ORIGINAL ARTICLE

Magnitude of asymptomatic microscopic hematuria and proteinuria in 7-12 years old school children in Addis Ababa, Ethiopia

Abate Yeshidinber (MD)[1], Damte Shimelis(MD)[2]

ABSTRACT

Background: *Hematuria or proteinuria or mixed hematuria and proteinuria are one of the most important signs of renal or bladder disease in children and it can represent a process that is simple and benign or complex and life threatening. There is no research done in this country pertaining to this problem in pediatric practice and this study will assess the magnitude of asymptomatic microscopic hematuria and proteinuria in apparently healthy school children in Addis Ababa, Ethiopia.*

Objective*: To assess the prevalence of asymptomatic microscopic hematuria and proteinuria in apparently healthy school children between the ages of 7-12 years in Addis Ababa, Ethiopia.*

Materials and Methods: *This is a cross sectional survey done in apparently healthy school children (7-12 years of age) from the beginning of April 2014 to the end of May 2014 over a period of 8 weeks. After obtaining written consent from parents, a labeled urine collection cup was given for each student with written instruction to the parents to take midstream early morning fresh urine to the level of the mark on the cup and send the cup to the child after proper sealing. The urine samples were received by the data collector and dipstick urinalysis was done within 1 hour of collection. A dipstick test (Multistix, Bayer Diagnostics, Miles Inc., USA) was performed on the un spun urine specimen by trained laboratory technician, 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. All positive hematuria results were screened for the second time after 2 weeks to check for persistence of hematuria. This time the positive dipstick results were confirmed by microscopy after centrifugation of 10ml of fresh urine and 5 or more RBC/HPF confirms hematuria.*

Results*: In the first screening out of 382 school children 32 (8.4 %) tested positive for hematuria. Among these 7 (1.8%) were males and 25 (6.5%) were females. The difference between males and females was statistically significant (p=0.009). When compared with the three age groups (7-8, 9-10, 11-12 years) the prevalence of hematuria was higher in the 7-8 age group (19%) as compared to 11-12 year old children (5.7%) and this is statistically significant (p=0.013). 75 students (19.6%) were tested positive for proteinuria. Among the children with proteinuria 32 (8.4%) were males and 43 (11.3%) were females and the difference was not statistically significant. 32 students (8.4%) were positive for leukocyte esterase all of which were females. Glycosuria and nitrituria was present in less than 1%.*

In the second screening, 14 children (3.7%) had isolated hematuria and 2 children (0.5%) mixed hematuria and proteinuria making the prevalence of hematuria and proteinuria 4.2% and 0.5% respectively. Age and sex differences in the prevalence of hematuria and proteinuria were not demonstrated. Among the 16 children with hematuria 6 children (37.5%) had red blood cell (RBC) casts in their urine suggesting glomerulonephritis as the possible cause of hematuria.

Conclusions*: The study demonstrated that the prevalence of hematuria (4.2%) and proteinuria (0.5%) is higher in Ethiopian children than most other African children and worldwide but nitrituria and glycosuria were rare.*

[1]Pediatrician, Department of pediatrics and Child Health, Saint Paul Hospital Millenium Medical College, Addis Ababa, Ethiopia

[2]Associate professor of pediatrics, consultant pediatric nephrologist, Department of pediatrics and Child Health, Addis Ababa University, Addis Ababa, Ethiopia.

INTRODUCTION

Hematuria is defined as a positive dip strip on urinary specimen with microscopic confirmation of the presence of >5 RBCs/HPF (centrifuged) or >6 RBCs/0.9 mm^3 (uncentrifuged) (1, 2, 3,). Hematuria may originate from the glomeruli, renal tubules and interstitium, or urinary tract (including collecting systems, ureters, bladder, and urethra). In children, the source of bleeding is more often from glomeruli than from the urinary tract (4).

Likely the most commonly used laboratory test for examining renal function or injury to the kidney or urinary tract, the urinalysis is easy to perform and is used as a screening test, a diagnostic test and, at times, a follow up examination (5). The commonest indicator of an abnormality of the urine is a "positive" or abnormal urine strip test for blood (4). When tested on urine samples in which a predetermined amount of blood has been placed, dipsticks have a sensitivity of 100 and a specificity of 99 in detecting one to five RBCs/hpf (2).However if the dipstick test is positive, the presence of red cells should be confirmed by microscopic examination (6, 7).

