Spot urine protein creatinine ratio compared with dipstick proteinuria as a primary screening tool for renal disease in a community setting

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Abstract

Background

Although, the use of manual dipstick urinalysis for proteinuria has been a common practice, the Kidney Disease Improving Global Outcomes (KDIGO) guideline on screening for chronic renal disease least advocate it use. Besides, several studies have assessed the performance of dipstick urinary in screening for proteinuria to be inaccurate, unreliable with a poor predictive values. The goal of this study was to determine and compare the presence of significant proteinuria (SP) in high-risk African children using the spot urine protein creatinine ratio (UPr/UCr) as a primary screening tool besides dipstick proteinuria screening.

Methods

This cross-sectional study involved 1,316 apparently healthy children recruited through a multi-stage sampling technique in Ogbomoso land, Nigeria. We performed a dipstick urinalysis on early-morning urine samples. Urinary protein content was determined using a turbidimetric method and Jaffe's reaction to measure the urinary creatinine concentration. Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS)^{TM}, Version 23.0 for Windows.

Results

The prevalence of SP using spot UPr/UCr (≥ 0.2) and dipstick proteinuria screening (≥1+) were 18% and 0.8%, respectively (p<0.001). Of the 224 subjects determined to have SP using UPr/UCr, the females (140; 20.1%) had a higher proportion compared to males (84; 15.4% -p=0.032). Nephrotic range proteinuria was detected in nine out of 10 subjects (90%) using UPr/UCr but in only three out of ten (30%) using the urinary dipstick method. The biserial correlation coefficient (r= 0.092; p=0.001) and inter-rater-agreement (Cohen's Kappa = 0.01) were poor, and the McNemar's test result was (p<0.001).

Conclusion

The UPr/UCr ratio technique appeared to perform better than dipstick urinalysis as a primary screening tool for renal disease. Hence, it may be adopted for early detection of SP as a kidney disease marker especially among the high risk population.

Introduction

Kidney disease is a huge public health problem. A recent report showed that about 860 million people in the world have kidney disease.[1] Children of African descent are three times more likely to develop kidney

disease than their Caucasian counterparts as a consequence of the high prevalence of infectious diseases, the lack of adequate vaccination and the constant exposure to nephrotoxic agents along with the backdrop of genetic predisposition.[2–5] In most low to middle-income countries, kidney replacement therapy is not publicly funded, and the treatment cost of end-stage kidney disease (ESKD) is high and unaffordable. Hence, the need for early diagnosis and prompt intervention to prevent disease progression.

One early marker of renal disease is proteinuria. Clinically, significant proteinuria is not only a useful early marker of renal disease, but it also serves as an index of disease severity and a determinant of disease progression.[6–8] The amount of protein excreted by children are less than 4 mg/m^2/hour or 100 mg/m^2/day.[9, 10] This value of proteinuria corresponds to a dipstick urinalysis reading of trace or negative proteinuria or a urinary protein creatinine ratio (UPr/UCr) of <0.5 for children between the ages of six and 24 months and <0.2 for children above two years of age according to the 2012 KDIGO guideline for evaluation and management of chronic kidney disease (CKD).[10] A UPr/UCr value above 0.2 in children over two years of age or a urinary dipstick proteinuria reading of ≥ 1+ defines significant proteinuria as a renal disease marker.[9, 10]

The 2012 KDIGO clinical practice guidelines for evaluation and management of CKD advocates UPr/UCr from early morning urine for evaluation of proteinuria in children.[10] This recommendation is far above the quantitative urine albumin ratio (ACR) and the automated or manual dipstick urinalysis for proteinuria. This may be consequent on the high predisposition of children to tubular disorders or injuries with predominant excretion of tubular proteinuria to dipstick urinalysis and ACR will be less sensitive. Previous efforts to use the prevalence of proteinuria as a renal disease indicator in Nigerian communities mostly used dipstick urinalyses.[4, 7, 11] However, the dipstick urinalysis used for this purpose have been judged to be poor and unreliable[3,4, 7, 11] In a population-based health check-up, Naruse *et. al*[12] showed that this approach generates a poor predictive value, a high rate of false positives and a significant number of false-negatives results compared to the qualitative measurement of the UPr/UCr.

