Paediatrica Indonesiana

VOLUME 49 November • 2009 NUMBER 6

Original Article

Diagnostic accuracy of single-voided urine protein/creatinine ratio for proteinuria assessment in children with nephrotic syndrome

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Abstract

Background Measurement of protein excretion is not only used for diagnostic purpose but also to monitor disease severity and prognosis in children with nephrotic syndrome (NS). The common method to measure proteinuria is 24-hour urine collection. However, 24-hour urine collection is cumbersome, time consuming, and tedious. An alternative simplified method is the measurement of protein/creatinine ratio in single-voided urine specimens.

Objective The aim of this study was to determine whether urine protein/creatinine ratio is accurate to predict pathologic (>100 mg/m^2/day) and massive proteinuria (>1 g/m^2/day).

Methods Seventy single voided and 24-hour urine specimens were collected from children aged 3-18 years. The relationship between urinary protein/creatinine ratio and total daily protein excretion was calculated using correlation and linear regression analysis. Diagnostic test was conducted to estimate the accuracy of protein/creatinine ratio for the diagnosis of pathologic and massive proteinuria in NS.

Results Correlation coefficient between quantity of protein in 24-hour urine specimens and protein/creatinine ratio in single-voided urine specimens was 0.96 (R^2=0.93). Both sensitivity and specificity of urinary protein/creatinine ratio were 87% in diagnosing pathologic proteinuria, whereas the sensitivity and specificity of the ratio to predict massive proteinuria were 88% and 91%, respectively.

Conclusion The urinary protein/creatinine ratio in single voided urine specimen has a good accuracy to predict pathologic and massive proteinuria in children with NS aged 3-18 years. **[Paediatr Indones. 2009;49:355-8]**.

Keywords: *proteinuria, nephrotic syndrome, protein/creatinine ratio*

Measurement of proteinuria has become more than just a diagnostic test for children with renal disease. The level of proteinuria is not only an important determinant for disease severity, but is also used to assess the effects of treatment and prognosis.[1,2] Healthy children have small amount of protein in their urine referred as physiologic proteinuria.[3] The normal rate of protein excretion in children is <4 mg/m^2/hour or <100 mg/m^2/day.[4] Proteinuria exceeding the normal value is considered as pathologic proteinuria.

The underlying pathologic process of nephrotic syndrome (NS) is inability of glomerular capillary wall to restrict the urinary loss of protein.[5] The annual incidence of NS in Indonesia is six per 100,000 children.[6] This chronic disease has many undesirable impacts, not only for the affected children but also for their families.[5,7] Nephrotic syndrome is characterized by massive proteinuria, defined as proteinuria exceeds 1 g/m^2/day.[5] Therefore, proteinuria is an important marker for children with NS.

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The standard method to measure protein excretion is 24-hour urine collection. However, 24-hour collection is cumbersome, time consuming, and inconvenient, so that this method can be fraught with problems.[3] The current evidence suggests that protein/creatinine ratio may represent 24-hour protein excretion.[1,8] Our purpose was to determine the accuracy of protein/creatinine ratio in single-voided urine specimen to predict pathologic proteinuria (>100 mg/m^2/day) and massive proteinuria (>1 g/m^2/day) in children with NS.

Methods

A cross-sectional study was conducted at inpatient and outpatient pediatric ward, Sardjito General Hospital, Yogyakarta. A consecutive sampling method was used to collect the subjects from January 2006 to December 2006. Signed informed consent was obtained from the parents of each child. We included all urine specimens from children aged 3-18 years with NS, either newly diagnosed, in relapse, or in remission. We excluded urine specimens from children who had glomerular filtration rate <10 ml/minute/1.73 m^2, had recently used drugs that altered creatinine excretion (cimetidin, pyrimethamine, salycilate, and trimethoprime), severely malnourished, and unabled to collect 24-hour urine specimens completely.

Antrophometric data were obtained from each child to determine the nutritional status according to WHO growth standards. In children with edema, we used upper arm circumference rather than body weight to assess the nutritional status.

Patients were asked to begin the 24-hour urine collection immediately after completing the first voiding in the morning and to collect all urine for 24 hours. We obtained 5 ml of urine specimens from the last final void at the completion of the 24 hour period. Twenty-four hour urine specimens were used for total daily urine measurement and 5 ml spot urine specimens for protein/creatinine urine determination. In order to avoid 24-hour urine collection error, written instructions were given to each of the parents. Each patient provided 5 ml blood sample for serum creatinine measurement to estimate the glomerular filtration rate.

Protein and creatinine urine measurement was performed at Sardjito Hospital Clinical Pathology Laboratory. Quantification of proteinuria was determined by using spectrophotometer and Biuret reagent. We used Autoanalyzer VITROS System for serum and urine creatinine measurement with Jaffe method. The urinary protein/creatinine ratio was calculated by dividing the urinary protein concentration (mg/dl) by the urine creatinine concentration (mg/dl). Glomerular filtration rate was calculated by using the Haycock-Schwartz formula.

