Original Article

Quantification of Proteinuria with Urinary Protein to Osmolality Ratios in Children

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Abstract

Background: The ratio of urine protein to urine osmolality has recently been suggested as an accurate method to determine proteinuria.

Objective: We studied the correlation of urine protein to urine osmolality ratio with 24-hr urinary protein excretion.

Methods: 150 children aged 0.11–17 years admitted to the Department of Pediatric Nephrology were included in this study. Early morning urine samples and 24-hr urine specimens were collected and analyzed for protein, creatinine, and osmolality. The patients with chronic renal failure were not excluded. Two groups were established: Children with no proteinuria (group 1) and those with proteinuria (group 2).

Results: The optimal cutoff value of abnormal proteinuria and nephrotic range proteinuria was determined to be a protein–osmolality ratio (Up/Uosm) 0.27 and 1.59 mg/l/mOsm respectively. The correlation of 24-hr urinary protein excretion with both urinary protein/creatinine ratio (Up/Ucr) and Up/Uosm was highly significant (p<0.001). According to the receiver operator characteristic (ROC) curves analysis, we found no differences between Up/Uosm and Up/Ucr ratios in detecting either abnormal proteinuria or nephrotic syndrome.

Conclusion: Urine protein to urine osmolality ratio seems to be a simple and a valuable test for the assessment of the degree of proteinuria in children.
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Keywords ● Validity ● Nephrotic syndrome ● Urine concentration ● Pediatric

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Introduction

The amount of protein excreted in urine is an important diagnostic marker. It is commonly used to evaluate the therapeutic response and to predict the progression of renal disease. Therefore, accurate quantitation of daily urinary protein excretion is an important part of nephrological evaluation.[1-3] The most common method for assessing the amount of urinary protein excreted relies on 24-hr urine collections. Nevertheless, obtaining these collections is cumbersome and time-consuming especially in younger children, infants and those suffering of incontinency

Table1: Demographic data and results for children in subgroups (Mean±SD) and in overall (Median; range).				
	Group 1 (n=51)	Group 2 (n=99)	Overall (n=150)	P value
Male:Female (n)	33:18	55:44	88:62	NS
Age (yr)	8.14± 5.0	8.94±4.2	9 (0.11-17)	NS
Weight (kg)	26.8±22	26.9±13.0	24 (3.5-85)	NS
Height (cm)	118±29	123.4±23.0	123 (50-182)	NS
Up/Ucr (mg/dl:mg/dl)	0.17±0.25	4.4±6.1	0.7 (0-42.9)	0.0001
Up/Uosm (mg/l: mOsmol/kg)	0.12±0.22	4.4±5.0	0.6 (0-20.7)	0.0001
24-hr Uprotein (mg/m^2/h)	1.52±1.38	69.8±13.0	13.9 (0-443.3)	0.0001

or enuresis and may be associated with over-collection or under-collection. Ratios of urine protein/osmolality and protein/creatinine in a spot urine sample have been offered as promising tools.[4-9] Excretion patterns of creatinine and protein may vary according to the severity and the type of glomerular disease and in newborns.[10] This may affect on the urinary protein/creatinine ratio. To avoid this problem; we have assessed the validity of urinary protein/osmolality ratio as an indicator of 24-hr urine protein excretion.

Patients and Methods

During a four-month period, 150 children (88 males and 62 females) were admitted to the Department of Pediatric Nephrology of Ali Asghar Children Hospital, affiliated to Iran University of Medical Sciences, Tehran, Iran. All patients with acute infection, who had taken antibiotics and or with a history of recent radio-contrast imaging were excluded from the study. Patients with chronic renal failure were included in both groups. Early morning urine aliquots were sent to laboratory as spot urine specimens for the measurement of urinary protein, creatinine and osmolality. Then 24-hr urine collection started at 08:00, and protein excretion (mg/m^2/hr), creatinine excretion (mg/day) and 24-hr urine volume were measured. The ratios of urine protein/urine osmolality (UP/UOsm) in mg/l/mOsm/kg and urine protein/creatinine (UP/UCr) were then calculated.

