Original Article

The First Report on the Frequency of Asymptomatic Proteinuria in Iranian School-aged Children

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Abstract

Background: Proteinuria is a well-known indicator of renal dysfunction. In this study, we evaluated the frequency of proteinuria in a sample of healthy Iranian elementary school students using both dipsticks and urine albumin-to-creatinine ratio (UACR) methods. **Materials and Methods:** This cross-sectional study was performed on 478 school students aged 7–9 years who were selected by multistage random cluster sampling from Isfahan city, Iran. A clean midstream first-morning urine sample was obtained from each subject. Urine samples were examined by dipstick method, and accordingly, they were reported as negative; trace; 1+; 2+; 3+; and 4+. UACR was determined in samples with positive dipstick proteinuria (defined as trace or greater). **Results:** This study included 478 students (42.8% boys), with mean age of 7.0 ± 0.4 years. Positive dipstick was detected in 124 (25.9%) cases. The frequency of positive dipstick proteinuria was significantly higher in the girls than boys (29.6% vs. 20.9%, respectively; $P = 0.04$). In cases with a positive dipstick, 10 (2.1%) cases had UACR 30–300 mg/g. The frequency of UACR of 30–300 mg/g was 1.4% and 2.5% in boys and girls, respectively. There was no significant difference in the frequency of UACR 30–300 mg/g in terms of gender ($P = 0.4$). None of the subjects had UACR above 300 mg/g. **Conclusion:** While the frequency of asymptomatic proteinuria varies widely across different studies, we found a higher rate of proteinuria in Iranian children. Cost-effectiveness analyses are needed to justify large screening program for detecting asymptomatic proteinuria, as a cardinal manifestation of kidney disease, in Iranian children.

Keywords: *Chronic kidney failure, epidemiology, Iran, pediatrics, proteinuria*

Introduction

Chronic kidney disease (CKD) is a major public health problem that imposes an enormous economic burden on health-care budgets worldwide. Patients with CKD are at increased risk for all-cause morbidity and mortality.[1,2] The rate of progression to the end stage renal disease (ESRD) is depended on the coexisting pathologies and risk factors.[3] Therefore, early identification of kidney disease through blood and urine tests can provide opportunities to slow progression of the renal damage and decrease the frequency of CKD in the populations.[4]

Congenital anomalies of the kidney and urinary tract and glomerulonephropathies are the leading causes of CKD in children.[5] In Iran, like other countries in the Middle East region, the prevalence of CKD in children is higher than the western countries.[6-8] Given the high prevalence of childhood CKD in Iran, some authors have suggested implementing low-cost and accessible CKD screening programs like an annual urinalysis for hidden proteinuria among school students.[6] A similar CKD mass screening program that targets the school children has been launched in eastern Asian countries for almost three decades. As an example, in China,[9] Japan,[4] Korea,[10] and Taiwan[11] all school students are mandated to have an annual urinalysis for detecting asymptomatic proteinuria as a screening test for detecting kidney diseases in annual health checkup. This screening is followed by health education and early referral to physicians. The studies on cost-effectiveness and budget impact analysis of these nationwide programs have demonstrated that CKD mass screening using dipstick is a sensible choice in populations with high prevalence of the disease.[12,13]

Despite the relatively high prevalence of CKD among Iranian children,[6,7] to date no study have investigated the frequency of

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asymptomatic proteinuria in this population. In this study, for the first time, we evaluated the frequency of proteinuria, as the cardinal manifestation of CKD,[13] among healthy and asymptomatic Iranian elementary school students using both dipsticks and urine albumin-to-creatinine ratio (UACR).

Materials and Methods

Study design and setting

This cross-sectional study was conducted in Isfahan, a large province located in central part of Iran. According to Iranian national census performed in 2011, the population of Isfahan was about 4,879,312 inhabitants, of whom 1,640,544 individuals were children below 18 years of age.

In the period between January and February 2014, 478 elementary school students aged 7–9 years were selected by multistage random cluster sampling from urban and rural areas of Isfahan province. The exclusion criteria were having any acute voiding symptoms including dysuria, urgency, frequency, suprapubic pain, and incontinence. Furthermore, cases with fever, vomiting, diarrhea, abdominal pain, malnutrition, or any other systemic diseases were excluded from this study. After enrolling the eligible subjects, the objectives and the protocol of the study were completely explained, and a written informed consent was obtained from parents/caregivers. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences.