The relationship between urinary protein/creatinine ratio and total daily protein excretion was studied using correlation and linear regression analysis. Since the protein/creatinine ratio and 24-hour urine protein were expressed in numerical scales, receiver operator characteristic (ROC) curves was used to determine the cut-off values of urinary protein/creatinine ratio. Accuracy of protein/creatinine ratio in single voided urine specimens was determined by calculating sensitivity, specificity, positive and negative predictive values, and likelihood ratio.

Results

A total of 70 paired urine specimens from 47 eligible children was collected during the study period. We collected another pair of urine specimens from the same subjects when there were alterations in their clinical course of the disease (became remission or relapse). Thus, there were twenty-three patients provided two pairs of urine specimens. Of 47 children enrolled in this study, 62% were male (**Table 1**). This data is appropriate with epidemiology of NS, whereas male to female ratio is ranging from 2:1 to 3:2.[6] Pathologic proteinuria was found in 56% urine specimens and 23% of all urine specimens contained massive proteinuria.

Table 1. Baseline characteristic of the children with NS

Variable	n (%)
Sex	
Male	29 (62)
Female	18 (38)
Age	
5-8 years	14 (30)
9-12 years	20 (42)
13-16 years	13 (28)
Nutritional state	
Overweight	1 (2)
Normal	34 (72)
Wasted	12(26)

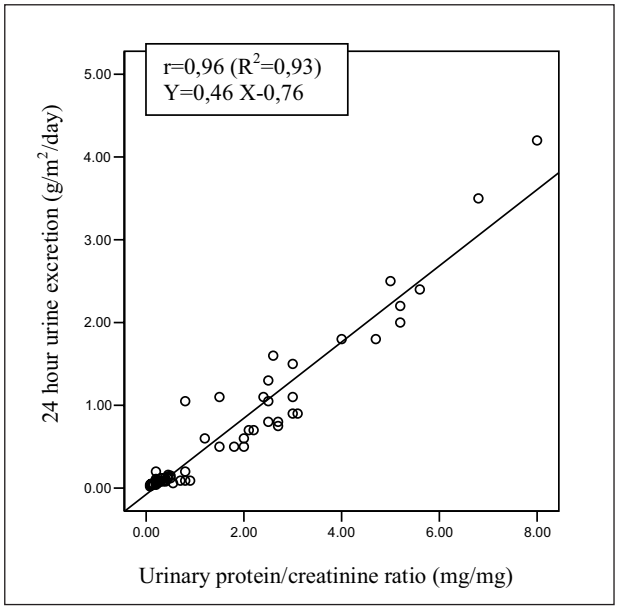

Figure 1. Scatter plot of urinary protein/creatinine ratio and 24 hour urine protein excretion

Table 2. Accuracy of urinary protein/creatinine ratio to detect pathologic proteinuria

	Value	95% CI
Sensitivity	87%	77% to 98%
Specificity	87%	75% to 99%
Positive predictive value	89%	80% to 99%
Negative predictive value	84%	72% to 97%
Positive likelihood ratio	6.76	2.7 to 17
Negative likelihood ratio	0.15	0.06 to 0.34

Table 3. Accuracy of urinary protein/creatinine ratio to detect massive proteinuria

	Value	95% CI
Sensitivity	88%	71% to 100%
Specificity	91%	83% to 98%
Positive predictive value	74%	54% to 93%
Negative predictive value	96%	91% to 100%
Positive likelihood ratio	9.45	4 to 22.2
Negative likelihood ratio	0.14	0.04 to 0.51

The correlation coefficient between urinary protein/creatinine ratio and 24-hour total urine protein was 0.96 (R^2=0.93). Total urinary protein excretion could be estimated by using regression equation obtained from the analysis (**Figure 1**).

By using the ROC curves, urinary protein/creatinine ratio cut-off values of 0.4 and 2.3 reliably predicted pathologic and massive proteinuria, respectively. The diagnostic values of urinary protein/creatinine ratio are showed in **Table 2** and **Table 3**.

Discussion

The concentration of protein in urine varies during the day. Therefore, 24-hour urine collection is required to quantify the amount of total protein excretion. The main reason for changes in protein concentration is variation in the amount of water excreted.[1,9] To support this hypothesis, several studies have demonstrated a smaller variation in the protein/creatinine ratio compared with the protein concentration alone in urine specimens collected throughout the day. Newman et al[10] found that the variation in the protein/creatinine ratio was much smaller than in protein concentration alone.[10] Based on this data, protein/creatinine can be used as an alternative diagnostic tool for urine protein measurement.

