Screening for CKD in Children: A Global Controversy

Ronald J. Hogg
The Children's Hospital at Scott & White, Temple, Texas

This review addresses the relevance of urinary screening for chronic kidney disease (CKD) in children. Ambiguity about screening children exists because of the uncertainty as to whether early detection of renal disorders in childhood will lead to effective interventions and reduction in the number of individuals who subsequently progress to ESRD. A related concern is whether the adoption of urinary screening programs is cost effective. The most common method that is used for screening children for CKD involves the measurement of spot samples of urine for hematuria and or proteinuria. Although mass screening is now well established in Japan, Taiwan, and Korea, there appears to be movement away from mass screening to detect CKD in children and adolescents in North America and Europe. In December 2007, the American Academy of Pediatrics published their latest recommendations, in which no urinalyses were recommended at any age during childhood. The second issue addressed in this review is the reporting of estimated glomerular filtration rates (GFR) in children by clinical laboratories.

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Although there is general agreement that screening for chronic kidney disease (CKD) in adults is of great importance (1,2), screening for CKD in children is more controversial. The primary basis for this controversy is the uncertainty as to whether early detection of renal disorders in childhood will lead to effective interventions and reduction in the number of individuals who develop end-stage renal disease (ESRD). There appears to be a clear consensus among Japanese, Taiwanese, and Korean investigators that the screening programs currently in place in these counties have led to early detection and effective intervention (3–12). However, this opinion is not shared by many investigators elsewhere. A related concern is whether the adoption of urinary screening programs is cost effective. Unfortunately, data that have been reported from the Asian programs do not include sufficient details to answer this question. Some analyses have been published from investigators in North America and Europe, but their estimates of the prevalence of CKD in children predate the recent emergence of obesity and childhood hypertension. This may well have led to an underestimation of the prevalence of CKD in children. In this review, I present studies from around the world that show a wide spectrum of viewpoints about the relative value of CKD screening in children. At the present time, I do not believe that it is possible to determine the cost effectiveness of such screening. Additional evidence must be obtained to answer this question.

The basic goals of any CKD screening program are shown in Table 1. The most common method of screening children for CKD involves the measurement of spot samples of urine for hematuria and or proteinuria. There are, however, many variations in methods; some are listed in Table 2. The number of children who are identified as having proteinuria varies according to the methodology used. This may have important implications for the cost effectiveness and viability of a screening program.

Countries with Established Annual Urinary Screening Programs for Children

Japan

Mandatory annual school screening for urinary abnormalities started in Japan in 1973. Over the past 20 yr, a large number of articles have described the results in that country. In 1988, Kitagawa *et al.* provided details of the methods used in Japan (3). Urine specimens are collected at home from first morning voids. Children who test positive are asked to repeat the procedure. Those with persistent abnormalities are investigated further. Renal biopsy results were reported by Kitagawa for 1023 patients who had asymptomatic proteinuria and/or hematuria. These patients were identified by the mass screening program between January 1984 and December 1985 and subsequently referred to 41 different pediatric departments at Japanese university hospitals. The number of children who were screened to identify this number of patients was not stated. Almost 36% of these patients (366/1023) were diagnosed with IgA nephropathy.

Murakami *et al.* described cross-sectional data from 7,349,928 urine specimens obtained from approximately 380,000 elementary school and 120,000 junior high school students over 13 yr in Tokyo, between 1974 and 1986 (4). Initial urine testing showed proteinuria to be present at a mean prevalence of 0.62% in elementary school children and 0.94% in junior high school children, whereas persistent proteinuria (2/2 specimens) was noted in only 0.08% of the elementary school students and 0.37% of junior high school students. The authors also

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Correspondence: Ronald J. Hogg, The Children's Hospital at Scott & White, 2401 South 31st Street, Temple, TX 76508. Phone: 254-724-8913, Fax: 254-724-5675; E-mail: rhogg@swmail.sw.org

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Table 1. Goals of a school screening program for CKD

1. The program should be based on relatively simple tests that have been documented to provide reproducible results.
2. The tests should have a high level of sensitivity (to avoid missing cases of CKD), preferably associated with a high specificity (to reduce the number of false positives). Unfortunately, this combination of features may be difficult to achieve.
3. The infrastructure of the screening program should be set up in such a way that is possible to identify abnormal results and schedule confirmatory tests in a reasonably short period of time.
4. Close communication with the parents of children with abnormal results should be maintained throughout all stages of the screening program.
5. Appropriate consultation with a pediatric nephrologist should be expedited for all children who have persistently abnormal results.
6. The cost effectiveness of the program should be confirmed periodically in order to maintain enthusiasm for the program

reported a three- to fourfold increase in the prevalence of proteinuria as the children grew older. Whereas the prevalence was initially higher in females, this pattern was reversed after 12 yr of age.