The prevalence of proteinuria determined by dipstick urinalysis currently reported from different parts of Nigeria showed a wide variation (1.0 to 77.4%), which reflects its' poor reliability.[6, 10, 11] Hence, a more reliable tool for urinary protein estimation-one that is accurate, sensitive, reproducible and perhaps automated. The screening tool should also address the subjects' hydration status and simplified for point-of-care service[4, 6, 9] Measuring the urinary protein creatinine ratio (UPr/UCr) using an automated biochemical analyser may be a primary screening tool that meets the above criteria.[6, 9, 13]

Thus, this study aimed to determine and compare the results for SP prevalence obtained using dipstick urinalysis and spot UPr/UCr screening among school children between the ages of five and 15 years in southwestern Nigeria.

Subjects And Methods

This is a cross-sectional study conducted between July and October 2018. The study recruited school children from primary and secondary schools in Ogbomoso, southwestern Nigeria. Ogbomoso is an inland community made up of five Local Government Areas (LGAs). The screening took place in the rural-Ogo-Oluwa and urban-Ogbomoso South LGAs.

The minimum sample size was estimated at the 95% level of confidence interval, a margin of error was set at 1.5% and 90% statistical powers using Cochran's formula for proportion.[14] The study used the 6% prevalence of proteinuria (using UPr/UCr) reported by Esezobor and colleagues[15] among apparently healthy Nigerian children for calculating the sample size.

We used a multistage sampling technique to recruit children for the study (**Figure 1**). The five LGAs were stratified into urban and rural LGAs based on Nigeria Bureau of statistics Household / Labour Force Survey definition. One LGA was selected at random by simple balloting from each of the urban and rural stratum. A computer based randonmization using Microsoft Excel 2010 version was used to select 30% of the schools (33 out of 109), classes and the arm in the two selected LGAs.

The number of children to be selected in each school was proportionate to the school population. In each school, a systematic random sampling was used to select subjects from an arm. The inclusion criteria included apparently well children aged 5-15 years. The study excluded subjects with the following; fever within one week preceding the study; presence of vomiting and diarrhoea with dehydration; children on drugs such as sulphonamides, vitamin C, penicillin and cephalosporin which can interfere with the analysis.

The recruited children received labelled universal bottle and instructed on how to obtain a clean catch six ml of early morning urine.[10]

Dipstick urinalysis was performed on the uncentrifuged urine specimen using Combi 9 dipstick test strips with Lot number URS6120036 (ACON Laboratories, Inc. 10125 Mesa Rim Road, San Diego, CA 92121, USA). The urine samples kept in the icepack were transported to the laboratory for onward analysis on the same day. The samples were analyzed using Roche-Hitachi Cobasc311 Chemistry Autoanalyzer (Roche Diagnostics GmbHD-68298 Mannheim Germany). Urinary creatinine was assayed using the kinetic Jaffe method while urinary protein was measured using the turbidimetric method.[16] Both urine protein and urine creatinine were converted to mg/dl and their ratio obtained. Significant proteinuria was defined as dipstick proteinuria ≥30mg/dl and UPr/UCr ratio ≥ 0.2mg/mg, respectively while nephrotic range proteinuria was defined as dipstick proteinuria ≥ 300 mg/dl and UPr/UCr ratio ≥ 2.0 mg/mg, respectively.[10]

Ethical approval was obtained from the Oyo State Research Ethical Review Committee, Ministry of Health, Secretariat, Ibadan with approval number/Ref.AD13/479/623. Permission with Ref: INS 75T/163 was obtained from the Ministry of Education, Science and Technology Quality Assurance Department, Oyo

State Secretariat, Ibadan, Nigeria. Parental consent and assent of emancipated minor was gotten prior to recruitment. All information obtained from the participants were kept strictly confidential.

Data analysis

Data collected on the study proforma were entered into a Microsoft access file and analysed using IBM Corp Statistical Package for Social Sciences (SPSS) TM for Windows version 23.0 (Armonk, NY: IBM Corp). Frequencies and proportions were computed for categorical variables. Results were presented in tables and figures such as line graphs for better visualisation of findings. Kappa statistics was used to determine the level of agreement between methods of determining significant proteinuria (dipstick proteinuria and UPr/UCr ratio).17 The differences in the paired proportion of the respective proteinuria detected were compared using McNemar test. The point biserial correlation coefficient was used to determine the relationship between the log transformed urinary protein-creatinine ratio and the dichotomous dipstick urinalysis. The confidence level was set at 95% and $p < 0.05$ level was significant.