Hematuria is a common finding in the unselected population of children and most of the data relative to prevalence of hematuria have come from population-based studies of school children (4). Microscopic hematuria may be transient, intermittent, or persistent. Since the persistent type seems to be uncommon, the results of an epidemiologic study depend on the number of specimens examined from each individual (2).
The prevalence of asymptomatic hematuria has been markedly variable**.** Generally microscopic hematuria in two or more urine samples is found in 1 to 2% of children 6 to 15 years of age (4) and reaches up to 4 % in a single urine sample (1,2,) where as Gross hematuria is an uncommon finding in an unselected Population of children with a prevalence of 0.13%(8). Variation in the detection rate of urinary abnormalities on screening in these studies may be due to varying ethnic backgrounds and the prevalence of renal diseases in these populations (9). There are also considerable differences in the pattern of renal disease around the world which arise from racial variation in the susceptibility to renal disease compounded with socioeconomic status further contributing to the variation (10).

Worldwide, screening for chronic kidney disease (CKD) is controversial, primarily because of the uncertainty 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 countries have led to early detection and effective intervention. This opinion is not shared by investigators from North America and Europe and differences in the effectiveness of mass urine screening between populations may be due to different incidence rates of renal diseases or to different approaches to an abnormal urine screening test (5, 7, 10-15).

However the case may be different for developing countries where renal replacement therapy (RRT) that is dialysis and transplantation is not readily available and the cost of prevention is by far lower than treatment. Some authors argued that, with some effort, prevention of the progression of renal disease with the combination of pharmacologic and non-pharmacologic approaches can be exported to less-developed countries. In line with this argument screening programs can be implemented with simple, cheap, and reliable tests, such as measurement of body weight, blood pressure, blood glucose, and dipstick urinalysis as has been seen In India and Bolivia (16-18).

The International Pediatric Nephrology association (IPNA) practical primary care approach to hematuria in children categorize hematuria in to 4 clinical category for the sake of ease approach; Gross hematuria, Microscopic hematuria with clinical symptoms, asymptomatic microscopic (isolated) hematuria and asymptomatic microscopic hematuria with proteinuria(1). Another goal of the design is to discourage the random and often unnecessary use of laboratory investigations in each child with hematuria (19).

Many studies have shown that most children with isolated microscopic hematuria do not have a treatable or serious cause for hematuria and do not require an extensive evaluation. Because the most common diagnoses in children with persistent

microscopic hematuria without proteinuria are benign persistent or familial hematuria(thin basement membrane disease), idiopathic hypercalciuria, IgA nephropathy, and Alport's syndrome, a more extensive evaluation is indicated only when proteinuria or other indicators are Present(1,2,20-23). Unlike microscopic hematuria macroscopic hematuria requires prompt evaluation to exclude potentially life-threatening causes. Painful gross hematuria usually is caused by infections, calculi, or urologic conditions. Children with macroscopic hematuria require urine culture and renal imaging by ultrasound (1, 8, 23, and 24).

In a study of 342 children with microscopic hematuria, no cause was uncovered in 274 patients and the authors Conclude that diagnostic evaluation for potential causes of asymptomatic microscopic hematuria in children may not be necessary (23). A recent study from china also showed similar results to the above studies with adverse renal events (proteinuria, hypertension, or impaired renal function) of 6.0% patients with asymptomatic isolated microscopic hematuria (AIMH) and 22.8% patients with asymptomatic microscopic hematuria with proteinuria (AMHP) (17).

African studies on the prevalence and long term follow up outcome are scarce with only few studies coming from Egypt and Nigeria (16, 25-28).

A short survey of the pediatric nephrology clinic log book in Tikur Anbessa Hospital, Department of Pediatrics and Child Health Addis Ababa, Ethiopia (the only pediatric renal follow up clinic in Ethiopia) showed only eight children followed for asymptomatic hematuria over a period of 10 years (from 2004-2014). This could be because of failure of detection/referral of such patients who may benefit from follow up by a pediatric nephrologist or because of the rarity of the condition. The objective of this study is to determine prevalence of asymptomatic microscopic hematuria in school age children in Addis Ababa and assess the coexisting urinary abnormalities in those children with persistent hematuria.

MATERIALS AND METHODS

This is a cross sectional survey done in apparently healthy school children (7-12 years of age) from the beginning of April 2014 to the end of May 2014 over a period of 8 weeks. Assuming that the prevalence of asymptomatic hematuria in school age children is 7.8 % (25), using the formula $n=z^2 p (1-p)/d^2$ taking 95% CI and precision of 2.5%, p as 7.8% and a 10 % non respondent rate, calculated sample size (n) was 488.

