Age and Sex Influence Cystatin C in Adolescents With and Without Type 1 Diabetes

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OBJECTIVE—To compare serum cystatin C levels, a novel biomarker of renal function, in adolescents with and without type 1 diabetes and to determine what factors affect cystatin C levels.

RESEARCH DESIGN AND METHODS—Cystatin C was measured in youth 12–19 years of age with (n = 259, diabetes duration 9 ± 3 years, HbA_{1c} 8.9 ± 1.6%) and without diabetes (n = 78). Data were compared by diabetes status, and linear regression was used to determine factors affecting cystatin C.

RESULTS—Cystatin C (0.698 ± 0.083 vs. 0.688 ± 0.127 mg/L, P = 0.40) was similar by diabetes status. In multiple linear regression, cystatin C was associated with age and serum creatinine in nondiabetic subjects and sex, age, and serum creatinine in subjects with diabetes ($P < 0.05$).

CONCLUSIONS—These data suggest sex differences and age-related changes in cystatin C in adolescents with type 1 diabetes. An understanding of these changes is needed to determine the potential role of cystatin C as a marker of renal function in this population.

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Despite improvements in care, diabetic kidney disease continues to cause early morbidity and mortality in type 1 diabetes (1). Current clinical markers of renal function include serum creatinine and urinary albumin excretion. Serum cystatin C is proposed as a superior biomarker than serum creatinine of renal function (2), progression of atherosclerosis (3), and clinical outcomes (4). Recent cross-sectional data in 12- to 19-year-old subjects in the National Health and Nutrition Examination Survey (NHANES) indicate that cystatin C levels are highest in females at age 12 years and in males at age 14 years and then are lower through age 19 years (or with a peak at Tanner stage II in females and Tanner stage IV in males) (5). However, to our knowledge, no data exist on cystatin C levels in 12- to 19-year-old patients with type 1 diabetes—in whom annual screening for early diabetic kidney disease is recommended (6)—and how levels compare with those in nondiabetic control subjects. Therefore, our objectives were to compare cystatin C levels in adolescents with and without type 1 diabetes and to determine what factors affect cystatin C levels.

RESEARCH DESIGN AND METHODS

—Fasting laboratories were collected from youth aged 12–19 years with (n = 259, duration 9 ± 3 years, HbA_{1c} 8.9 ± 1.6%) and without type 1 diabetes (n = 78), who were part of a larger cohort (n = 402) being screened for early cardiovascular disease. All subjects with available serum samples were included in this study, and no differences existed for age, sex, race/ethnicity, HbA_{1c}, BMI, serum creatinine, C-reactive protein (CRP), or albumin-to-creatinine ratio between subjects with (n = 337) and without (n = 65) the cystatin C sample.

Cystatin C was measured in a batch in the University of Colorado Hospital clinical laboratory using the commercially available Dade-Behring assay following package insert instructions on a BNII instrument. Baseline characteristics were compared by diabetes status. Next, linear regression (first univariate, second stepwise with backward selection, and then multivariate) was used to determine factors affecting cystatin C. Sex, age, serum creatinine, HbA_{1c}, BMI, and CRP were considered as factors potentially affecting cystatin C levels, but not race/ethnicity because of the lack of power (5). ANOVA with a Tukey-Kramer P value adjustment was used to compare cystatin C among groups and ages. A P value <0.05 was considered statistically significant using SAS 9.2 for analysis. The study was approved by the Colorado Multiple Institutional Review Board, and all participants provided informed consent.

RESULTS

—Subjects were similar for age and sex, but type 1 diabetic subjects had higher BMI, HbA_{1c}, and CRP than nondiabetic subjects (Table 1). Mean serum creatinine was higher in nondiabetic than type 1 diabetic subjects (0.71 ± 0.15 vs. 0.65 ± 0.14 mg/dL, P = 0.003), but cystatin C (0.698 ± 0.083 vs. 0.688 ± 0.127 mg/L, P = 0.40) was similar. As with NHANES data (5), when examined by Tanner stage, cystatin C levels were highest in Tanner stage II females (0.740 ± 0.090 mg/L) and in Tanner stage III males (0.801 ± 0.116 mg/L). Averaged across all age-groups, females had lower cystatin C than males with type 1 diabetes ($P < 0.0001$).

In nondiabetic subjects, cystatin C was higher in males and positively associated with serum creatinine in univariate analyses. Then, in multiple linear regression stratified by diabetes, cystatin C was associated with age (β = –0.018, P = 0.0002) and serum creatinine (β = 0.313, $P < 0.0001$) (R^2 = 0.2475).