Screening protocol

A team of trained nurses collected demographic and clinical features including age, sex, height, weight, and blood pressure. They instructed the parents on how to obtain a clean midstream first-morning urine sample. Immediately after urination, the samples were examined by dipstick method (Combostick; YD Diagnostics, Korea) by a trained nurse. Visual reading of the urinary dipstick was performed in accordance with the instructions of the manufacturer. Urine dipstick bottles were stored at room temperature and expire dates also checked before use. According to the dipstick test results, the samples were divided into 6 groups as follows: negative; trace; 1+; 2+; 3+; and 4+. We confirmed that these samples were negative for the white blood cells and the urine pH of the samples was lower than 7.0 by dipstick tests. In addition, we excluded the samples with urine specific gravity higher than 1025 as it is suggested to be associated with false positive proteinuria in some studies.[14] Samples with positive dipstick proteinuria (defined as trace or greater) were subsequently subjected to examine the UACR. These samples were refrigerated on site, transported to a single validated laboratory promptly and processed within 24 h when received. The urinary albumin was measured by nephelometry methods and the urinary creatinine was assayed using the Jaffé reaction. The children with positive dipstick results and UACR >30 mg/g were referred to specialists for further evaluations.

Statistical analysis

Descriptive data are reported as mean ± standard deviation or number (percentage) as appropriate. Chi-square test was used for comparison of categorical variables. Statistical analyses were performed using MedCalc version 12.1.4.0 (MedCalc Software, Mariakerke, Belgium) and a $P < 0.05$ was considered the significance threshold.

Results

Of 478 eligible students, 205 (42.8%) were boys and 273 (57.1%) were girls. The mean age was 7.0 ± 0.43 years (range: 7–9 years), and the mean body mass index was 16.7 ± 3.8 kg/m^2. Detailed demographic and clinical characteristics of the study population are presented in Table 1.

Overall, positive dipstick proteinuria was detected in 124 (25.9%) of the cases. These cases were consisted of 43 boys (20.9% of the boys) and 81 girls (29.6% of the girls). The frequency of positive dipstick proteinuria was significantly higher in the girls (Chi-square test, $P = 0.04$). The total frequency of dipstick proteinuria ≥1+ was 15.2%. The details of urine dipstick results in boys and girls are presented in Table 2. The mean specific gravity was 1012 ± 4 in cases with proteinuria and 1011 ± 6 in cases without proteinuria and the difference between the two group was not significant ($P = 0.08$). Table 3 presents the details of UACR in cases with positive dipstick results. In total, 10 (2.1%) cases had UACR 30–300 mg/g, among them 7 samples were obtained from girls. Thus, the frequency of UACR 30–300 mg/g was 1.4% and 2.5% in boys and girls, respectively. There was no significant difference in the frequency of UACR 30–300 mg/g in terms of gender (Chi-square test, $P = 0.4$). In none of the samples, the UACR exceeded 300 mg/g.

Discussion

Proteinuria is a well-known indicator of renal disease and an important predictor of risk of progression to CKD.[13,15] While the UACR is the preferred method for evaluating proteinuria in the clinical settings[16,17] the semi-quantitative urine protein measurement using dipstick has also been demonstrated to be highly valuable for mass screening in healthy communities.[18] A recent study on 7-year follow-up of a community-based cohort showed that dipstick proteinuria has a high diagnostic utility for identifying patients with rapid kidney function decline.[19] Several studies have demonstrated that early detection of proteinuria by a simple urine screening may help to decrease or delay the progression of renal diseases.[4,20]

In this study, we presented the frequency of proteinuria among healthy and asymptomatic elementary school

Table 1: Demographic and clinical characteristics of the students

Variable	Total (*n*=478)	Boys (*n*=205)	Girls (*n*=273)	*P*
Age (years)	7.0±43	7.0±38	7.0±46	0.25
Weight (kg)	26.3±10.8	26.6±10.1	26.1±11.5	0.1
Height (cm)	126.3±13.0	126.6±11.3	126.2±14.6	0.2
BMI (kg/m^2)	16.7±3.8	16.9±3.8	16.6±3.9	0.72
Systolic blood pressure (mmHg)	102.8±13.7	103.9±13.9	101.5±13.6	0.2
Diastolic blood pressure (mmHg)	65.9±10.8	66.8±11.1	64.7±10.4	0.2