The relationship between protein/creatinine ratio in single voided urine specimen and 24-hour protein excretion was established using correlation and linear regression analysis before the diagnostic values calculation. We found a strong correlation between urinary protein/creatinine ratio and 24-hour urine total protein (r=0.96; R^2=0.93). This result is similar with other study from different settings and subjects, such as in hypertensive pregnant women,[11] in adults with renal diseases,[1] and in patients with nephritis lupus.[12] The 24-hour protein excretion can be calculated from urinary protein/creatinine ratio using a formula from regression equation:

Total 24-hour protein excretion =
(0.459 x protein/creatinine ratio)-0.76

The strong linear association between the protein/creatinine ratio in single voided urine specimen and 24-hour protein excretion indicated that the ratio could be used as a reliable indicator of total protein excretion.[1]

Cut-off values should be established before calculating the diagnostic value of urinary protein/creatinine ratio. Using ROC curves, we can precisely choose the appropriate cut-off point depend on the type of the diagnostic test. If false positive labeling is very harmful, specific diagnostic tool is preferred. If false negative misses are dangerous,

then more sensitive rather than specific diagnostic tool is selected.[13] In the case of NS, the harm that occurs from false positive and false negative is equal, therefore, both sensitive and specific diagnostic method is similarly important. The cut-off protein/creatinine ratio of > 0.4 has the best sensitivity and specificity to predict pathologic proteinuria. Massive proteinuria could be diagnosed using cut-off protein/creatinine ratio of 2.3. Abitbol et al[14] used a different cut-off protein/creatinine ratio compared to this study. They reported using cut-off point of 0.1 and 1 to estimate pathologic and massive proteinuria, respectively. However, they did not used ROC curves to obtain the exact values. Moreover, the difference in these cut-off values might be due to different research settings and samples as well.

Both sensitivity and specificity of urinary protein/creatinine ratio were equally 87% for the diagnosis of pathologic proteinuria, whereas the sensitivity and specificity of the ratio to predict massive proteinuria were 88% and 91%, respectively. The positive likelihood ratios in this study were 6.76 to diagnose pathologic proteinuria, and 9.45 to diagnose massive proteinuria. Positive likelihood ratio refers to the possibility of the person with disease gets a positive result compared with possibility of the healthy person gets the same result. The likelihood ratios > 5 are indicative of strong diagnostic method. Hence, this study indicates that protein/creatinine ratio is a reliable diagnostic tool for proteinuria.

High protein diet might increase the creatinine excretion as much as 5-9%. However, considering that diet restriction will be impractical to be implemented in daily clinical setting, we did not restrict the protein diet of the subjects. The correlation between protein/creatinine ratio and 24-hour urine protein excretion is significant despite of the free diet.

This present study is demonstrated a good accuracy of protein/creatinine ratio in single voided urine specimen to predict pathologic and massive proteinuria in children with NS aged 3-18 years.

References

1. Price CP, Newall RG, Boyd JC. Use of protein: creatinine ratio measurements on random urine specimens for prediction of significant proteinuria: a systematic review. Clin Chem. 2005;51:1577-86.
2. Eknoyan G. On testing for proteinuria: time for a methodical approach. Cleve Clin J Med. 2003;70:493-501.
3. Milford DV, Robson AM. The child with abnormal urinalysis, haematuria, and/or proteinuria. In: Webb N, Postlethwaite R, editors. Clinical pediatric nephrology. 3rd edition. New York: Oxford; 2003.
4. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the national kidney foundation conference on proteinuria, albuminuria, risk, assessment, detection, and eliminati (PARADE). Pediatrics. 2000;105:1242-9.
5. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res. 2005;122:13-28.
6. Wila Wirya IGN. Sindroma nefrotik. In: Tambunan T, Trihono P, Pardede SO, Alatas H, editors. Buku ajar nefrologi anak. Vol. II. Jakarta: Balai Penerbit FKUI; 1999.
7. Roth KS, Amaker BH, Chan JCM. Nephrotic syndrome: pathogenesis and management. Pediatr Rev. 2002;23:237-48.
8. Mustafa G, Khan PA, Iqbal I, Hussain Z, Iqbal MM. Simplified quantification of urinary protein excretion in children with nephrotic syndrome. J Coll Physicians Surg Pak. 2007;17:615-8.
9. Levey AS, Coresh J, Balk E, Kausz A, Levin A, Steffes MW, et al. National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137-47.
10. Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM. Urinary protein and albumin excretion corrected by creatinine and specific gravity. Clin Chim Acta. 2000;294:139–55.
11. Cote AM, Brown MA, Lam E. Diagnostic accuracy of urinary spot protein/ creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ. 2008;336:1003-6.
12. Leung YY, Szeto CC, Tam LS. Urine protein-to-creatinine ratio in an un-timed urine collection is a reliable measure of proteinuria in lupus nephritis. Rheumatology. 2007;46:649–52.
13. Sacket DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: A Basic science for clinical medicine. Boston: Little Brown and Company; 1991.
14. Abitbol C, Zilleruelo G, Freundlich M, Strauss J. Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children. J Pediatr. 1990;116:243-7.