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Table 1—*Subject characteristics*

	Nondiabetic control subjects	Type 1 diabetes	*P*
n	78	259	
Age (years)	15.5 ± 2.2	15.4 ± 2.2	0.73
Sex (% male)	44	50	0.31
Race/ethnicity (% non-Hispanic white)	69	80	0.03
Diabetes duration (years)	NA	8.7 ± 2.9	NA
Tanner stage [*n* (%)]*			
I	3 (4)	7 (3)	
II	9 (12)	21 (8)	
III	11 (14)	26 (10)	
IV	20 (26)	72 (28)	
V	33 (42)	133 (51)	0.08
Cystatin C (mg/L)	0.698 ± 0.083	0.688 ± 0.127	0.40
Serum creatinine (mg/dL)	0.71 ± 0.15	0.65 ± 0.14	0.003
BMI *z* score	0.22 ± 1.07	0.62 ± 0.77	0.003
HbA_{1c} (%)	5.3 ± 0.3	8.9 ± 1.6	<0.0001
CRP† (mg/dL)	0.40 (0.07–2.62)	0.63 (0.13–3.81)	0.004
Urine albumin-to-creatinine ratio† (μg/mg)	10 (4–53)	9 (3–26)	0.39
Systolic blood pressure (mmHg)	109 ± 8	113 ± 8	<0.0001
Diastolic blood pressure (mmHg)	64 ± 6	68 ± 7	<0.0001
ACE/ARB [*n* (%)]	0	1 (0.4)	NA
Total cholesterol (mg/dL)	147 ± 27	158 ± 35	0.006
HDL cholesterol (mg/dL)	49 ± 9	51 ± 10	0.06
LDL cholesterol (mg/dL)	82 ± 22	89 ± 27	0.03
Triglycerides† (mg/dL)	75 (46–134)	76 (46–140)	0.82
Statin use [*n* (%)]	0	4 (1.5)	NA

Data are means ± SD unless otherwise indicated. *Tanner stage was missing for two nondiabetic control subjects. †Geometric mean and 10–90th percentile.

In subjects with diabetes, cystatin C was higher in males and negatively associated with age, HbA_{1c}, BMI, and CRP and positively associated with serum creatinine ($P < 0.05$) and in multiple linear regression with female sex ($\beta = -0.039$, $P = 0.008$), age ($\beta = -0.022$, $P < 0.0001$), and serum creatinine ($\beta = 0.404$, $P < 0.0001$) ($R^2 = 0.2530$).

CONCLUSIONS—Serum cystatin C levels were similar in adolescents with and without type 1 diabetes. As previously reported in nondiabetic adolescents in NHANES data, age, sex, and serum creatinine are all associated with cystatin C levels (5). Our data demonstrate similar cross-sectional associations in nondiabetic adolescents, and expand this observation to adolescents with type 1 diabetes in a cohort that includes nondiabetic control subjects. In adolescents with type 1 diabetes or nondiabetic control subjects, cystatin C levels decrease on average by 0.02 mg/L every year from 12–19 years of age, and in type 1 subjects, these levels are 0.039 mg/L higher in males than in females, similar to NHANES data (5). These data suggest sex differences and age-related changes in cystatin C during adolescence in this population with implications for its use as a marker of renal function. Further study on whether these data reflect changes in the biomarker or a true change in GFR is needed.

Our data have limitations to consider. First, these data, like those reported from NHANES (5), are cross-sectional. Second, we do not have data on all of the markers examined by Groesbeck et al. (5), including blood urea nitrogen, uric acid, and fat-free mass. Additionally, our cohort is predominantly non-Hispanic white (77%), and we do not have statistical power to investigate differences in cystatin C by race/ethnicity and associations within the nondiabetic subjects, such as sex, which was not significantly associated in the multivariable model. Further data are needed on cystatin C in minority youth with diabetes.

Identification of biomarkers to improve clinical decision making to monitor and prevent diabetic kidney disease is needed, and cystatin C has emerged as perhaps the most promising biomarker (7). Early identification of incipient diabetic kidney disease and risk stratification for who will progress to clinical diabetic nephropathy remains a major research priority for preventing diabetes complications, including renal disease itself (1), and as a risk factor for cardiovascular disease and mortality (8,9). Moreover, collection of urine samples from adolescents presents a challenge in clinical care; therefore, a biomarker not requiring fasting or overnight collection would improve current screening and diagnostic capabilities. However, before widespread clinical use, issues such as assay standardization and consistency need to be addressed (7). In a cohort of adults with and without type 1 diabetes, we reported a 10–15% systematic shift, corrected by regression adjustment, in the commercially available Dade-Behring cystatin C assay between 2006 and 2010 (10).

Understanding these reported age- and sex-related effects on cystatin C in adolescents (which are similar by diabetes status) is a first step in determining the potential role of cystatin C to diagnose and then monitor changes in early renal disease in adolescents with type 1 diabetes.

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