ORIGINAL ARTICLE

# Quantification of proteinuria with urinary protein to osmolality ratios in children with and without renal insufficiency

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**BACKGROUND:** Spot urine is recommended as an accurate method to determine proteinuria in children and adults. However, urinary excretion of creatinine may vary in newborns and spot urine may be influenced by the hydration-dehydration condition of patients. The study was done to assess the validity of the urine protein to osmolality ratio versus the urine protein to creatinine ratio in health and disease conditions.

**METHODS:** We studied the correlation of the urine protein-osmolality ratio (Uprot/Uosm) and the urine protein to creatinine ratio (Up/Ucr ) and compared results with the 24-hour urinary protein excretion. Three groups were compared: children with normal renal function and without proteinuria (group 1, n=53), children with normal renal function and with proteinuria (group 2, n=52) and patients with renal insufficiency (group 3, n=45). Early morning urine samples and 24-hour urine specimens were collected for protein, creatinine, and osmolality.

**RESULTS:** The optimal cutoff value of the Uprot/Uosm ratio was determined to be 0.33 mg/L/mosm/kgH2O for abnormal proteinuria and 1.75 mg/L/mosm/kgH2O for nephrotic range proteinuria. In comparing ROC curves, we found no differences between the Uprot/Uosm and Up/Ucr ratios in detecting abnormal proteinuria or nephrotic syndrome in children with normal or decreased renal function ($P$>0.05).

**CONCLUSION:** Both the Uprot/Uosm and Up/Ucr ratios from random urine specimens are good predictors of 24-hour urinary total protein excretion in children with and without renal insufficiency.

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A small amount of protein is normally excreted in urine. The hallmark of kidney disease is increased urinary protein excretion beyond the amount normally excreted. Monitoring proteinuria is valuable in evaluating response to therapy and in predicting the progression of renal damage. Therefore, accurate detection of daily urinary protein excretion is an important part of nephrological evaluation.[1,2,3] Timed urine collection is the most common method for assessing urinary protein. Collecting these specimens accurately is difficult and time consuming, especially in infants and in patients suffering from incontinency or enuresis. Ratios of protein to osmolality[5,6] and protein to creatinine in single-voided urine specimens have been offered as appropriate tools for assessing urinary protein.[4,7,8,9] Urinary excretion of creatinine may vary in newborns[10] and spot urine may be influenced by the hydration-dehydration condition of patients. To avoid the problem of variability in creatinine excretion, we used the urinary protein-osmolaity ratio (Uprot/Uosm) versus urinary protein to creatinine ratio

(Uprot/Ucr) to compare their validity as indices of 24-hour urine protein level in children with normal renal function and renal failure.

## Methods

Between 2001 and 2003, 150 hospitalized children were included in our study. Early morning urine specimens were collected as spot urine and measured for urinary protein (mg/dL), creatinine (mg/dL) and osmolality (mosmol/kgH2O) to calculate protein to osmolality (Uprot/Uosm) (mg/l/mosm/kg H2O) and protein to creatinine (UProt/UCr) ratios. The same day, 24-hour urines were collected from 9 am to 9 am. Protein excretion (mg/m$^2$/h), creatinine excretion (mg/day) and volume (mL) of 24-hour urinary specimens were measured. Blood samples were drawn for serum creatinine (mg/dL).

The protein concentration was measured by the quantitative turbimetric method using sulfosalicylic acid. The creatinine concentration was measured by the Jaffe method and urine osmolality was measured by the freezing point depression methodology. The normal urinary creatinine excretion was estimated to be between 500 and 800 mg/m$^2$/day. Proteinuria was defined by protein excretion >4 mg/m$^2$/h and the cut off point 40 mg/m$^2$/h used to define nephrotic protein excretion using a 24-hour urine. Renal insufficiency was defined by glomerular filtration rate < 80 mL/min/1.73m$^2$ using UV/P formula. We divided the children in three groups based on renal function and proteinuria: children with normal renal function without proteinuria (group 1) and with proteinuria (group 2) and children with renal insufficiency (group 3). Student's t test was used to compare means. Receiver operator characteristic (ROC) curves were generated to assess the sensitivities and specificities and the negative predictive value (NPV) and the positive predictive value (PPV) of UProt/UOsm and UProt/UCr ratios. A P value of less than 0.05 was considered significant.

