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Urinary screening in asymptomatic Indian children: a cross sectional epidemiological study

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ABSTRACT

Background and aims

Early detection and management of renal abnormalities in children can reduce the progression of paediatric chronic kidney disease. Currently, data on the prevalence of routine abnormal urinary parameters are scarce in Indian population. This study aims to identify the prevalence of asymptomatic kidney diseases in Indian school children and the population who may benefit from routine urinary screening tests for timely identification and intervention of asymptomatic renal diseases.

Materials and methods

A total of 1675 children from a North Indian, multiethnic population aged 5-19 years were screened for hematuria and proteinuria by dipstick test from a midstream, clean urine specimen. The children who tested positive had their urine tested further for

microscopy. The incidences of proteinuria and hematuria were also separately checked in hypertensive children.

Results

76 children had urinary abnormalities with the prevalence of isolated haematuria in 1.9%, isolated proteinuria in 0.35% and glycosuria in 0.06%. When these children were followed with urine microscopy, 44 were observed to have abnormal findings. Of these, 4.5% children had proteinuria, 34% had isolated hematuria, and 47.7% had isolated WBCs. The prevalence for proteinuria was 0.60% and the prevalence for hematuria was 2.99% (in upper decile of SBP) in hypertensive children, both of which were more than the prevalence in otherwise healthy children.

Conclusion

Urine screening is a non-invasive, inexpensive test for early detection of occult renal diseases. A large-scale study with follow-up of children with urinary abnormalities will further establish the benefit, if any, of a national paediatric urine screening programme.

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1. INTRODUCTION

Chronic Kidney diseases (CKD) in children, although relatively uncommon, can be a devastating illness with long-term consequences. Data on prevalence of routine urinary abnormalities are unfortunately very scarce in Indian population when compared to global data. Early detection and management of kidney disease would reduce the progression and therefore national burden of paediatric CKD. Paediatric societies and government regulation in certain countries suggest routine periodic urine analysis in children for early diagnosis and timely management of CKD in children. Presently there is no national epidemiologic data on prevalence of CKD among Indian children and therefore the proportion of children who would possibly benefit from a routine periodic urinary screening tests are uncertain.

Urinalysis is a simple and inexpensive test which is the cornerstone in the evaluation of kidney functions. It can be easily employed in screening of renal abnormalities. Several urinary screening programs have been carried out using reagent strips, and their effectiveness in detecting urinary abnormalities at relatively low cost has been evaluated [1,2]. Abnormalities detected in routine urinalysis in patients who have no symptoms of renal or urologic disease such as glycosuria, pyuria, haematuria, and proteinuria are a common finding in clinical practice. Renal diseases are often accidentally discovered during routine urine analysis in asymptomatic healthy individuals [3]. With the aid of routine dipstick examinations early symptoms of diseases of the kidneys and the urinary tract (pyuria, haematuria and proteinuria) can be identified. An abnormal urinary test may be the earliest warning of a significant renal pathology [4,5]. Mass urinary screening helps to determine the prevalence of renal diseases and to improve the outcome in the population [6,7].

Although the incidence of urinary abnormality may be clinically insignificant or false positive in certain cases, studies from Korean, Taiwanese and Japanese paediatric screening program indicate a clear advantage of early detection and effective intervention to prevent progression to End-stage Renal Disease (ESRD) [8]. Murakami *et al.* carried out a large-scale screening among Japanese children and reported a fourfold decrease in incidence of progression to ESRD among Japanese children when compared to the US. Although the lower incidence of ESRD among Japanese children might be multi-factorial, early screening and timely management is a crucial factor.

Common causes for renal abnormalities in children include haematuria due to renal stones, structural deformities, urinary tract infection, glomerulonephritis, or proteinuria due to nephrotic syndrome can be effectively screened by routine urine analysis. Therefore, the present study was planned to determine the prevalence of occult renal diseases in asymptomatic school children & adolescents. The findings of the study may aid in identification of prevalence of asymptomatic renal diseases in Indian children and proportion of children who may benefit from routine urinary screening tests resulting in timely identification and intervention of asymptomatic renal diseases.