In 2005, Murakami *et al.* provided an update on the Japanese program, reporting data from 1974 to 2002 (5). The data, shown in Figure 1, did not vary significantly over 28 yr of observation. These authors reported in 2002 that urinalyses were conducted on 246,368 elementary school children and 115,736 junior high school children. Proteinuria was detected on initial testing in 0.11% and confirmed in 0.06% of the elementary school children; initial and confirmatory rates were 0.6% and 0.32% of the junior high school children. These data are very similar to those in the 1991 report (4).

Murakami *et al.* also reported that the number of Japanese adolescents who developed ESRD decreased from 174 in 1984 to only 108 in 2002. This was despite the fact that, in 2002, ESRD therapy was offered more readily to infants <12 mo of age. When these infants are excluded from the comparison, the number of children and adolescents reaching ESRD decreased from 166 in 1984 to 86 in 2002. Murakami *et al.* subsequently compared the situation in Japan and the United States (6). They noted a fourfold lower incidence of patients <20 yr of age reaching ESRD in Japan. The data are most striking in the 15 to 19 yr age group where the number of patients starting ESRD therapy is 6 per million in Japan compared with 30 per million in the United States. However, the role of primary screening in producing this disparity is unclear. The cause for the lower rate in Japan may be multifactorial and may include issues such as differences in disease type and presence of comorbidities such as obesity, which may have contributed to a higher rate of progression in U.S. children. In 2007, Urakami *et al.* reported on

Table 2. Variations in the methods used for the detection of albuminuria or proteinuria

Time of initial specimen collection—may be individual sample or timed specimen.	1) Random specimen—with confirmation on a FMU[a] specimen if initial test is positive 2) FMU specimen 3) Timed specimen (*e.g.*, 0.24 h or overnight)
Method used for measuring albumin/protein in the laboratory	1) Albumin concentration (mg/dl) 2) Total protein (mg/dl) 3) Albumin/creatinine ratio (mg/g) 4) Protein/creatinine ratio (mg/mg)
Number of positive specimens needed to define results as being abnormal	1) One 2) Two 3) Two out of three 4) Four or more
Frequency of Screening	1) Annual 2) Biannual 3) Twice during childhood

The units shown above represent one convention only.
[a]FMU = first morning urine.

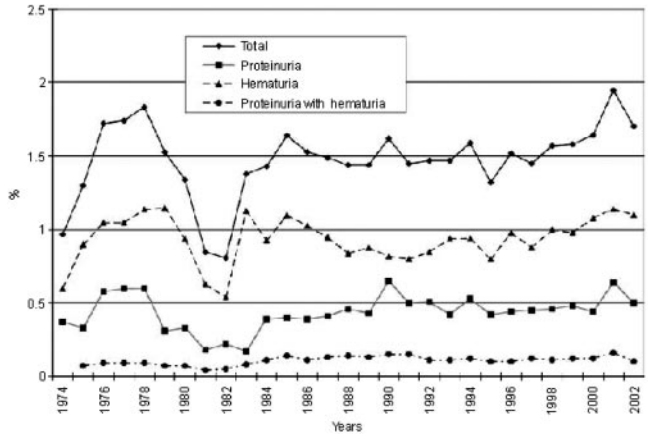

Figure 1. Annual prevalence of proteinuria, hematuria, and combined proteinuria/hematuria on first screening in junior high school children in Tokyo, Japan between 1974 and 2002. Reprinted by permission from Nature Publishing Group: *Kidney International* (Murakami *et al.* 67: 523 to 527. 2005)

the benefits that were realized by the early detection of childhood type 2 diabetes in Japanese children (6).

In an earlier contribution to this series of articles on screening, Imai *et al.* (7) quoted data from the 1999 Report of the Japanese National Registry Data on Pediatric End-Stage Renal Program (8), which reported that glomerulonephritis was responsible for the development of ESRD in 34.5% of children. This figure contrasts with 68.9% reported between 1978 and 1980. Imai *et al.* reported that early referral and intervention for glomerulonephritis in Japanese children identified by the screening program may have reduced the occurrence of childhood ESRD.