Results

Sociodemographic characteristics of the study Subjects

Out of the 1,316 subjects enrolled in the study, 71 were excluded (52 did not produce urine samples and 19 failed to return their questionnaires) giving a response rate of 94.6%. The recruited children were from 16 primary and 4 secondary schools in rural-Ogo-Oluwa and 8 primary and 5 secondary schools in urban-Ogbomoso South LGA. Six hundred and fifty-five (52.7%) of the 1,245 subjects were recruited from the rural settings. The mean age of the study population was 10.6 ± 3.0 years. Five hundred and forty-seven (43.9%) were males.

Results of dipstick urinalysis in study subjects screened for proteinuria

Of the 1,245 subjects who had dipstick urinalysis, only 10 had significant proteinuria giving a proportional prevalence of 0.8% (95% CI: 0.4%-1.5%).Age adjusted prevalence rate was 0.8% (95% CI: 0.4%-1.5%) using the 2006 census population standard. The peak age prevalence of dipstick proteinuria (Figure 2) was at age 12 years [4/160 (2.5%)]. Fifty-eight subjects (4.7%) had leucocyturia while 18(1.4%) tested positive for haematuria. Nitrite was positive in one subject.

Age-specific prevalence of proteinuria among 1245 subjects

Using spot urine protein-creatinine, 224 children had a ratio of ≥ 0.2, placing the crude prevalence of proteinuria at 224/1245 (18.0%; 95% CI: 15.9- 20.2%). The age-adjusted prevalence rate was 20.3% (95% CI: 18.1 - 22.6%) using 2006 census results as population standard. The prevalence of proteinuria had double peak, first at age group 5 year; 23/80-(28.8%) and thereafter at age 15-year 23/96 (24.0%). The prevalence of significant proteinuria reached its nadir at age nine-year 8/80 (10.0%) as shown in Figure 2.

Gender-specific prevalence of proteinuria

Of the 224 subjects with significant proteinuria by UPr/UCr ratio, 140 out of 698 (20.1%) were females while 84 out of 547 (15.4%) were males (p=0.032).Out of the ten subjects with significant proteinuria by dipstick urinalysis, 2/10 (20.0%) were females while 8 of the 10 (80.0%) were males (p=0.026).

Proportion of subjects with nephrotic range proteinuria

Ten (0.8%) of 1,245 had nephrotic range proteinuria giving a crude prevalence of 0.8% (95% CI: 0.4% – 1.5%) by the two methods of assessing for proteinuria. Of these methods, spot UPr/UCr ratio identified 9/10 (90%) while 3/10 (30%) were detected by dipstick method.

Agreement between methods of testing proteinuria

The paired analysis (UPr/UCr and Dipstick) with McNemar test showed a statistically significant difference in the proportion of proteinuria detected by the methods (McNemar; p < 0.001) as shown in Table I. The biserial correlation coefficient was low (r= 0.092; p=0.001).Seven of the ten subjects with significant dipstick urinalysis proteinuria were negative for significant UPr/UCr ratio. The odds for spot urine protein creatinine ratio to detect proteinuria was two times more than the dipstick method. Cohen's Kappa coefficient showed very poor agreement (Kappa = 0.01; 95% CI: -0.015 - 0.036).

Follow up

Of the 224 subjects with significant proteinuria who were followed up for significant proteinuria, only 118 (52.64%) were accessible for further evaluation. One hundred and sixty-two (72.3%) belong to the lower social class. Estimated glomerular filtration rate (eGFR) was 92.81 ± 16.82 ml/min/1.73m2 and 53 (44.5%) had eGFR of less < 90 ml/min/1.73m2. Eight (6.8%) of the subjects were found to have Schistosoma haematobium and were treated with praziquantel. One (0.8%) had E coli urinary tract infection and received antibiotics. Five (4.2%) subjects were hepatitis BsAg positive while two (1.7%) of the students tested positive to Anti HCV. Three (2.5%) of the participants tested positive to HIV rapid diagnostic test, they were further evaluated and enrolled on treatment. Six (5.1%) subjects had haemoglobinopathy on haemoglobin electrophoresis (three with haemoglobin SS, one haemoglobin CC & one haemoglobin SC) and were referred to Paediatric Haematology clinic for further follow up. Seven (5.9%) of the 118 subjects had elevated blood pressure (pre-hypertension), and 4 (3.4%) had hypertension. The four with hypertension are follow up at Paediatric Nephrology Clinic. Five (4.2%) subjects had renal abnormalities on ultrasonography with two having grade II renal parenchymal disease.

