The Effect of Age, Sex, and Race on Urinary Markers of Kidney Damage in Children

Felicia Trachtenberg, PhD,[1] and Lars Barregård, MD, PhD[2]

Background: The aim of this study is to examine the effects of age, sex, and race on the excretion and concentrations of albumin, γ-glutamyl transpeptidase (γ-GT), *N*-acetyl-β-D-glucosaminidase (NAG), α_1-microglobulin (α1M), and creatinine in children.

Study Design: Secondary analysis of a clinical trial, The New England Children's Amalgam Trial, which examined effects of amalgam dental fillings.

Setting & Participants: 534 children aged 6 to 10 years at baseline were recruited from Boston, MA, and rural Maine.

Predictors: Age, sex, and race.

Outcomes & Measurements: Urine samples were collected annually for 5 years and analyzed for creatinine, albumin, γ-GT, NAG, and α1M concentrations. Repeated-measures analysis of covariance was used to model effects of age, sex, and race on these values, as well as calculated excretion rates.

Results: All measures of creatinine and γ-GT increased significantly with age. Albumin and γ-GT concentration and excretion (milligrams per gram of creatinine or units per gram creatinine) were significantly greater for girls compared with boys. α1M concentration and creatinine excretion were greater for boys compared with girls. Creatinine concentration was significantly greater for blacks than for whites and Hispanics. Creatinine excretion and all γ-GT levels were significantly greater for blacks and Hispanics compared with non-Hispanic whites.

Limitations: The study population, recruited for a clinical trial, was of lower socioeconomic status than the general population. The high limit of detection for α1M resulted in a majority of samples less than the detection limit.

Conclusions: We recommend considering age, sex, and race in the interpretation of urinary markers. It also is recommended that epidemiological studies and clinical trials account for age, sex, and race in statistical models comparing urinary markers of kidney damage.

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INDEX WORDS: Age; sex; race; renal damage; children; albumin; γ-glutamyl transpeptidase; *N*-acetyl-β-D-glucosaminidase; α_1-microglobulin.

The excretion of various proteins in urine is widely used for assessment of kidney function in clinical practice, as well as in epidemiological studies of populations exposed to nephrotoxic compounds, for example, mercury.[1,2] Albumin is the commonly used marker of glomerular integrity, whereas such low-molecular-weight proteins or enzymes as β_2-microglobulin, α_1-microglobulin (α1M; also called protein HC), *N*-acetyl-β-D-glucosaminidase (NAG), or γ-glutamyl transpeptidase (γ-GT) are used for assessment of effects on renal tubular cells.

To interpret test results and make valid comparisons in epidemiological studies, it is necessary to take into account any effects of age, sex, and race on the excretion of these kidney markers. There are some previous studies of the effects of age and sex on these measures, including many studies of creatinine[3-17] and albumin,[5-10,18-23] but few for NAG[10-13,24-26] or α1M[7,9,18,27] and only 1 for γ-GT.[11] Furthermore, only 1 racial study (of albumin)[6] was conducted in children, with only 1 racial study of NAG[12] (in adults) and none of γ-GT or α1M.

It consistently was shown that creatinine excretion and concentrations increase with age in children and adolescents[9-11,16] and then decrease with age in adults.[3,5,6,15] It also is well documented that creatinine excretion[3-5,13-15,17] and concentrations[6-8,12,17] are greater in men than women. This occurs because creatinine excretion

From the [1]New England Research Institutes, Watertown, MA; and [2]Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital and Academy, Göteborg, Sweden.

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Address correspondence to Felicia Trachtenberg, PhD, New England Research Institutes, 9 Galen St, Watertown, MA 02472. E-mail: ftrachtenberg@neriscience.com

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increases with muscle mass, since most endogenous creatinine excretion comes from muscle tissue. It also was found that creatinine excretion[10] and concentrations[6] were greater in boys than girls, but there was much less research in children than in adults. Creatinine excretion[5,14] and concentrations[8,12] in adults also were shown to be greater in blacks than whites; one study[8] also showed greater concentrations in Hispanics than non-Hispanic whites.