## Results

Demographic and clinical data for the 150 children are shown in Table 1. Table 2 shows the urinary excretion of protein, creatinine and osmolality. Overall Uprot/Ucr had higher sensitivity, specificity, positive predictive value and negative predictive value for detection of abnormal proteinuria. Uprot/Uosm showed higher specificity and PPV for detection of nephrotic range proteinuria, and this result did not differ by adding or excluding the renal insufficiency group. The cut-off point for detecting nephrotic range proteinuria was lower in the whole population compared to those without renal insufficiency. This decrement was remarkable for Up/Ucr (Table 3).

ROC curves generated to compare Uprot/Uosm and Up/Ucr ratios showed no significant differences between these ratios ($P$>0.05) (Figure 1).

## Discussion

According to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, a spot urine sample should be used to evaluate proteinuria in children and adults.[12] A random urinary protein-to-creatinine ratio has been suggested as the suitable method to quantify proteinuria in diabetes and renal insufficiency. In many centers, sulfosalicylic acid turbidimetric assessments are used to measure proteinuria. This test is sensitive to the concentration of urine. On the other hand, daily creatinine excretion is constant in normal subjects, but is variable during the neonatal period.[10] Progression of renal failure increases urinary creatinine excretion.

Creatinine is measured by the Jaffe method, which is influenced by some noncreatinine chromogenes. Conversely, the measurement of urine osmolality is a valuable test for estimating concentration ability of the kidney. The test is based on the number of particles in solution. When glomerular filtration declines, the number of osmoles excreted per nephron increases, leading to osmotic diuresis.[13] Kim et al reported cutoff values for protein-to-osmolality ratios of 0.23 for abnormal proteinuria (NPV 93.5% and PPV 100%) and 1.9 for nephrotic range proteinuria (NPV, 97.5% and PPV, 92.3%).[5] The Uprot/Uosm ratio of 0.16 (sensitivity, 81.3% and specificity, 83.4%) and 1.44 (sensitivity, 100% and specificity, 94.4%) was determined by Serdaroglu et al[6] for defining proteinuria and nephrotic range proteinuria, respectively. Optimal values for detecting abnormal protein excretion at different ages, according Morgenstern et al[11] were a Uprot/Uosm of 0.15 (<2 years), 0.14 (2-8 years), 0.17 (>8 years). Comparing ROC curves, they concluded that the protein-creatinine ratio was superior to protein-osmolality ratio in predicting abnormal proteinuria in young children. We found a higher cut-off point for the Uprot/Uosm ratio compared with previous studies. This difference is due to the various laboratory methods of measuring protein. By including patients with renal failure, the cut-off point of Uprot/Ucr and Uprot/Uosm in detecting nephrotic range proteinuria decreased. This decrement was remarkable in

**Table 1.** Demographic and clinical data of patients with and without renal insufficiency (Group 1: normal renal function without proteinuria; Group 2: normal renal function with proteinuria; Group 3: renal insufficiency).

| | Group 1 Mean (SD) n= 53 | Group 2 Mean (SD) n= 52 | Group 3 Mean (SD) n=45 | *P* value |
|---|---|---|---|---|
| Age (y) | 7.41(4.9) | 8.47(4.08) | 10.49 (3.83) | 0.001 |
| M:F | 31:22 | 28:24 | 29:16 | NS* |
| S Cr (mg/dl) | 0.58 (0.15) | 0.6 (0.14) | 2.69 (2.3) | 0.0001 |
| Weight (Kg) | 24.73 (15.26) | 27.17 (13.3) | 28.53 (12.13) | NS |
| Height (cm) | 114.93 (29.27) | 122.46 (21.18) | 129.3 (21.5) | 0.01 |

*Chi square test

**Table 2.** Urinary excretion of protein, creatinine and osmolality in 24-hour urinary collection and spot urine samples (Group 1, normal renal function without proteinuria; Group 2, normal renal function with proteinuria; Group 3, renal insufficiency).

| | All children | Group 1 | Group 2 | Group 3 | *P* value* |
|---|---|---|---|---|---|
| 24-h urinary protein (mg) | 263 (0-11986) | 31 (0-134) | 1490 (176-11986) | 766 (4-8800) | 0.0001 |
| 24-h urinary creatinine (mg) | 425 (120-2750) | 420 (184-1324) | 445 (120-2738) | 368 (490-1227) | NS |
| 24-h urinary volume (mL) | 820 (40-4610) | 750 (400-4120) | 852 (1500-4610) | 850 (170-3440) | NS |
| Urinary protein (mg/dL) | | 2.3 (0-240) | 225 (1-1700) | 68 (1-760) | 0.0001 |
| Urinary creatinine (mg/dL) | | 46 (4-220) | 52 (1.4-260) | 49 (8-198) | NS |
| Urinary osmolality (mg/L/osmol/kgH2O) | | 442 (119-1270) | 554 (189-1197) | 312 (76-809) | 0.03 |
| Urinary protein to urinary creatinine ratio | | 0.07 (0-3.33) | 3.91 (0.006-42.8) | 1.1 (0.003-17.5) | 0.0001 |
| Urinary protein to urinary osmolality ratio | 0.71 (0-43) | 0.03 (0-2.5) | 3.98 (0.01-19.4) | 1.4 (0.02-20.68) | 0.0001 |