2. METHODOLOGY

2.1 Ethics

The study was carried out following the principles of the Declaration of Helsinki regarding medical research involving human subjects. Ethical clearance was obtained from the Institutional Ethics Committee. Informed consent was obtained before enrolling all participants in the study.

2.2 Study population and screening protocol

The present study is a cross sectional epidemiological study carried out in India. The study subjects were apparently healthy children attending a leading school in Jammu and Kashmir, India. The study was carried out among asymptomatic school children of 5-19 years of age within the span of one year. The children came from multiethnic background from all socioeconomic strata of Northern India. Sampling was carried out following a simple random sampling method. Children with pre-existing renal or any other systemic diseases, children on steroid therapy, and children whose parents refused to give consent were excluded. A total of 1675 students were recruited after obtaining informed consent from parents. Participants were instructed to void a mid-stream clean urine specimen into a 100 ml vessel, which was examined by a trained lab technician with the help of analyser.

The study was started in a small lab established at the school for the period of two months. The first morning urine sample was obtained from each child in a clean 100 mL vessel, which was tested with a urinary dipstick (Multistix, Nicolas Piramel) for haematuria and/or proteinuria as a first screening test. The second screening test was performed 2–4 weeks later by microscopic method on 44 children who had tested positive in the first screening. Blood investigations, including renal function, liver function and lipid profile, as well as abdomen ultrasonography (USG) were carried out.

2.3 Dipstick analysis

Dipstick test (Multistix, Nicolas Piramel) was performed on the unspun urine specimen with reagent strip designed to react progressively producing color changes at given intervals. The results were decided by visual comparison of the test strip with a color chart provided on the bottle label.

Urinalysis was considered abnormal by dipstick if the following findings were detected:

1. Haematuria if >5 RBC/µl (Green dots on yellow test: intact erythrocytes; Uniform green coloration of test: free hemoglobin or hemolysed erythrocytes);

2. Proteinuria (>30 mg/dl)

3. Glycosuria (>100 mg/dl)

4. Leukocyturia (>25 WBC/µl)

Haematuria

According to the American Urological Association, the presence **of three or more** red blood cells (RBCs) per high-powered field (HPF) in two of three urine samples is the generally accepted definition of haematuria [9,10].

Proteinuria

It is defined as urinary protein excretion of 30-150 mg/day and is the hallmark of renal disease. As per reagent kit insert, clinical proteinuria is defined with strip result of > 30mg/dL. Microalbuminuria is defined as the excretion of 30-300 mg/day of protein and is a sign of early renal disease.

Glycosuria

The urine analysis has been performed using Multistix reagent strips. Small amounts of glucose (<30 mg/dL) was below the sensitivity level of this test. The sensitivity of the test was 75-125 mg/dL and a value above 100 mg/dL was interpreted as positive result by the Multistix reagent strips

Pyuria

It is defined as ≥6 WBC/HPF in the urine sample by microscopic method.

2.4 Hypertensive population

The hypertensive population was determined by sorting the children having systolic blood pressure (SBP) or diastolic blood pressure (DBP) above the 90th percentile. The selected individuals were then checked for the presence of proteinuria and hematuria.

2.5 Statistical analysis

Data were analysed using Microsoft Excel and RStudio. Qualitative data were expressed in the form of numbers and percentages. Comparison between data was performed by using the Chi-square test. P value <0.05 was considered statistically significant.

3. RESULTS

3.1 Prevalence of urinary abnormalities

The study sample consisted of 1675 children with a male to female ratio of 1.53:1. In total, 76 children had urinary abnormalities with the prevalence of isolated haematuria in 1.9%, isolated proteinuria in 0.35% and glycosuria in 0.06% (Table 1). Under urine microscopic examination, urinary crystals were observed in 9 children. When 76 children with abnormal urine dipstick tests were followed with urine microscopic examination, 44 children were observed to have abnormal findings (Figure 1). Of these 44 children, 4.5% children were having protein in urine, 34% had isolated RBCs, and 47.7% were found to have isolated WBCs in urine (Figure 2).