The study was conducted in apparently healthy school children from Medhanialem Primary School in Addis Ababa city which is the capital city of Ethiopia. Medhanialem Primary School is one of the government primary schools under Gullele sub city Education Office and currently having 3238 students. The school was selected based on its number of students and its geographic location for ease of the study.

Informed written consent was obtained from parents and the school administration. A consent form with the research information written in Amharic was sent to the parents /guardians before the study. This study was approved by the Department of Pediatrics and Child Health research and publication committee.

All six grade students (grades 1-6) and both sexes were equally represented. Two sections from each class were randomly selected by lottery method each having an average of 50 students with a total number of 600, but only 490 students fulfilled the inclusion criteria and included in the study population. From the 490 students only 382 gave consent to participate in the study.

Students with previous history of known renal disease, female students seeing menses during the study and those students whose parents did not give consent were excluded from the study.

A day before the screening urinalysis, a labeled urine collection cup was given for each student with written instruction to the parents to take midstream early morning fresh urine to the level of the mark and send the cup to the child after proper sealing. The urine samples were received by the data collector and dipstick urinalysis was done within 1 hour of collection. A dipstick test (Multistix, Bayer Diagnostics, Miles Inc., USA) was performed on the unspun urine specimen by trained laboratory technician, 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.

In this screening program, the dipstick adopted consists of 10 reagents: pH, specific gravity, protein, blood, glucose, leucocytes, nitrites, urobilinogen, bilirubin and ketone label.

All positive hematuria results were screened for the second time after 2 weeks to check for persistence of hematuria. This time the positive dipstick results were confirmed by microscopy after centrifugation of 10ml of fresh urine and 5 or more RBC/HPF confirms hematuria.

Those children with persistent hematuria for the second time underwent focused history and physical examination including blood pressure measurement, hearing assessment, throat exam, and evaluation for edema.

After the examination these children were referred to a pediatric nephrologist for follow up and further work up according to the guideline on the evaluation of children with hematuria.

During the supervision, quality and completeness of gathered information by the data collector was checked periodically by the principal investigator. The collected data was cleaned manually.

The statistical analysis was performed using statistical package of social science SPSS version 16.0. Chi-squared and Fisher's exact test were applied to compare proportions and mean differences, respectively. A P value of less than 0.05 was considered significant.