Taiwan

In Taiwan, mass urinary screening is conducted twice each year in approximately 3 million elementary and high school students (9). The tests include a urinalysis on first morning specimens and BP measurements; blood tests such as serum creatinine, glucose, albumin, and cholesterol are measured with a repeat urinalysis in children who are positive on first testing. Lin *et al.* reported results from 10,288,620 urinary screenings of children from 1992 to 1996 in the Taiwanese program (10). The 4-yr prevalence of proteinuria in this large population was 5.81×10^{-4}, with females affected more often than males (6.87×10^{-4} *versus* 4.83×10^{-4}). Progression to chronic renal insufficiency (defined as serum creatinine >1.7 mg/dl) was identified in 189 children.

Korea

In Korea, annual urinalyses in all school children have been mandatory since 1998. First morning urine specimens from >7 million Korean children are tested each year for blood, protein, and glucose; additional studies, including microscopy of the urinary sediment, are performed in children who have two positive tests. In 2001, Cho *et al.* described 405 Korean children who had isolated hematuria ($n = 228$), isolated proteinuria ($n = 98$), or combined hematuria/proteinuria ($n = 79$) (11). Renal biopsies in 173 patients showed mesangial proliferative glomerulonephritis in 99 children (56%), and IgA nephropathy in 51 (30%).

In a subsequent report in 2005, Park *et al.* reported on the abnormalities found in 1044 children with hematuria and/or proteinuria, who were identified by the school screening program and were subsequently referred to pediatric nephrologists in 13 hospitals throughout Korea (12). The distribution of urinary abnormalities was similar to those reported by Cho *et al.*, with isolated hematuria being seen in 60.1%, isolated proteinuria in 26.4%, and combined hematuria/proteinuria in 13.5%. It is noteworthy that proteinuria was persistent in only 7% of the patients who were found to have isolated proteinuria on initial testing. Renal biopsies were performed in 113 (11%) of the 1044 children reported by Park *et al.* Thirty-four of the 51 patients with combined hematuria/proteinuria had IgA nephropathy.

Park *et al.* did not indicate how many children were screened to identify the 1044 patients. However, they quoted data from the Korean Ministry of Education and Human Resources. In 2002, the prevalence of hematuria identified by the Korean school screening program was reported to be 0.64%, 0.61%, and 0.48% in elementary, junior, and senior high school students, respectively. The prevalence of proteinuria was 0.17%, 0.34%, and 0.39% in the same school categories.

Other Countries Where Large Screening Studies Have Been Performed

Pakistan

The first report on the prevalence of proteinuria in South Asian children was published by Jafar *et al.* in 2005 (13). They reported that 3.3% of 3621 children aged 5–15 years in Pakistan had proteinuria ≥30 mg/dl—based on random midstream urine specimens. Follow-up confirmation specimens were not obtained. The mean prevalence was higher in children 10–15 years of age (3.7%) than in younger children (2.8%).

Singapore

In 2001, Ramirez *et al.* reported the results of a nationwide screening program in Singapore that involved 2083 sixth grade students (14). They reported that 14 children (0.7%) had combined hematuria/proteinuria and 28 (1.3%) had isolated proteinuria on initial testing. Patients with proteinuria had significantly lower mean body weight at the time of testing.

China

In 2007, Zhai *et al.* described the results from a large urine screening program in Shanghai, China (15). The study cohort, 28,903 middle school students and 17,268 elementary school children, collected midstream first morning urine specimens that were examined within 4 h of collection. Hematuria and/or proteinuria were found in 2410 (5.2%) of the 46,171 children. Repeat urinalyses were done in most of the children who were positive on the first test. Approximately 1% of the children were positive for hematuria and/or proteinuria on both tests.

England

Meadow *et al.* conducted one of the first large urinary screening studies between 1967 and 1969 in Birmingham, England (16). Most of the specimens were reported to be from first morning voids. Two consecutive urine specimens showing 1+ or more proteinuria were seen in 17 (0.8%) of 2122 students who participated in the study.

Australia

The prevalence of proteinuria and glycosuria in 5–yr-old school children in Canberra, Australia was surveyed by Johnson *et al.* in 1974 (17). The urine specimens were obtained in the schools; children were required to have three consecutive urines showing ≥1+ protein before they were regarded as having proteinuria. This was observed in 21 (0.6%) of 3626 children.

Canada

In 1973 and 1974, Silverberg *et al.* reported urine screening results in 23,424 Canadian girls (18) and 27,722 boys, aged 5 to 14 yr (19). No first morning urines were tested. Proteinuria was detected on two occasions in 378 (1.6%) of girls (18) and in 136 (0.49%) of boys (19). This was confirmed in 109 (33%) girls and 47 (37%) boys among those who were further evaluated. The prevalence of proteinuria increased progressively with age in girls, from 0.6% in 6-yr-olds to 2.6% in 12-yr-olds.