These children were then categorized according to proteinuria. Group 1, children with no proteinuria; and group 2, those with proteinuria exceeding 4 mg/m^2/hr. A cutoff point of 40 mg/m^2/hr measured in 24-hr urine was used to define nephrotic protein excretion. The protein concentration was measured by the quantitative turbidometric method using sulfosalicylic acid.[11] The creatinine concentration was measured by Jaffe method and urine osmolality by freezing point depression method.[12] The normal urinary creatinine excretion was estimated to be 500–800 mg/m^2/day.

Statistical analysis

Data are presented as means±SD. Independent Student's t test was used to compare the means of the two groups. Data was analyzed using log-linear regression to find linear correlation. Receiver operator characteristic (ROC) curves were generated to assess the appropriate cutoff point of UP/UOsm and UP/UCr ratios. The negative (NPV) and positive predictive value (PPV) of these ratios were calculated and P<0.05 was considered as statistically significant.

Results

150 children from the Pediatric Nephrology Department were found eligible to have their data entered. Demographic data concerning these children are listed in Table 1. The data are presented as median (range) for whole population and mean±SD for subgroups. By log regression analysis in total population, a significant correlation was found between 24-hr Up, Up/Ucr (r=0.64, p<0.01) and Up/Uosm (r=0.56, p<0.0001).

As shown in Table 1, there were no significant differences between two subgroups for age, sex, body weight and height. 24-hr urinary protein excretion in group 1 had no significant correlation with UP/UCr (r=0.02, p=0.27). However, it seemed that it had a low correlation with UP/UOsm (r=0.003, p=0.07). 58 out of 99 patients of group 2 had proteinuria in nephrotic range, the correlation coefficients between 24-hr urine protein excretion and UP/UCr in early morning urine specimen (r=0.75, p<0.0001), and UP/UOsm (r=0.79, p<0.0001) were significant.

ROC curve analyses revealed cutoff points of 1.02 for Up/Ucr and 1.58 (mg/l/mOsmol/kg H$_2$O) for Up/Uosm to diagnose the proteinuria in the nephrotic range. The same analysis showed cutoff values of 0.48, and 0.27 (mg/l/mOsmol/kg H$_2$O) respectively, to discriminate the normal from abnormal protein excretion (Table2).

The specificity, sensitivity, PPV and NPV of UP/UCr and UP/UOsm for diagnosis of abnormal proteinuria (>4 mg/m^2/h) and nephrotic

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Table 2: Comparison of the results for spot urine protein to osmolality vs. urine protein to creatinine reported in the literature.

Authors (n) Method of detecting protein	Cut off Point Up/Uosm (Up/Ucr)		Sensitivity %	Specificity %	NPV %	PPV %
Kim[5](53)	P	0.23 (0.18)*	NA	NA	93.5 (90)	100 (100)
Turbidometric	N	1.9 (1.5)*	NA	NA	97.5 (90)	92.3 (100)
	P	0.16 (0.15)	81.3 (81.3)	83.7 (76)	NA	NA
Serdaroglu [6] (177) NA	N	1.44	100	94.4	NA	NA
Morgenstern [13] (284)	<2 yr P	0.15				
Pyrogallol red molybdate	2-8 yr P	0.14 (0.2)	90.3 (96.6)	89.7 (96.3)	93.5 (97.8)	85 (94.4)
	>8yr P	0.17 (0.2)				
This study (150)	P	0.27 (0.48)	88.2 (92.2)	88 (81.8)	93.5 (95.3)	79 (72.3)
Turbidometric	N	1.59 (1.02)	89.7 (89.7)	90.2 (84.8)	93.3 (93)	85.2 (79)

P= proteinuria, N= nephrotic, NA= not available, NPV=negative and PPV=positive predictive value,
Up/Ucr=Urine protein to urine creatinine ratio
*used Houser's data for cut off value,[15]