Discussion

This appears to be one of the largest community-based study that evaluated the UPr/UCr ratio as a primary marker of renal disease among children in South-western Nigeria. The few available studies that used UPr/UCr ratio recruited few subjects and are hospital-based.[4, 15]

The wide disparity obtained in the present survey between UPr/UCr ratio (18.0%) and dipstick proteinuria (0.8%) support the previously document superiority of UPr/UCr ratio over dipstick proteinuria.[12, 17, 18] The findings in the present study is also in tandem with the reported misclassification of 0.36-3.52g/d proteinuria as a dipstick proteinuria of 15mg/dl to 100mg/dl by Khan *et al*.[18] The wide disparity could also be explained by the inability of the dipstick to detect the presence of different forms of protein in the urine as shown in the AusDiab[19] study. Urine protein-creatinine ratio measures total protein which include all forms of albumin and non-albumin proteins in contrast with the tetrabromophenol blue based manual dipstick urinalysis which is insensitive to the varieties of albumin identified by the UPr/UCr ratio.

A biserial correlation coefficient of 0.092 between the two test methods as obtained in this study is far less than the moderate correlation ($r = 0.6$; $p < 0.001$) observed by Abibtol *et al*[17] in a hospital-based study that involved 64 Caucasian children with nephrotic syndrome. The present study involved subjects in the community with different spectrum of renal diseases that are not limited to nephrotic syndrome to which dipstick urinalysis may be less sensitive.[9] Previous reports showed that dipstick urinalysis in screening for proteinuria missed 8-56% of cases in a sample population, further highlighting a possible reason for the observed disparity.[20–22] The McNemar test of significance for the paired proportions shows 70% discordant result between UPr/UCr and dipstick proteinuria reflecting the higher false positive value for dipstick urinalysis at sub-nephrotic range proteinuria as previously reported.[3,6] The reason could be poor sensitivity of dipstick to proteinuria or its' inability to detect other forms of non-albumin proteinuria.[3, 22]

The 18% prevalence using UPr/Cr ≥ 0.2 found in this study is higher than the average prevalence of 12.2% (1.6-26.4%) in the reviewed studies in Table IIa. The few reported studies in Nigeria (Lagos-6.0% & Calabar-1.6%) and Turkey (7.2%) among apparently healthy children were far lower than the 18.0% observed in this study. This study measured urinary proteinuria by the turbidimerty method found to form a more stable compound[23] with protein compared the unstable compound formed by the sulfosalicylic acid test and Biuret test which is capable of causing a false negative result beside other reasons documented in Table IIa.

The prevalence of 18% (using UPr/UCr ratio) from this study is however lower than the 26.4% prevalence obtained from a mass screening from South Korea by Park *et al*[24] and the 20.5% observed among HIV infected children in Lagos. However, the study by Park *et al*[24] utilized a UPr/UCr ratio cut-off value of ≥ 0.15 compared to ≥ 0.2 in the present study to define significant proteinuria and the high risk nature of the sample population from a mass urinary screening from a school programme.

With respect to dipstick urinalysis proteinuria, the present study's prevalence of 0.8% is lower than the average prevalence of 9.7% (0.6-52.0%) in the reviewed studies in Table IIb. The lower prevalence of 0.8% in this study may due to the use of early morning urine sample capable of obviating orthostatic proteinuria and the lower prevalence of *Schistosomiasis* studied population compared with studies from part of Nigeria and Zimbabwe.[25–27] The age range of children in this study is also younger than the age

distribution of some of the studies from Nigeria and other part of Africa; the prevalence of proteinuria has been reported to rise with age from several reports.[11, 13, 27, 28] However the observed prevalence of 0.8% compares with the reported prevalence from mass urinary screening programme in Japan and South Korea, perhaps the good sample handling and the use of early morning urine may be a plausible explanation for the similarity in result obtained.

The strength of this study includes the fairly large, multistage, population-based study that used UPr/UCr ratio in assessing significant proteinuria in children. The use of early morning urine has the potential to have excluded orthostatic proteinuria and other confounders like exercise induced proteinuria (please add more confounders). This study also used automated means to determine urinary protein and creatinine ratio to obviate inter-observer errors in contrast with other colorimetric and visually assessed turbidometry or precipitates methods. This study could not have excluded subjects with intermittent proteinuria because of the cross-sectional nature of the study design. A longitudinal study with enormous resources would be required to identify subjects with intermittent proteinuria.