Two children had both hematuria and urinary crystals on follow-up, while one other child simultaneously had pyuria and the presence of urine crystals. Interestingly, none of the children

Table 1 Descriptive statistics of children having urine abnormalities by dipstick method (N=76)

Abnormality	N	%
Proteinuria	4	5.2
Haematuria	32	42.1
Glycosuria	1	1.31
WBC	39	51.3

Figure 1 Number of pediatric population at each step of the screening

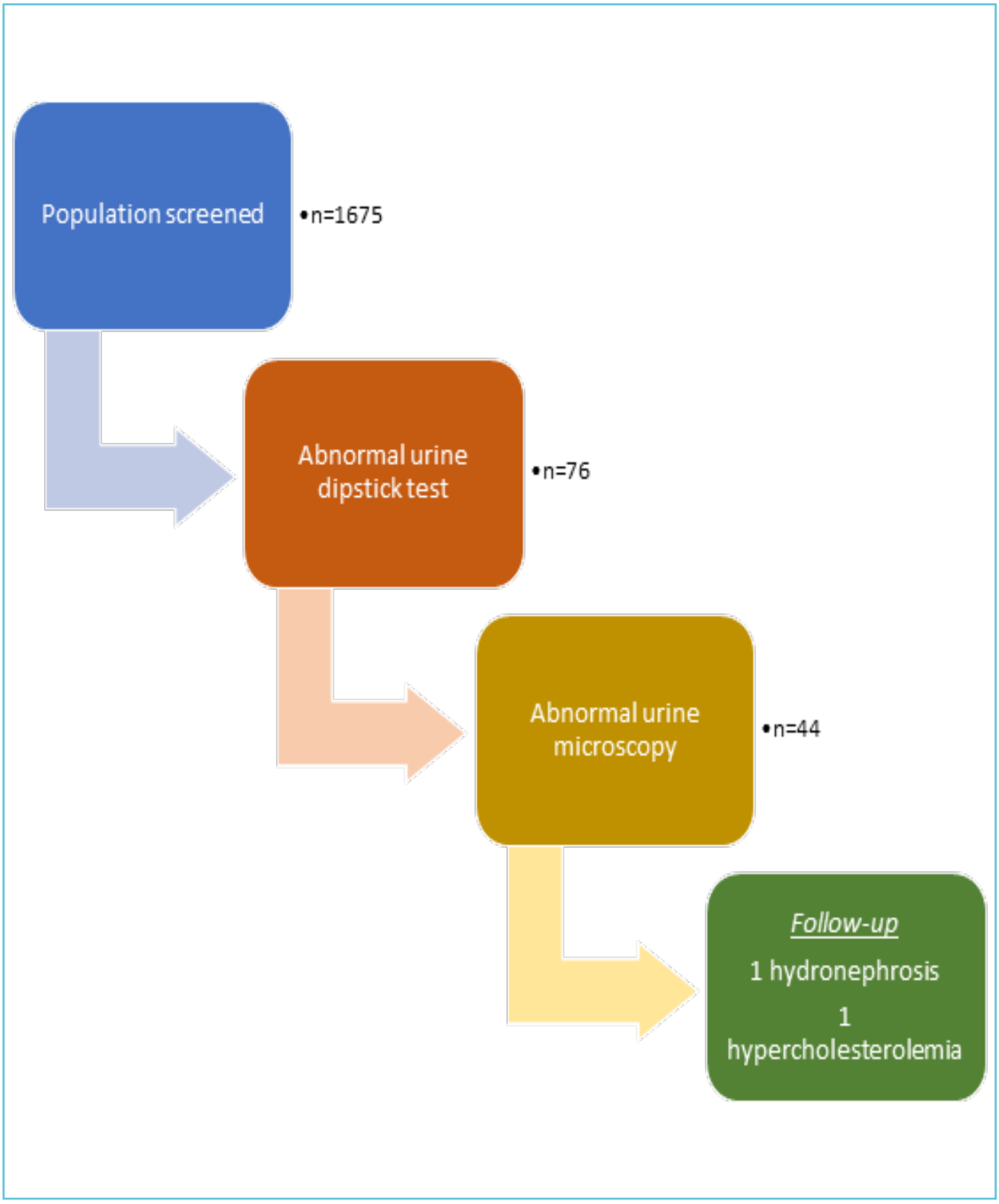
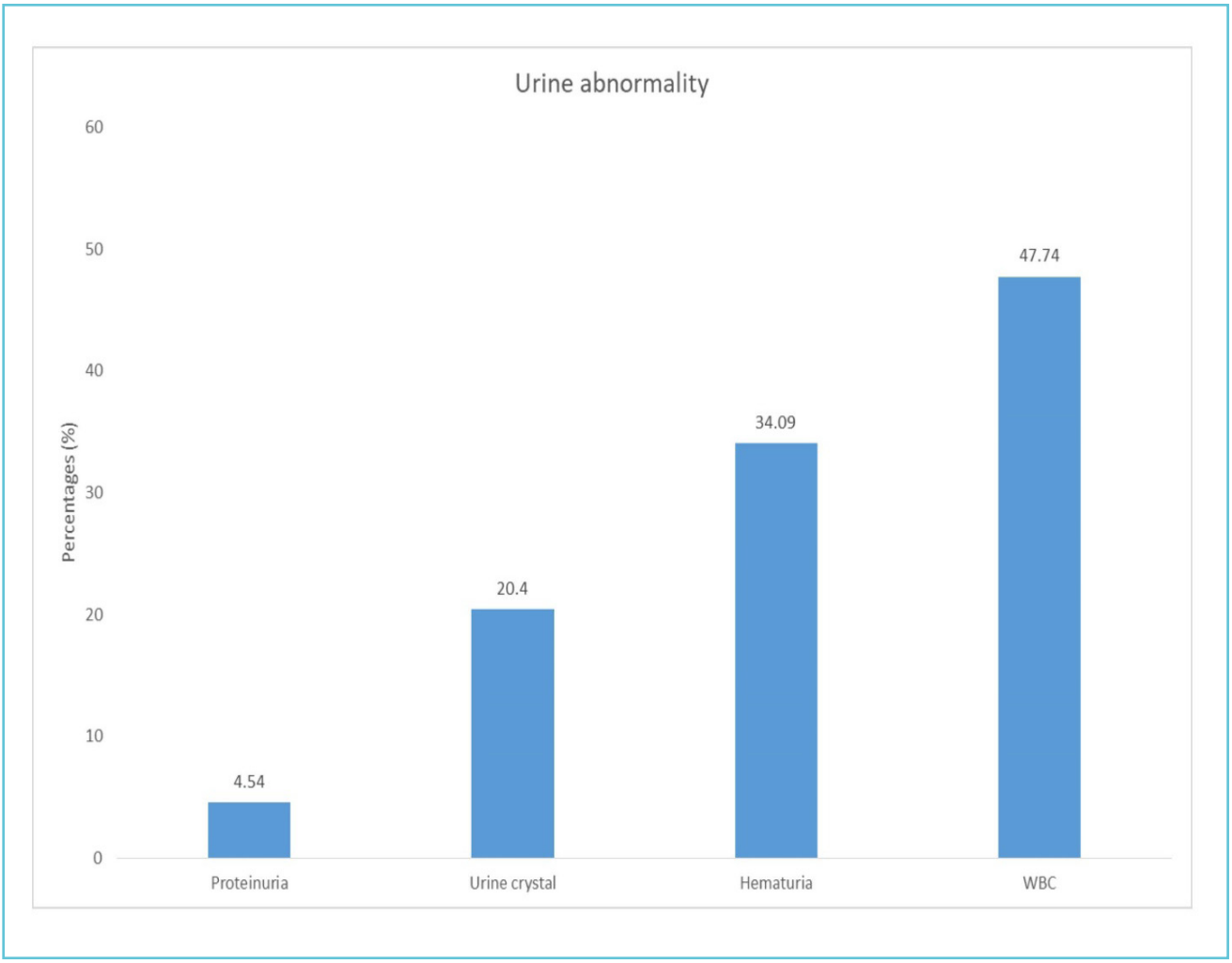


Figure 2 Prevalence of urinary abnormalities as per urine microscopy (n=44)



20 children had pyuria, 13 had hematuria, 6 had urine crystals, and 2 had proteinuria. 2 children had both hematuria and urinary crystals, while 1 child simultaneously had pyuria and the presence of urine crystals.