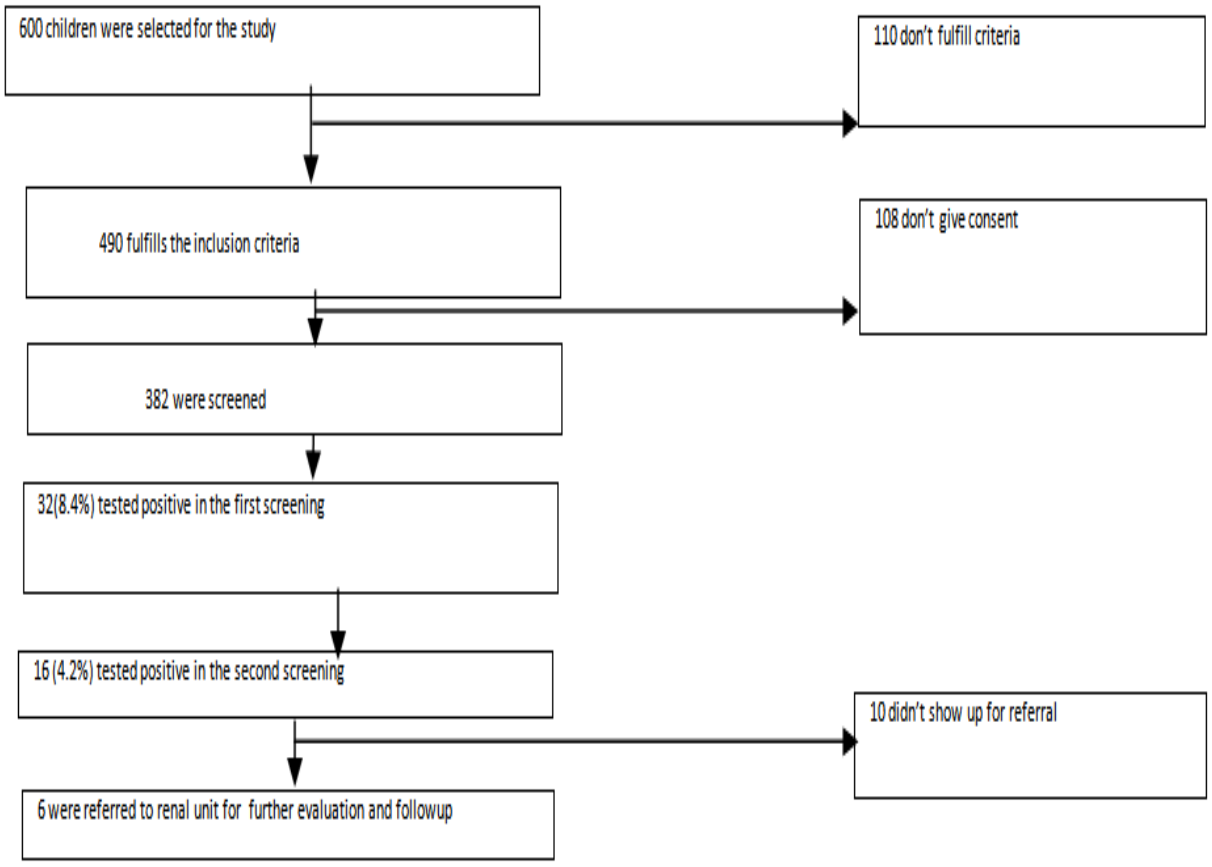

fig. 1 study flow and screening protocol

RESULTS

The study was performed from the beginning of April 2014 to the end of May 2014 for a period of 8 weeks. Consent forms were given to 490 asymptomatic school children aged 7–12 years, but only 382 completed forms were returned (response rate of 78%). Out of a total of 382 children, 173 were males (45.3%) and 209 were females (54.7%). In the first urinalysis 32 children (8.4%) were found to be positive for hematuria and 75 (19.6%) had proteinuria. Among the 32

children with hematuria 7 (1.8%) were males and 25 (6.5%) were females in the first screening and the difference between males and females is statistically significant (p = 0.009). The female to male ratio was > 3:1 in children with hematuria. The frequency of positive children for hematuria and proteinuria in the first screenings is presented in table 1.

The school children were divided into three age groups: group A (7–8 years), group B (9-10 years) and group C (11–12 years). There were 42 children in the 7–8 year age group, 146 in 9-10 and 194 children in the 11–12 year age group. The age distribution of hematuria is seen in table 2.

In the first screening the prevalence of hematuria was higher in group A and B than group C (19, 8.9 and 5.7 % respectively). But the difference was statistically significant in only between groups A and C with a p value of 0.013.

Table 1. Relative frequency of abnormal urinary findings in the first urinalysis of asymptomatic school children age 7-12 years in Addis Ababa, Ethiopia**.**

Variable	**Gender**			**P value**
	Male	Female	Total	
Isolated Hematuria	7(1.8%)	25(6.5%)	32(8.4%)	0.009
Proteinuria	32 (8.4%)	43 (11.3%)	75 (19.6%)	NS*
Leukocyte esterase	0	32 (8.4%)	32 (8.4%)	0.000
Nitrituria	1(0.3%)	0	1(0.3%)	NS
Glycosuria	0	1 (0.3%)	1(0.3%)	NS

* NS-not significant

Presence of proteinuria increases with increasing age with prevalence of 14.3, 17.9 and 22.2% in groups A, B and C respectively (table 3). However the difference is not statistically significant. Unlike hematuria proteinuria was not found to be gender dependent being seen in 19.5% males and 20.6 % females (p=0.218). 63 students (16.5) had trace proteinuria whereas significant proteinuria (+1 and above) was found only in 12 students (3.1%).

Table 2. Age distribution of asymptomatic microscopic hematuria cases in the first urinalysis in the 7-12 year old school children in Addis Ababa, Ethiopia**.**

Age(yrs)	Hematuria	No hematuria	Total	Prevalence (%)
7-8	8	34	42	19
9-10	13	133	146	8.9
11-12	11	183	194	5.7
Total	32	350	382	8.4

In the first screening out of 382 students only 1 child (0.3%) was found to have glycosuria, one child tested positive for nitrite (0.3%) where as leukocyte esterase was positive in 32 children (8.4%), all of which were females.