In conclusion, asymptomatic proteinuria is quite prevalent among children in South-Western Nigeria. This study confirms the previously reported advantages of UPr/UCr ratio over dipstick in the early detection of asymptomatic proteinuria, which may make it a more appropriate screening tool for renal diseases in children.

Recommendations

1. Health care service providers, School health workers, other appropriate individuals and groups should become more effective in educating the community and creating awareness on renal disease.
2. Broad based screening for renal diseases using urinary protein creatinine ratio should be undertaken from time to time in order to identify children with renal disease early

Declarations

Author Contributions

MAA: Substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; critically revised the manuscript for important intellectual content; gave final approval; agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AOA: Contributed to conception or design; acquisition, analysis, or interpretation of data; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

ROI Critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AIL: Contributed to design; acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Ethics approval was obtained from the Oyo State Research Ethical Review Committee, Ministry of Health Secretariat in Ibadan (Ref.AD13/479/623) and permission (Ref: INS 75T/163) from the ministry of education

Informed Consent

Written informed consent was obtained from all participants for this study

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Tables

Tables I and II are available in the Supplementary Files section.

Figures

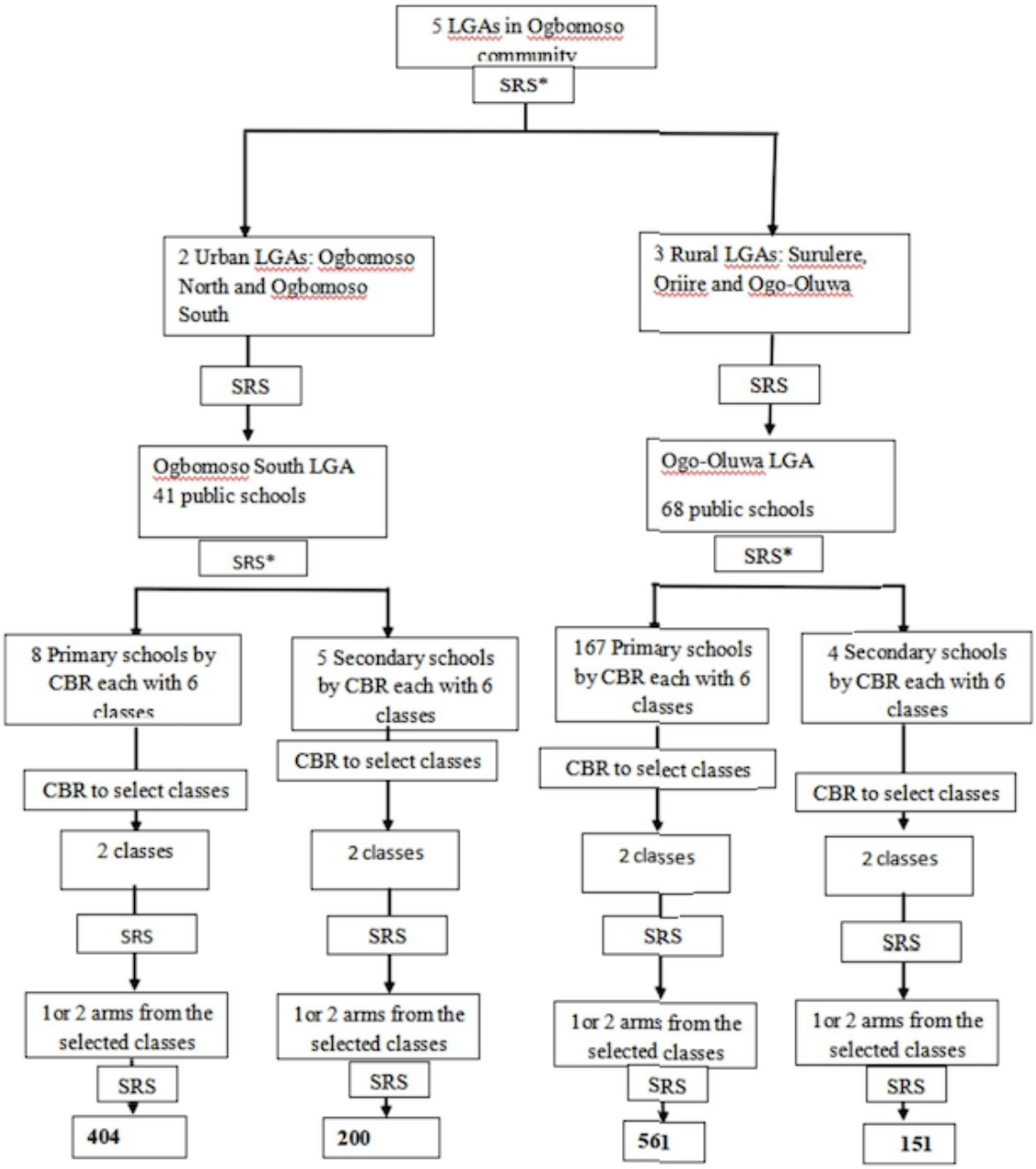

Figure 1. Flow diagram for selection of 1,316 study respondents. (SRS-Simple random sampling, SRS*-Stratified random sampling, CBR-Computer based randomization)

Figure 1

See image above for figure legend.

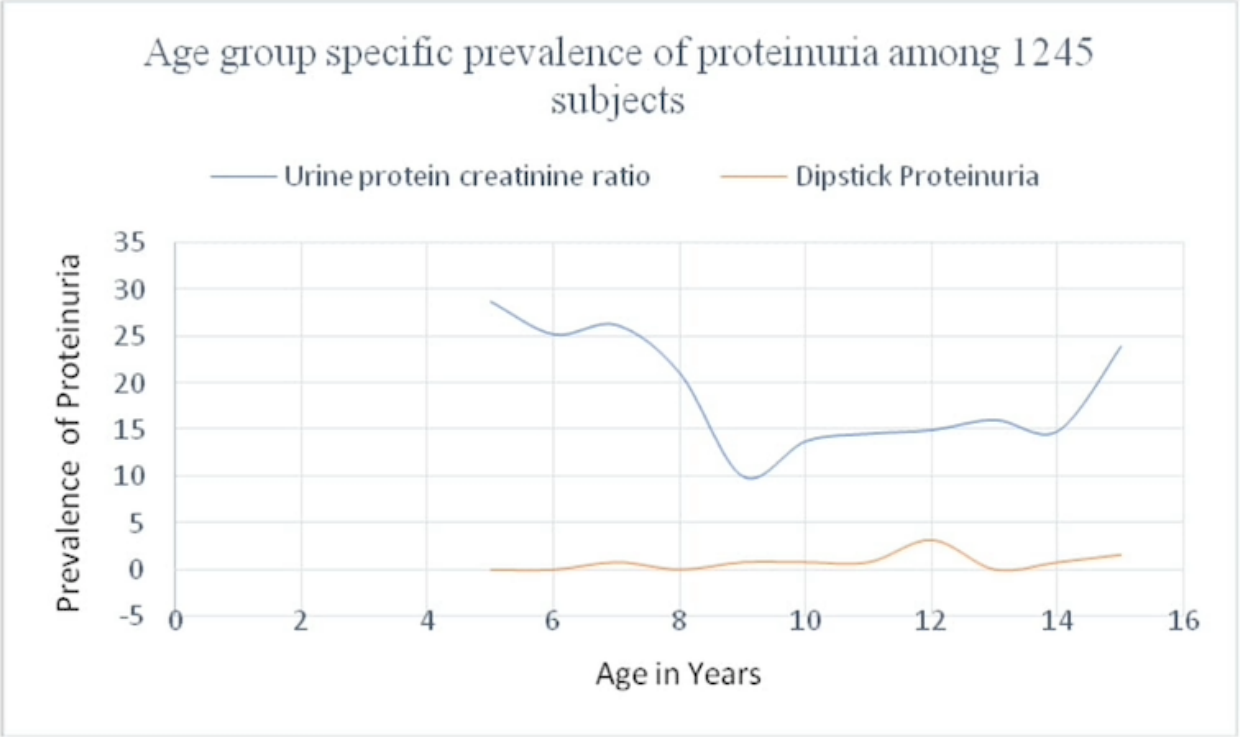

Figure 2: A line graph showing age specific prevalence of significant proteinuria.

Figure 2

See image above for figure legend.

Supplementary Files

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- TableI.png
- TablesComparisonofindexstudywiththeprevalenceofproteinuriainchildhood1.jpg
- TablesComparisonofindexstudywiththeprevalenceofproteinuriainchildhood2.jpg