Finland

In 1982, Vehaskasi and Rapola published one of the few large school urine screening studies that have been conducted in Europe (20). This involved 8954 children aged 8 to 15 yr. Each child collected two first morning urine samples and two evening samples. Proteinuria was found in at least one of four specimens in 10.7% of the participants; in two or more of four specimens in 2.5%, and in all four specimens in only 0.1% (9 / 8954 children). Combined hematuria / proteinuria was detected in one or more samples in 59 / 8954 (0.7%) of the participants.

Bolivia

Few large-scale urinary screening programs have been attempted in developing countries. One such program, in Bolivia, was reported by Plata *et al.* in 1998 (21). They enrolled 14,082 individuals, the majority of whom were children (64% were less than 15 yr of age; median age 12.25 yr). The urine specimens were collected at random times during the day. Hematuria was reported in 14.3% of the participants; proteinuria in 2.1%, and combined hematuria/proteinuria in 0.1%.

Iran

In 2007, Shajari *et al.* described a study in 1601 Iranian students 6 to 7 yr of age (22). Midstream first morning urine specimens were analyzed. Proteinuria was detected in 56 (3.6%) and hematuria in 16 (1%) of the subjects. Confirmatory tests were done in most of the children who initially tested positive.

United States

A landmark study in the United States was published in 1976 by Dodge *et al.*, who screened 12,252 first, second, and third grade children in south Texas (23). Five annual examinations were carried out in 6070 of these children. One to four examinations were performed in the remainder. Whereas 1440 (11.7%) of the children had proteinuria (>10 mg/dl) in a single specimen, only 736/1440 (51%) were also positive in either a second or third specimen collected within 2 to 7 d. Only 18% to 27% of the 1440 children (2.1% to 3.2% overall) were positive in all three specimens, the actual percentage varied by age and sex. Dodge described an increase in the point prevalence of proteinuria in children from 6 to 12 yr of age, particularly in girls. Sixty-two percent (210 of the 340 children with proteinuria who were tested) were subsequently found to have orthostatic proteinuria. This not surprising, because the urine specimens were not obtained from first morning voids.

In 1999, Mueller and Cardill provided an analysis of data regarding albuminuria from the Third National Health and Nutrition Examination Survey (NHANES III) (24). This survey included 4088 children 8 to 18 yr of age. The data analysis included urine albumin to creatinine (UAC) ratios and urine albumin concentrations in specimens obtained throughout the day. Approximately 12% of the participants had UAC ratios >30 mg/g, and 2.4% (97/4088) had UAC ratios >200 mg/g. Girls at all levels of puberty were from 2 to 3 times as likely as boys to have UAC ratios more than 30 mg/g. Higher UAC ratios were observed in participants with a lower BMI (25).

In 2007, Ferris *et al.* conducted a study using data from the third wave of the National Longitudinal Study of Adolescent Health (Add Health Wave III Study) (26). The study was designed to determine whether a relationship exists between obesity and albuminuria in young adults. Individuals 12 to 19 yr of age, who were followed for 6 yr, provided urine samples at any time during the day. A total of 9371 specimens were available for urine protein measurements by dipstick and 4463 for measurement of UAC ratios. Hematuria was detected in 4.6%; proteinuria (≥ 30 mg/dl by dipstick) in 0.8% (as an isolated finding in 0.5%), and albuminuria (UAC >17 mg/g in males and >25 mg/g in females) in 4.4% of the specimens. Only 11.9% of those with elevated UAC ratios were found to have proteinuria. Albuminuria was positively correlated with BMI >35 kg/m^2, but not with lower categories of overweight.

Outstanding Questions

It is clear that there is no global consensus as to whether screening for CKD should be undertaken in children and adolescents. Although mass screening programs are now well established in Japan, Taiwan, and Korea, there appears to be movement away from mass screening to detect CKD in children and adolescents in North America and Europe because of a prevailing question as to whether such screening is cost effective. To answer this question, it is necessary to have long-term follow-up studies of individuals diagnosed with early manifestations of CKD in screening programs. Unfortunately,

such data are not available in most countries, although in Japan it has been reported that screening for CKD in children has reduced the risk of progressive kidney failure. Would similar results be forthcoming if similar screening programs were developed in North America and Europe? Is the standardized method of using first morning urine specimens in the Asian screening programs superior to that employed in the previous surveys in North America and Europe?

The Importance of Screening First Morning Urine

Although the timing of urine samples used in screening programs around the world has been quite variable, all currently active national screening programs stress the importance of obtaining a first morning urine (Table 3) to exclude orthostatic proteinuria. Therein may lay one of the most important reasons for the varying levels of enthusiasm for screening programs seen in different parts of the world. The lower frequency of false positive findings from first morning urines and the subsequent reduction in the need for repeat testing may explain the differences in perceived cost effectiveness and enthusiasm for mass urinary screening between Eastern and Western countries.