* NPr median test
Data are median (range)

**Table 3.** Urinary protein-urinary creatinine ratio (Uprot/Uosm) versus urinary protein-urinary creatinine ratio (Uprot/Ucr) in patients with and without renal insufficiency.

| | | Cut-off point | Sensitivity (%) | Specificity | NPV | PPV | *P* value |
|---|---|---|---|---|---|---|---|
| Proteinuria (Group 2) | | | | | | | |
| Uprot/Uosm | NRF | 0.32 | 77.8 (40.1-96.5) | 83.3 (67.2-93.6) | 93.8 | 53.8 | NS |
| | Total | 0.33 | 82.3 (70.5-90.8) | 83.0 (73.4-90.1) | 86.9 | 77.3 | |
| Uprot/Ucr | NRF | 0.48 | 90.6 (79.3-96.8) | 88.5 (76.5-95.6) | 90.2 | 76.8 | |
| | Total | 0.5 | 87.1 (76.1-94.2) | 86.4 (77.4-92.7) | 90.5 | 88.9 | |
| Nephrosis (Group 3) | | | | | | | |
| Uprot/Uosm | NRF | 1.75 | 88.2 (72.5-96.6) | 95.0 (86.1-98.9) | 93.4 | 90.9 | NS |
| | Total | 1.58 | 83.6 (71.2-92.2) | 90.5 (82.8-95.6) | 90.5 | 83.6 | |
| Uprot/Ucr | NRF | 1.41 | 94.1 (80.3-99.1) | 88.7 (79.0-95.0) | 96.9 | 80 | |
| | Total | 1.02 | 92.7 (82,4-97.9) | 84.2 (75.3-90.9) | 95.2 | 77.3 | |

NRF: normal renal function, RF: renal failure, NS: not significant, NPV: negative predictive value, PPV: positive predictive value (values expressed as percentage with 95% confidence interval)

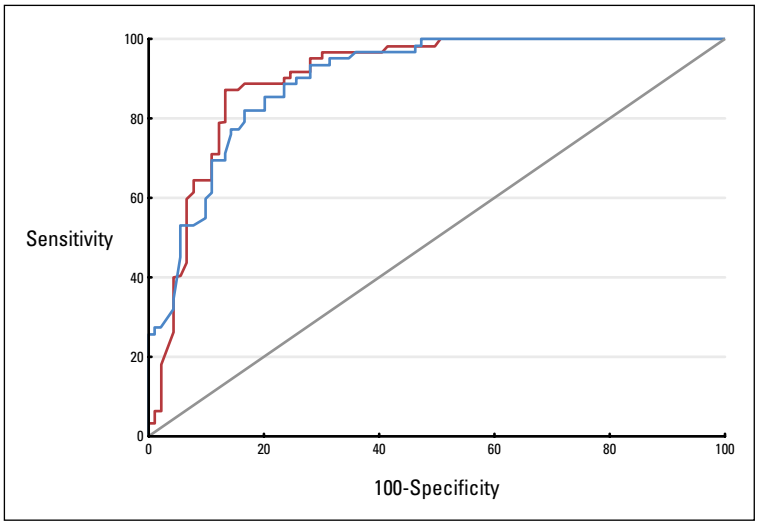


**Figure 1.** Comparison of receiver operating curves for urinary protein to urinary osmolality ratio versus urinary protein to urinary creatinine ratio

the Uprot/Uosm ratio, which was caused by the increment in urinary creatinine excretion and the osmolar load in renal failure, which influences the denominator.

In our study, the NPV and PPV of Uprot/Uosm was less than that of Uprot/Ucr in evaluating abnormal proteinuria. Whereas the PPV of Uprot/Uosm exceeded that of Uprot/Ucr in the diagnosis of nephrotic syndrome (Table 3). According to the ROC curve comparison we found no differences between these two ratios in detecting abnormal proteinuria or nephrotic syndrome.

In conclusion, both the Uprot/Uosm and Uprot/Ucr ratios in random urine specimen are good predictors of 24-hour urinary total protein excretion in patients with and without renal insufficiency.

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