACR did not vary substantially with race/ethnicity ($P = 0.55$, non-Hispanic white vs. other than non-Hispanic white). In contrast, for youth with type 2 diabetes, the percentage having an elevated ACR was higher among the group made up of minorities than it was in non-Hispanic whites ($P = 0.032$). Patterns of elevated ACR by BMI differed by type of diabetes; in youth with type 2 diabetes there were no significant differences between BMI categories, but in youth with type 1 diabetes the prevalence was highest in the leanest children ($P = 0.007$).

The variables that explained the effect of diabetes type (type 1 versus type 2) on the prevalence of elevated ACR are presented in Fig. 1. In model 1, adjustment for age, sex, race/ethnicity, and duration of diabetes explained little of the excess in elevated ACR in patients with type 2 diabetes (OR 2.08 [95% CI 1.47–2.95]). In model 2, the addition of A1C actually in-

Table 2—*Adjusted ORs of an elevated ACR in SEARCH participants*

	OR (95% CI)	*P**
Age (per 1 year)	1.03 (0.98–1.08)	0.24
Sex (female vs. male subjects)	1.40 (1.09–1.81)	0.0090
Race/ethnicity (all others vs. non-Hispanic whites)	1.01 (0.75–1.36)	0.95
Type 2 vs. type 1 diabetes		
BMI ≥95th percentile	2.10 (0.83–5.32)	0.12
BMI <95th percentile	1.48 (0.79–2.77)	0.23
Diabetes duration (months)		
12 to <60 vs. <12	0.62 (0.43–0.89)	0.027
≥60 vs. 0 to <12	0.78 (0.52–1.16)	
A1C (per 1%)	1.22 (1.13–1.31)	<0.0001
Hypertension (present vs. absent)	2.11 (1.49–3.00)	<0.0001
Waist circumference (per 1 cm)	1.00 (0.98–1.01)	0.77
LDL cholesterol (per 1 mg/dl)	1.00 (1.00–1.01)	0.29
HDL cholesterol (per 1 mg/dl)	1.00 (1.00–1.01)	0.90
Triglycerides (per 1 log mg/dl)	1.49 (1.17–1.88)	0.0010

**P* values are for overall effects on elevation of the ACR from the multiple logistic regression model. Diabetes type †BMI interaction: $P = 0.0002$ (model with BMI continuous).

creased the OR for the association between diabetes type and elevated ACR (2.42 [1.68–3.49]). In model 3, features related to insulin resistance were added to model 1 (presence of hypertension, BMI, waist circumference, LDL and HDL cholesterol, and triglyceride concentrations), and the OR dropped to 1.68 (1.05–2.67). Thus, the variables added in model 3 explained 19% of the increased prevalence of elevated ACR in type 2 versus type 1 diabetic patients. The OR of 1.68 indicates that even after accounting for all of these factors, patients with type 2 diabetes were still 68% more likely to have an elevated ACR than were those with type 1 diabetes. Simultaneous adjustment for age, sex, duration of diabetes, race/ethnicity, A1C, hypertension status, HDL and LDL cholesterol, log triglyceride, waist circumference, and BMI (model 4) did not further reduce the difference by type of diabetes; indeed, it became marginally higher (1.79 [1.11–2.88]). In a subset of 2,561 patients (model 5), with all of the model 4 covariates available plus measurements of fibrinogen and CRP available, this addition of inflammatory markers reduced the difference by type of diabetes slightly (1.68 [1.00–2.81]) from that seen in model 4, again suggesting that features related to insulin resistance (obesity, hypertension, dyslipidemia, and inflammation) mediate a portion of the increased prevalence of elevated ACR in youth with type 2 versus type 1 diabetes.