Values are expressed as mean±SD. SD: Standard deviation, BMI: Body mass index

Table 2: Urine dipstick results in boys and girls

Proteinuria	Male (%)	Female (%)	*P*
Trace	20 (9.7)	31 (11.3)	0.68
1+	12 (5.8)	24 (8.8)	0.30
2+	8 (3.9)	19 (6.9)	0.21
3+	3 (1.5)	6 (2.2)	0.80
4+	0	1 (0.4)	0.88
Negative	162 (79.1)	192 (70.3)	0.04

Data presented as *n* (%)

Table 3: Details of urine albumin-to-creatinine ratio in cases with positive dipstick results

	Male	Female	*P*
UACR in trace group			
<30	19	29	0.69
30-300	1	2	0.68
UACR in group with 1+ proteinuria			
<30	12	23	0.71
30-300	0	1	0.7
UACR in group with 2+ proteinuria			
<30	7	18	0.88
30-300	1	1	0.84
UACR in group with 3+ proteinuria			
<30	2	4	0.45
30-300	1	2	0.47
UACR in group with 4+ proteinuria			
<30	0	0	NM
30-300	0	1	NM

UACR: Urine albumin-to-creatinine ratio, NM: Not meaningful

students in Iran using both dipsticks and UACR methods. Based on our findings, the total frequency of dipstick proteinuria ≥1+ was as high as 15.2% in Iranian children. Moreover, the frequency of UACR 30–300 mg/g, which is generally termed "microalbuminuria," was 2.1%. Girls had a significantly higher frequency of proteinuria, but there was no significant difference in the frequency of microalbuminuria in terms of gender. In the literature, the existing data on mass urine screening for proteinuria in asymptomatic school-aged children is almost limited to the reports derived from eastern Asian countries. In a survey on 288,620 Chinese elementary and junior high-school students, the frequency of proteinuria was 10.5%.[20] In another study on 6197 Japanese school children, Pugia *et al*. reported that the frequency of albuminuria (defined as UACR >30 mg/g) was 2.1% and proteinuria was nearly 4.3%.[21] In a mass screening of 45,149 Malaysian primary school children, proteinuria was found in 0.12% of the students.[22] In Pakistan, the screening of 4977 elementary school and junior high school children for urinary abnormalities showed the overall prevalence of proteinuria of about 3.3%.[23] In nearly all these studies girls had a positive dipstick more frequently than boys. While the frequency of reported proteinuria varies widely across these studies, we have observed a higher rate of proteinuria in our survey. This observation might be due to the relatively smaller sample size in our study and also differences in the methodological approaches and research settings used across the studies.

Microalbuminuria is not only an indicator of renal disease but is also a significant risk factor for cardiovascular diseases[24] and all-cause mortality.[25] However, it is typically asymptomatic in the first stages and must be detected by screening. The cost-effectiveness and usefulness of urine screening in asymptomatic children for kidney disease is still a matter of debate in the literature. Kondo *et al*.[26] in a study on cost-effective analysis of mass screening for renal diseases using dipstick have suggested that CKD screening program using dipstick is cost-effective in Asian countries with high prevalence of childhood CKD. This notion is mainly suggested on the basis that the incidence of glomerulonephropathy-related CKD markedly increases from school and thus a screening program that targets school-age children in countries with high prevalence of glomerulonephropathies is a sensible choice.[14,27]

In Iran, the prevalence of pediatric CKD is relatively high, and glomerulonephropathies are the most common underlying cause.[6,7] Despite this, there has been no report on screening for proteinuria in Iranian children in the English-language literature. Hence, this study can be considered the first report on this population. However, the relatively small sample size is the main limitation of the present study. Moreover, our study only included children with 7–9 years of age, which may limit the generalizability of our findings to other age groups. More studies with larger sample size and wider age ranges are warranted to shed light on this topic. Cost-effectiveness analyses are also needed to justify a large screening program for pediatric CKD in Iran.

Conclusion

In Iran, the frequency of proteinuria in asymptomatic school-aged children is high. Cost-effectiveness analyses

are also needed to justify a large screening program for pediatric CKD in Iran.

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Conflicts of interest

There are no conflicts of interest.

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