Table 2 Proteinuria and hematuria in hypertensive children

	SBP >90th percentile N (%)	DBP >90th percentile N (%)
Proteinuria	1 (0.60)	1 (0.60)
RBC+	5 (2.99)	8 (4.79)

Hypertensive children were sorted according to SBP or DBP above the 90th percentile cut-off.

For SBP, there was one case of proteinuria and five cases of hematuria above the cut-off, whereas for DBP, there was one case of proteinuria and 8 cases of hematuria.

had the presence of hematuria and proteinuria together. Further, when these 44 children were followed up with USG and blood investigations (renal function, liver function, and lipid profile), one child was identified to have hydronephrosis (right kidney) on USG, and another had hypercholesterolemia.

3.2 Blood pressure and urinary abnormalities

A high SBP of >130 mmHg was observed in 15 children and DBP >80 mmHg was observed in 19 children.

There was 1 case of proteinuria and 5 and 8 cases of hematuria, respectively, in the upper deciles of SBP and DBP. The prevalence for proteinuria was 0.60% and the prevalence for hematuria was 2.99% (in upper decile of SBP) in hypertensive children, both of which were more than the prevalence in otherwise healthy children (Table 2). Overall, the study found a prevalence of 0.12% proteinuria, 1.91% haematuria and 1.25% pyuria in otherwise healthy children. Those with abnormalities were referred to pediatrician/pediatric nephrologist for detailed evaluation.

4. DISCUSSION

CKD in children, although uncommon in nature, can cause devastating illness with long-term consequences in children. The current increase in the incidence of paediatric obesity leading to increased incidence of hypertension, may further contribute to increased burden from renal disorders in children [11]. Indeed, in the 44 children with renal abnormalities in follow-up, two children were obese; and both of them had SBP and DBP above the 90th decile. The prevalence of proteinuria and haematuria in hypertensive children which is more than normal underscores the importance of long term follow up in these children so that progression to Chronic Kidney disease can be monitored. Renal diseases in children can be silent (asymptomatic) in early stages and advance to ESRD requiring dialysis or renal transplantation. Mortality of children undergoing dialysis for ESRD is much greater (30-100 times) than general paediatric population [12].

Routine urine analysis is a simple and effective means to screen for potential underlying renal disorders. Routine mass screening in paediatric population has been a part of national scheme in countries like Korea, Taiwan and Japan. Routine urine screening programs are recommended as a basic fundamental step in early identification of renal damage. This has proved to be extremely important in reducing the growing burden of CKD in both developed and developing countries. In the present study, urinary abnormalities was present in 2.6% of the studied group which was comparable to that reported in Northern Iran (2.5%), Malaysia (2.3%), Tokyo (0.6%) and Egypt (0.72%) and lower than the 7.2% and the 9.6% reported in Bolivian and Nigerian studies respectively [13–17]. A cross-sectional study on 1597 Indian children aged 5-16 years revealed a prevalence of urinary abnormalities at 7.82% [18]. Proteinuria, haematuria, and pyuria were found in 4.3%, 5.2%, and 2.5% of school children aged 6-18 years in a study conducted by Vinoth et al. [19]. They also found that the urinary abnormalities were more prevalent in males.