Albumin excretion was found to increase with age in children,[19] with a peak at midadolescence.[10] For creatinine-corrected albumin levels, results in children were inconsistent.[9,18,19] The effect of sex on albumin level is not clear in either children or adults.[5-10,18,19,21] A few studies[5,6,8] found creatinine-corrected albumin levels to be greater in blacks than whites; however, others[20,22] found no significant racial differences in albumin levels. Data for Hispanics showed conflicting results,[6,8,21] with greater albumin levels in Hispanics in some studies.[6,21]

The one study of γ-GT[11] consisted of a large sample (N = 442) of healthy adults and children. They found that creatinine-corrected γ-GT excretion decreased with age. They also reported significant sex differences in adults (greater in women), but not in children.

Skinner et al[10] found that NAG excretion peaked in early adolescence in children, and 2 studies[11,24] found that creatinine-corrected NAG excretion decreased with age in children. Skinner et al[10] found no sex differences in NAG excretion in children, whereas Jung et al[11] found no sex differences in creatinine-corrected NAG excretion through age 12 years, but found they were greater in adolescent boys than girls. Agirbasli et al[12] found no racial differences in creatinine-corrected NAG excretion.

α1M[9] concentration and creatinine-corrected α1M excretion[9,18] did not vary significantly with age in children after the first month of life. No sex differences in children were found.[9,18]

Overall, the literature contains few studies of the effect of age and sex on γ-GT, NAG, and α1M levels in children, with no such studies on the effect of race. The aim of the present report is to examine the influence of age, sex, and race on the excretion and concentrations of albumin, γ-GT, NAG, and α1M, as well as creatinine, in a large longitudinal racially diverse sample of healthy children.

METHODS

Data Source

Data for this report were collected for the New England Children's Amalgam Trial (NECAT).[28,29] The NECAT was designed to examine effects of amalgam dental fillings in 534 children in Boston and Maine, aged 6 to 10 years at the beginning of the study, for 5 years. Although the main outcome of this trial was neuropsychological function, including IQ, secondary outcome measures included effects on the kidney, measured using creatinine-corrected albumin, γ-GT, NAG, and α1M levels. Eligibility criteria for the trial included: (1) 6 to 10 years old at last birthday, (2) fluent in English, (3) no prior amalgam dental fillings, (4) 2 or more dental caries on posterior occlusal (ie, chewing) surfaces, and (5) no evidence of psychological, behavioral, neurological, immunosuppressive, or renal disease. The sample was balanced by sex and was racially diverse (Table 1).

The initial NECAT protocol called for yearly timed overnight urine samples for 5 years (with up to 2 extra samples collected early in the trial for safety monitoring purposes), with daytime spot samples collected at the dental appointment for children who did not provide overnight samples. However, because of noncompliance, the trial switched to collecting only spot urine samples during follow-up. Therefore, this analysis contains a mix of spot samples during varying times of the day and timed overnight samples of varying duration.

Laboratory Methods

γ-GT and creatinine were measured yearly for all NECAT children. Albumin, NAG, and α1M were measured at years 3 and 5, with additional measurements for 57 children in a substudy at year 4.

Urine specimens were sent to Rochester General Hospital and Strong Hospital clinical laboratories in Rochester, NY for analysis of creatinine and γ-GT, as well as to the Sahlgrenska University Hospital in Göteborg, Sweden for analysis of creatinine, albumin, NAG, and α1M. When the specimen was not sufficient for both, priority was given to the laboratories in Rochester, NY. Creatinine was measured in both places for use as a creatinine correction; however, creatinine concentrations and excretion reported here are from the laboratories in Rochester, NY.

Table 1. Demographic Information for the 534 Children

Age at beginning of 5-year study (y)	7.9 ± 1.4
Sex	
Boys	247 (46.3)
Girls	287 (53.8)
Race	
Non-Hispanic white	323 (62.1)
Non-Hispanic black	98 (18.9)
Hispanic	38 (7.3)
Other	61 (11.9)

Note: Values expressed as mean ± SD or number (percent).