Recommendations for the Future: When and Whether to Screen, That Is the Question

Few of the studies reported here have incorporated specific recommendations for urinary screening in children outside of the national programs. In 1997, Kaplan *et al.* evaluated the cost-effectiveness of urinary screening using a hypothetical cohort of 2000 asymptomatic children (27). Their basic premise was that initial screening in primary care practice would result in abnormal urinalysis in 95 of the patients and that 1.5% would have persistence of the abnormality on re-testing. They estimated the costs of undertaking four screenings during childhood, and also the cost of a subsequent pediatric nephrology consultation for children with a persistently abnormal urinalysis. Kaplan *et al.* recommended that all school children have a single screening dipstick urinalysis performed on a first morning urine specimen and that this should be obtained when the child is 5 to 6 yr of age.

Recommendations on Urinary Screening From the American Academy of Pediatrics (AAP)

A number of recommendations regarding urinary screening as part of well child care have been published by the AAP over the past 20 yr. The recommended number of screenings was set at four during childhood in 1977 and 1991; in 1995 this was revised to two (preschool and during adolescence) (25). In December 2007, the AAP published their latest recommendations, in which no urinalyses were recommended at any age during childhood (28). This guideline will be modified in the near future such that selective screening for renal disorders will be recommended for children who have risk factors.

Reporting eGFR in Children: Too Difficult for Clinical Laboratories?

The second issue to be addressed in this review involves the reporting of eGFR in children by clinical laboratories. Three reports between 2002 and 2003 (29–31) described a series of clinical practice guidelines for the evaluation, management, and stratification of CKD in adults (29,30) and children (31) that were developed by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF). The K/DOQI report recommended "clinical laboratories should report an estimate of GFR using a prediction equation in addition to reporting the serum creatinine".

The response to these guidelines has been quite heartening, at least with regard to adults. However, it appears that the situation with regard to children has proved to be too daunting. One stumbling block that has led to variation in acceptance of this guideline in children is the fact that currently available prediction equations for individuals <18 yr of age require height information (31).

This dilemma was highlighted recently by McDonough, who reported that in September 2005, New Jersey became the second state to "mandate legislatively the reporting of the estimated GFR (eGFR) by clinical laboratories when a serum creatinine test is performed" (32). Unfortunately, the primary legislative sponsor agreed to "focus eGFR reporting for adults aged ≥ 18 years" because of "obstacles facing clinical laboratories for reporting pediatric eGFR, including the lack of height information on test requisition forms."

Table 3. National mass school urinary screening programs

Year instituted	Country	Frequency of screening	Specimen	Follow-up studies
1974	Japan	Biannual: 1974 to 1979 Annual: 1979 to present	Dipstick test on midstream first morning urine	Repeat urinalysis in all patients with initial positive test. Two positive tests were defined as proteinuria.
1990	Taiwan	Biannual: 1990 to present	Dipstick test on first morning urine	Repeat urinalysis 10 to 15 days after positive initial test, (BP also measured in all students)
1998	Korea	Annual: 1998 to present	Dipstick test on first morning urine	Repeat urinalysis if initial test positive. Urine specimen examined by microscopy if both tests positive.

A similar situation exists in the United Kingdom. Shah and Feehally recently reported that "the reporting of eGFR is now mandated in all UK clinical laboratories" (33). However, this mandate applies only to individuals aged 18 yr and older (J. Feehally, personal communication).

Summary and Conclusions

It is evident from this review that global consensus has not been reached regarding (*1*) the cost benefit (or even absolute benefit) of urinary screening for proteinuria and other markers of CKD in children or (*2*) the inclusion of children and adolescents in the mandates for clinical laboratories to report eGFRs when serum creatinine is measured. In addition, European and North American pediatric nephrologists express opinions regarding urinary screening for school children that are diametrically opposite to those expressed in Asian nations. Does this mean that renal disease is more prevalent in Asian children, and therefore of greater importance to identify early in the course of disease? Alternatively, do the efficiencies and methodologies involved in these screening programs make them more cost effective and therefore more palatable? Unfortunately, we do not have sufficient data to answer this question.

It is timely for pediatric nephrologists around the world to discuss these issues and, if possible, develop a consensus/global response regarding the need for screening studies to permit the early identification of children with CKD. However, it is unlikely that such consensus can be achieved until the prevalence data for CKD in children in Western countries can be updated.

Disclosures

None.

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