Out of 32 children who had hematuria in the first screening the second urinalysis done after 2 weeks

showed 16 children tested positive for hematuria. Out of these 14 students (3.7%) had isolated hematuria and 2 students (0.5%) had mixed hematuria and proteinuria. The overall prevalence of hematuria was 4.2% and proteinuria was 0.5% in the studied population (table 4).

Repeat urinalysis showed leukocyte esterase positive in 4 children (1%), urine microscopy done in 16 children with hematuria in the second screening showed casts in 12 children (75%). The casts were RBC in 6 (37.5%), suggesting glomerulonephritis as the possible cause for hematuria. The type of glomerular lesion was not possible to ascertain as these study subjects were referred to a nephrologist for further workup and it is beyond the scope of the study objective. Granular casts were seen in 3 (18.8%), and WBC in 1 (6.25%) and a combination of two of the above in 2 (12.5%). No ketone or bilirubin was detected in the urine of study subjects and all children had normal urine PH and specific gravity.

Table 3. Age distribution of proteinuria cases in the first urinalysis in the 7-12 years old school children in Addis Ababa, Ethiopia.

Age (yrs)	Proteinuria	No proteinuria	Total	Prevalence (%)
7-8	6	36	42	14.3
9-10	26	120	146	17.9
11-12	43	131	194	22.2
Total	75	287	382	19.6

Table 4. Category and relative frequency of urinary findings in the two steps of the study in asymptomatic school children age 7-12 years in Addis Ababa, Ethiopia.

Finding	First sample	Second sample
Isolated asymptomatic hematuria	25 (6.5%)	14 (3.7%)
Isolated proteinuria	68 (17.8%)	0
Mixed asymptomatic hematuria with proteinuria	7 (1.8%)	2 (0.5%)
Leukocyte esterase	32 (8.4%)	4 (1%)
Nitrituria	1 (0.3%)	0
Glycosuria	1 (0.3%)	0
No finding	282 (73.8%)	366 (95.8%)
Total	382 (100%)	382 (100%)

DISCUSSION

In our study 32 children (8.4%) had hematuria,75 students (19.6%) were positive for protein,7 students (1.8%) were positive for both blood and protein, 1 student (0.3%) was positive for glucose,1 students (0.3%) was positive for nitrite and 32 students (8.4%) were positive for leukocyte- esterase in the first sample.

In the Galveston County epidemiology study [20], approximately 4.0% of school-age children had microscopic hematuria in one of the three samples

tested. When the criteria for "persistent" hematuria was defined as the presence of blood in the second and third of the three consecutive samples, the prevalence decreased to approximately 1% and <0.5% respectively.

Our study shows a prevalence of 8.4% for hematuria in a single sample and decreased to 4.2% on repeat urinalysis which is higher than the above study. However, the prevalence could further decrease if a third sample is taken. The result of our study is comparable to a recent Egyptian study where 7.8% of their study subjects showing positive results for blood in the second sample. 5 students (0.7%) were positive for both blood and protein but in our second sample it was 0.5% which is comparable. 1 student (0.1%) was positive for glucose, 11 students (1.6%) were positive for nitrite, 32 students (4.5%) were positive for leukocyte- esterase (25). These findings are similar to our findings except a slightly higher rate of nitrite and leukocyte esterase in their sample.

Our result is also comparable with a recent Indian study in 100 subjects with proteinuria and hematuria occurring in 16 % and 5% respectively in the first sample (18).

In the Finnish study, 16% of their study subjects had hematuria and proteinuria in at least one sample with an overall prevalence of 0.7% [2]. In our study 62 students (16.2%) had trace proteinuria where as significant proteinuria (+1 and above) was found only in 13 students (3.4%) in the first sample. The overall prevalence of isolated hematuria, and combined hematuria and proteinuria were 4.2%, and 0.5%, respectively, among our study population. The difference in the prevalence of proteinuria among different studies might be due to ethnic, socio-economic and geographic variation in the prevalence of kidney disease or in the sensitivity of the dipstick test.

The similarity in most studies is in the prevalence of persistent hematuria associated with proteinuria which is 0.5 % in our study, still slightly higher than an Egyptian study which is 0.28% (Maha etal, 25).It is the most important indicator of renal disease as compared to isolated hematuria which usually follows a benign course (28).