The adjusted ORs (95% CI) for the association between elevated ACR and each covariate included in model 4 are shown in Table 2. Further analysis found a significant interaction between diabetes type (type 2 versus type 1) and BMI on the prevalence of ACR was noted ($P < 0.0002$), suggesting that the difference in elevated ACR by type of diabetes increases with increasing BMI. Female sex, higher A1C, hypertension, and increased triglyceride concentrations were independently associated with elevated ACR, regardless of age, race/ethnicity, waist circumference, and LDL and HDL cholesterol (Hypertension is no longer significant if subjects on antihypertensive medications with normalized blood pressure are excluded.) Additional adjustment for self-reported habitual physical activity, current smoking status, and the presence of diabetes autoantibodies (either GAD65 or insulinoma-associated protein-2) did not change the results above. Elevated ACR is more prevalent as diabetes duration increases (Table 1), but once the other risk factors are controlled for (Table 2) the relationship of duration to elevated ACR changes, suggesting that these other risk factors account for the increasing prevalence of elevated ACR with duration.

CONCLUSIONS — This study finds a high prevalence of elevated ACR (22.2%) in youth with type 2 diabetes, well over twice the percentage for participants with type 1 diabetes (9.2%). Variables related to insulin resistance and inflammation explain part, but not all, of the increased prevalence in youth with type 2 diabetes. Major strengths of this study are the large sample, the geographically and ethnically diverse population, and the extensive demographic, anthropometric, biochemical, and behavioral data collected in these children.

That 22.2% of youth with type 2 diabetes could already have an elevated ACR at a mean age of 16.2 years and a mean duration of diabetes of 1.9 years suggests the possibility of a relatively more rapid progression to diabetes-related vascular complications in this population, since elevated ACR was shown to predict progression to diabetic nephropathy (3) and cardiovascular disease (4). This may result in increased morbidity and mortality in the future, in part due to the younger age at onset of type 2 diabetes, as previously reported in the Pima Indian population (30). Previous data on microalbuminuria in youth with type 2 diabetes are limited and based on much smaller samples but with similar estimates of 22% (19), 22.7% (20), and 40% (17). While longitudinal data are needed to better understand the determinants of type 2 diabetes–related complications in youth, our data suggest that efforts to prevent or delay type 2 diabetes in children could have a dramatic public health impact in terms of future burden of related vascular complications.

Our finding of an elevated ACR in 9.2% of youth with type 1 diabetes is comparable with published estimates of microalbuminuria in type 1 diabetic youth (6,7,10–15). As expected, older age, female sex, and duration of diabetes >5 years were associated with higher estimates (Table 1). These data also support the current recommendation for screening (for microalbuminuria) in youth with type 1 diabetes.

In adults, a diagnosis of microalbuminuria can precede type 2 diabetes and is a component of the World Health Organization's definition of the metabolic syndrome (22). Accordingly, microalbuminuria might be an early marker of type 2 diabetes as well as diabetic nephropathy. Previously, focal segmental glomerulosclerosis has been reported in obese children (31), and the possibility of fatty kidney disease analogous to nonalcoholic fatty liver disease and of whether obese youth without diabetes should be screened for microalbuminuria deserve further study. In our study, the higher prevalence of elevated ACR in youth with type 2 diabetes remained significant after controlling for potential risk factors with differential distribution between type 2 and type 1 diabetes cases (Fig. 1). Adjustment for variables related to insulin resis-

tance, however, explained more of the difference in elevated ACR by type of diabetes than did the other pathways considered. This result suggests that elevated ACR in youth with type 2 diabetes may primarily be a marker of underlying obesity-associated insulin resistance. The fact that the difference in elevated ACR by type of diabetes increased with increasing BMI ($P < 0.0002$ for the interaction between diabetes type and BMI) supports this notion. However, even after accounting for all potential contributors to an elevated ACR measured as part of the SEARCH study, the difference in prevalence between youth with type 2 and type 1 diabetes remained largely unexplained. Other unmeasured factors reflecting obesity, insulin resistance, inflammation, or genetics could be explanatory. In addition, Burgert et al. (32) have discussed the "oxidative stress theory " as a possible hypothesis linking recurrent postprandial hyperglycemia to vascular oxidative stress and subsequent endothelial dysfunction and microalbuminuria in obese youth without diabetes. The situation may be different in type 1 diabetic youth, among whom being leaner was associated with a higher prevalence of an elevated ACR (Table 1). The less overweight individuals with type 1 diabetes may exhibit weight loss associated with chronic poor glucose metabolism, in turn related to elevated ACR.