range proteinuria (>40 mg/m^2/h) were calculated. Sensitivity of 92.2% (CI$_{95\%}$: 81–97.8) and a NPV of 95.3% for Up/Ucr were higher than those for Up/Uosm (sensitivity: 88.25% [CI$_{95\%}$: 76–95.5]; NPV: 93.5%). On the other hand, the specificity of 88% (CI$_{95\%}$: 80–93.6) and a PPV of 79% for Up/Uosm were much better than those for Up/Ucr (sensitivity: 81.8% [CI$_{95\%}$: 72.8–88.8]; PPV: 72.3%) for detecting proteinuria. For proteinuria in the nephrotic range (>40 mg/m^2/h), both Up/Uosm and Up/Ucr ratios showed equal sensitivity of 89.7% (CI$_{95\%}$: 78.8–96.1) and NPV of 93%. The former, however [90.2(82.2-95.4) & 85.2] had a higher specificity of 84.8% (CI$_{95\%}$: 75.8–91.4) and PPV of 79% than the latter index (Table2).
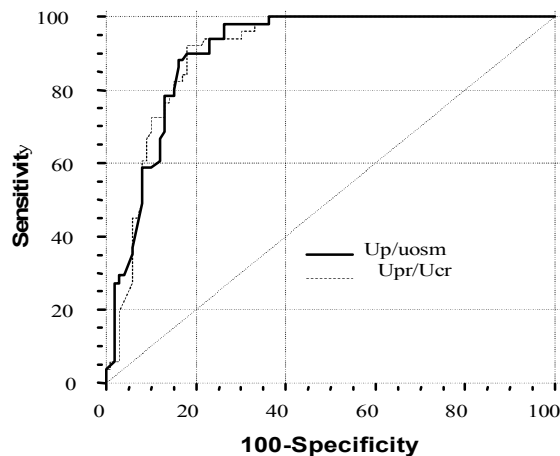
ROC curves generated for Up/Uosm and Up/Ucr ratios are shown in Fig 1. The graph shows that there was no significant difference between these ratios at predicting abnormal amounts of proteinuria in children.

Discussion

Measurement of proteinuria is important for the accurate diagnosis of renal disease and in follow-up of response to therapy .The most commonly used method for quantitation urinary protein is still 24-hr urine collection. The test however is time-consuming and may be associated with remarkable collection errors—especially in newborns and infants and children with enuresis and incontinency.

Recently spot urine sample is suggested to be used to detect and monitor proteinuria in children and adults.[14] Up/Ucr ratio in single voided sample is a simple index of 24-hr urine protein level. Random Up/Ucr ratio is affected by age, gender, body size and hydration.[14] To correct for the changes in urine hydration-dehydration, a random spot Up/Uosm ratio has been suggested. As shown in Table 2, there are few investigations for random Up/Uosm. We found a cutoff point of 0.27 for the diagnosis of abnormal proteinuria. This figure is close to that reported by Kim et al.[5] Reported cutoff points might be different since different methods for detection of proteinuria were used. In our study, the distribution of cases was not normal; the patients with renal failure were not excluded and according to turbidometric method we found a higher cutoff point value as compared with other results. In our study, the NPV and sensitivity of Up/Uosm was lesser than that of Up/Ucr to evaluate abnormal proteinuria. They were, however equal in detecting nephrotic proteinuria. The PPV and specificity of Up/Uosm exceed those of Up/Ucr for diagnosis of the abnormal proteinuria and nephrotic syndrome (Table 2). Kim *et al,* found that NPV for Up/Uosm ratio was better than that of Up/Ucr ratio and the PPV was 100% for both ratios in distinguishing normal from abnormal proteinuria.[5] Serdaroglu, however, reported a higher specificity for Up/Uosm ratio.[6] Morgentein and colleagues reported a higher validity for Up/Ucr and argued that inconstant osmole excretion and effect of body size of children on defining the normal value versus adults may play a role in diminishing the validity of Up/Uosm vs. Up/Ucr.[13] Based on ROC curve comparison, they concluded that Up/Ucr ratio was superior to Up/Uosm ratio in predicting abnormal proteinuria in young children.[13] In our study, both ratios were significantly correlated with 24-hr urine protein

Difference between areas= 0.002
Standard error= 0.020
95% Confidence interval= -0.038 to 0.042
Significance level P = 0.918

Fig1: Comparison of ROC curves for Up/Uosm and Up/Ucr in children with proteinuria (24-h Uprotein >4mg/kg/h)

excretion. According to ROC curves, we found no differences between these two ratios in detecting either abnormal proteinuria or nephrotic syndrome (Fig 1).

In conclusion, both Up/Uosm ratio and Up/Ucr ratio measured in random urine specimen are good predictors of 24-hr urinary total protein excretion.

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