Unlike the above studies our finding is significantly higher than a Nigerian study (which reveals 0.6% for hematuria as compared to ours which is 3.7%. 1 % prevalence of proteinuria is slightly higher than ours which is 0.5%.) (26). In the Korean study isolated proteinuria was about 0.2%, occult blood was about 0.8%, and glycosuria was about 0.07% from January 1998 to December 2004)(30).

In one Nepalese study 5.5% children tested positive in the first screening for isolated hematuria and proteinuria and for combined hematuria and proteinuria. Of these children only 0.71% cases tested positive in a second screening. Glomerulonephritis was the most commonly detected disorder (50%) in this study (9).In line with this observation in our study of the 16 children who tested positive in the second screening, 6/16 (37.5%) showed RBC casts suggestive of glomerulonephritis as the possible cause of hematuria. This was also the case in another Egyptian study (27). This conclusion however is impossible to draw in our case as no further workup was done to ascertain the causes.

Our finding is also similar to Turkish study. In 1848 healthy school-age children aged 7 to 14 years isolated hematuria, isolated proteinuria, and combined hematuria-proteinuria were found in 92 (4.9%), 16 (0.8%) and 10 (0.5%) patients, respectively. In addition, 11.9% (11/92) of cases of isolated hematuria and 40% (4/10) of cases of combined hematuria- proteinuria were observed to have persisted. Persistent hematuria and persistent hematuria-proteinuria were found in 11 (0.5%) and 4 (0.2%) patients, respectively.

There is no ideal method for screening of hematuria and most of the differences are likely due to variations in methods and definitions (2).

Whether the prevalence of asymptomatic hematuria depends on age and gender is not obvious from the previous studies. Silverberg et al showed in general higher percentages for older girls, but there is no consistent trend in their figures, and the total number of boys is too small to draw any conclusions. Dodge et al found the prevalence to increase with age in girls up to 11 years, but at 12 years their oldest group, there was a marked drop. For boys their results do not show any constant pattern. The Finnish study, with a fairly large number of subjects in each age and sex group, showed no significant variation with age. Silverberg et al found almost a tenfold higher prevalence in girls than in boys; a much smaller difference was reported by Dodge et al, (20). The Finnish study showed no significant difference.

There was no readymade explanation for the disagreement (2, 20, 32, and 33). No difference in the prevalence in male and female was found from India (18).

However hematuria is found to be age dependent in our study with significant prevalence in the age group 7-8 yrs (prevalence=19%) despite the small number of samples in this age group. Females are also 3 times more affected (OR 3.2 and p value 0.009) in our study even if results are inconsistent in previous studies.

There is no significant difference by age and sex in children with proteinuria in this study. However Indian study showed female preponderance in the age group b/n 10-13 yrs (18).

Despite the absence of detailed workup as to the cause of the hematuria in our case nearly half of the children with persistent hematuria, 6 /16(37.5%) do have RBC casts suggesting a glomerular origin for the hematuria possibly glomerulonephritis. In line with this observation a recent Nepalese study found that 50 % of the hematuria was from glomerulonephritis (9). Egyptian researchers also found glomerulonephritis as the cause of asymptomatic hematuria in two-third of the cases (27).

One child (6.3%) from those having persistent hematuria was found to have associated pyuria, leukocytes and WBC casts which is suggestive of urinary tract infection but urine culture was not done.

After the repeat urinalysis; 16 students (4.2%) are found to have persistent hematuria. The parents of these children were communicated for referral to the pediatric renal unit of Tikur Anbessa Hospital, However; only 6 (37.5%) showed up for referral and the other 10 (62.5%) didn't come for a referral despite repeated communication. We didn't know the reason for it but the fact that the children are asymptomatic and low health seeking behavior of our society may have contributed for their absence.

Limitation of the study

This study was done in a single governmental school with poor representation of the different socio-demography despite the fact that previous studies didn't show differences in the prevalence. Age distribution was also the limitation as most children (89%) were 9 years and above with only 11% being 7-8 yrs. This could be because these young children might have failed to deliver the consent forms to their parents/guardians as most respondents were from the older age groups.

Conclusion and Recommendation

As this study shows high prevalence of hematuria in Ethiopian children a larger sample size including different ethnic, geographic and socio-economic groups should be done to see the reproducibility of the result, determine the common causes of hematuria and if routine screening helps to prevent end-stage renal disease decreasing the cost of unavailable costly therapeutic interventions.

The issue of health awareness and preventive medicine and the community's knowledge about asymptomatic renal disease and its prevention may need to be assessed altogether before recommending a routine urinalysis for all school children.

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