We found that high blood pressure, hyperglycemia, and high triglyceride concentrations are associated with elevated ACR, independent of type of diabetes (Table 2). In a retrospective clinic population with type 1 diabetes over 6 years of follow-up, Gorman et al. (33) found that persistence or progression of albuminuria occurred in two-thirds of type 1diabetic children, with A1C and initial ACR as independent predictors. Although studies in adults report variable rates of progression (3,34), generally type 1 diabetic patients with microalbuminuria have a significantly higher risk of progression to clinical proteinuria and death from a cardiovascular cause (35). Detection of increases in excretion of urinary albumin is clinically important, as safe and effective treatment with ACE inhibitors have been demonstrated (36–39). In our study, however, only 12% of youth with elevated ACR were treated with antihypertensive medication.

Certain limitations of our data set must be discussed. A single spot urine specimen for the ACR was obtained. Due to the variability in albumin excretion rates, repeated abnormal ACR measurements are required to diagnose albuminuria (5), and, therefore, a single elevated value cannot be used to establish the clinical diagnosis. As SEARCH is a large epidemiologic study conducted in an outpatient setting, a single ACR measurement was used to define elevated ACR. The ACR using a spot morning urine has high sensitivity and specificity when compared with two 24-h urine collections (40), and ACR is highly correlated to the 24-h albumin excretion rate in healthy 4- to 16-year-old subjects (41) and type 1 diabetic children (42,43). Our estimates of the greater frequency of elevated ACR in type 2 diabetes (versus type 1) are very similar to that of microalbuminuria by Eppens et al. (19), in which three timed overnight urine samples were obtained (22 vs. 6% reported by Eppens et al. and 22.2 vs. 9.2% reported in SEARCH). Importantly, physical activity, which can falsely elevate the ACR, was not a significant predictor of elevated ACR in multiple logistic regression analysis (data not shown).

Another concern is that the youth included in this report represent a sample of all youth ascertained by SEARCH. To evaluate the potential bias due to incomplete research visit participation, the prevalence of elevated ACR was also estimated using a reweighting, semiparametric efficient estimator developed for two-stage study designs (44). Estimates were calculated using data on study site, age, sex, race/ethnicity, diabetes type, and duration and were combined by inversely weighting based on SEs. The crude and reweighted estimates of prevalence were similar, suggesting that any possible selection bias is unlikely to influence our estimates.

Finally, our cross-sectional design limits assessment of causality in the interpretation of independent associations of elevated ACR. The design also limits our ability to definitively identify which factors and pathways account for the increased ACR in youth with type 2 diabetes relative to those with type 1 diabetes. Residual confounding resulting from incomplete adjustment for differences in age, duration of diabetes, and body size between youth with type 1 and type 2 diabetes may also be an issue. The availability of better markers of insulin resistance and visceral adiposity, difficult to obtain in large epidemiologic studies like SEARCH, may have provided more conclusive answers.

In conclusion, we report that 9.2% of youth with type 1 diabetes and 22.2% of youth with type 2 diabetes had an elevated ACR. Variables related to insulin resistance and inflammation explain part of the increased prevalence in youth with type 2 diabetes. For either type, hyperglycemia, high blood pressure, and hypertriglyceridemia are significant determinants of elevated albumin excretion. Longitudinal data on the natural evolution, screening, and treatment of microalbuminuria in youth with diabetes are needed, as both type 1 and type 2 diabetes are increasing (1,2) and diabetic vascular complications in general and nephropathy in particular could have overwhelming consequences.

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