Haematuria was the most common abnormality found in our study group in agreement with Vinoth et al [19]. This was in contrast to other studies in Egypt and Nigeria where proteinuria was the most common positive finding [16]. Hematuria had a prevalence in Malaysia, Egypt and Shanghai (0.21%, 0.36% and 0.46% respectively) which is comparable to our results which showed a prevalence of 1.91%. Nigeria and Xiamen City (China) reported a comparable prevalence of 1.5% and 1.21% respectively [15,16,20]. In an Indian study, hematuria was found in 5.8% children [18]. Infection constitutes of 14% of gross hematuria in children, according to one study [21]. Among these, parasitic hematuria,

particularly due to Schistosomiasis, is prevalent in tropical and subtropical countries [22]. A careful history and physical examination as well as focused laboratory investigation may provide sufficient insight in these cases. Bergstein et al. evaluated 342 children referred to their nephrology clinic for asymptomatic isolated microscopic haematuria. Among these patients, they found no abnormality in 274 children [23]. Other authors like Vehaskari et al. performed biopsy from 22 children with microscopic haematuria having no family history of kidney disease and a negative evaluation for causation. All but three biopsies were normal and showed non-specific focal tubular changes [24]. In a screening study done in Japan, they found 6 cases of IgA nephropathy and 7 cases of minor glomerular abnormalities among 220 children with asymptomatic haematuria [15]. These studies suggest a benign nature of microscopic asymptomatic haematuria that may be an important sign of underlying disease. However, limitations of these studies were the absence of long term follow-up and thus, the frequency of development of complications and occult kidney disease was not known.

Furthermore, in patients with microscopic haematuria from occult glomerular disorders, progression to clinically significant disease will be accompanied by the development of hypertension with or without proteinuria or gross haematuria. Thus, long term follow-up in children with microscopic haematuria is crucial. Proteinuria can be a major cause of underlying kidney disease or a transient finding in normal children. In our study, first morning urine sample helped in excluding orthostatic proteinuria as a cause of isolated proteinuria in children. The dipstick is mainly sensitive to albumin, whereas quantitative methods detect all kidney proteins. Proteinuria is a strong and independent risk factor of ESRD. Therefore, asymptomatic proteinuria warrants further work up to detect and even prevent ESRD [25]. Furthermore, an increased prevalence of proteinuria in hypertensive children demands more attention towards renal work-up to prevent the possibility of renal diseases in the future.

Until recently, American Academy of Paediatrics (AAP) had recommended routine urinalysis by dipstick method for children under 5 years of age. However, with the recent evidence of low incidence of CKD from multiple large-scale studies in paediatric population, AAP no longer recommends routine urinalysis in children. Prevalence of paediatric CKD, cost of screening and burden of ESRD are the important factors in determining the effectiveness of routine urinary screening programmes. Studies from Korean, Taiwanese and Japanese paediatric screening program indicate a clear advantage of early detection and effective intervention to prevent progression to ESRD [8]. All these studies emphasize the importance of following up children with silent renal diseases.

5. CONCLUSION

Our study found a prevalence of 0.12% proteinuria, 1.91% haematuria and 1.25% pyuria in otherwise healthy children in a North Indian population. Those in whom these abnormalities were found were referred to pediatrician/pediatric nephrologist for detailed evaluation. Urine screening is a feasible, non-invasive, and inexpensive test for early detection of occult renal diseases, which can be helpful if incorporated into school health programmes. A structural framework can also be developed based on data for the diagnosis, prevention and management of renal diseases. Due to scarcity of national data on prevalence of renal abnormalities in Indian children, the national burden of providing medical care for children with CKD remains unknown. A large-scale study with follow-up of children with urinary abnormalities will further add to the findings of our study and establish

the benefit, if any, of a national paediatric urine screening programme.

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Author contributions

Mithu Banerjee: Conceptualization, Methodology, Investigation, Writing-Reviewing and Editing.

Dipayan Roy: Software, Writing-Reviewing and Editing, Visualization.

Malavika Lingeswaran: Writing-Original draft preparation, Writing-Reviewing and Editing, Visualization.

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Aliza Mittal: Writing-Reviewing and Editing.

Prem Prakash Varma: Methodology, Investigation, Writing-Reviewing and Editing.

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