

Correlation of spot urinary protein: Creatinine ratio and quantitative proteinuria in pediatric patients with nephrotic syndrome

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ABSTRACT

Introduction: Nephrotic Syndrome is the commonest glomerular disease in children and is often characterized by multiple relapses. 24 hour urinary protein excretion is the accepted method used in quantification of proteinuria, but it's a time consuming, inconvenient and cumbersome method and difficult in very young children. Spot urine examination would be a simpler, easy, acceptable, and less time consuming method for detection of proteinuria in children. **Aim:** To evaluate the utility of protein: Creatinine ratio in random urine samples as a reliable diagnostic tool to quantify proteinuria and to determine the correlation of protein: Creatinine ratio to 24 hour protein excretion which is the gold standard reference method. **Materials and Methods:** The study was done on forty pediatric patients with nephrotic syndrome admitted in relapse, or presenting for the first time. Nephrotic syndrome was diagnosed on the basis of massive proteinuria (>40 mg/m²/hr), hypoalbuminemia (<25 mg/l) and generalized oedema. Urine protein analysis was done using the sulphosalicylic acid method and creatinine estimation by a modified Jaffe's method. **Result:** The correlation between spot protein and creatinine ratio and 24 hour proteinuria was statistically significant with $r = 0.833$ ($P < 0.01$) using Pearsons correlation coefficient. **Conclusion:** Spot protein creatinine ratio can be used as reliable test for detection of proteinuria in the pediatric age group in patients with nephrotic syndrome.

Keywords: Creatinine, child, nephrotic syndrome, proteinuria, ratio, urine

Introduction

Nephrotic syndrome is a clinical manifestation of glomerular diseases associated with heavy proteinuria. The clinical triad associated with nephrotic syndrome arising from large urinary losses of protein are hypoalbuminemia (<2.5 gm/dl), oedema, and hyperlipidemia (cholesterol >200 mg/dl). Nephrotic syndrome affects 2-7 per 100,000 children annually.^[1] Without treatment, nephrotic is associated with high risk of death. Most children with nephrotic syndrome have a primary or idiopathic nephrotic syndrome. The proteinuria and low albumin levels in nephrotic syndrome is due to increase in permeability of glomerular

capillary wall due to podocyte foot process effacement.^[1,2] The quality of protein (mainly albumin) excreted in urine can be assessed by using dipstick test.^[3] Visual changes in the color of the dipstick are a semi-quantitative measure of increasing urinary protein concentration. The dipstick is reported as negative, trace (10-20 g/dL), 1+ (30-99 mg/dL), 2+ (100-299 mg/dL), 3+ (300-999 mg/dL), and 4+ (>1000 mg/dL). False-negative test results can occur in patients with dilute urine (specific gravity <1.005) or in disease states in which the predominant urinary protein is not albumin. More appropriate quantitative test for proteinuria is spot urine protein: creatinine ratio (UPr: UCr).^[4] This ratio is calculated by dividing the UPr (mg/dL) concentration by the UCr (mg/dL) concentration and is best performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (postural) proteinuria. Ratios <0.5

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Received: 16-05-2019 Revised: 16-05-2019 Accepted: 03-06-2019

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_403_19

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How to cite this article: Singh R, Bhalla K, Nanda S, Gupta A, Mehra S. Correlation of spot urinary protein: Creatinine ratio and quantitative proteinuria in pediatric patients with nephrotic syndrome. J Family Med Prim Care 2019;8:2343-6.

in children <2 years of age and <0.2 in children ≥ 2 years of age suggest normal protein excretion. A ratio >2 suggests nephrotic-range proteinuria. UPr: UCr ratios have been shown to have a high correlation with protein excretion determinations in timed urine collection (24 hours).^[3,5-7] A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr (0.15 g/24 hr). More specifically, normal protein excretion in children is defined as <4 mg/m²/hr; abnormal proteinuria is defined as 4-40 mg/m²/hr; and nephrotic range proteinuria is defined as > 40 mg/m²/h.^[8] 24-hour urine collection, which is the gold standard used to estimation proteinuria, is cumbersome and in older children, specially teenage girls may find it socially repressive, hence a spot urine examination would be more acceptable and less time consuming. It would also help school going children from missing an extra day of school. The usefulness of spot urine sampling using the protein: creatinine ratio and albustix was thus tested against the commonly used 24-hour urine protein excretion. The protein/creatinine ratio takes into accounts the fact that creatinine remains fairly constant in the presence of a stable GFR. The protein excretion would also likewise be fairly stable.

Hence, the ratio of the two in a single voided sample would reflect the cumulative protein excretion over the day, as the two stable rates would cancel out the time factor.^[9] The protein: Creatinine ratio takes into accounts the fact that creatinine remains fairly constant in the presence of a stable GFR. The protein excretion would also likewise be fairly stable. Hence the ratio of the two in a single voided sample would reflect the cumulative protein excretion over the day, as the two stable rates would cancel out the time factor.

Methods

The present study was done on 40 pediatric patients admitted in a tertiary care hospital in North India, on the clinical suspicion of nephrotic syndrome, either presenting for the first time or relapse case. Nephrotic syndrome was diagnosed on the basis of massive proteinuria (>40 mg/m²/hr), hypoalbuminemia. Pre-informed written consent was obtained from every caregiver before their inclusion in the study. Biochemical and renal parameters for diagnosing nephrotic syndrome were evaluated and recorded on the proforma. A 24-hour urinary sample collection for protein estimation was commenced at 8 AM on the first day (excluding the first voided morning urine sample) and completed on the second day at 8 AM (including the first voided morning urine sample). A random urine sample was collected either before starting or after completion of the 24-hour urine collection. Samples were processed as early as possible after collection, but were stored in refrigerator in case of inevitable delay in processing. Urine protein analysis was done using the sulphosalicylic acid method and creatinine estimation by modified Jaffe's method.^[10] Similar investigations were repeated weekly until the patient was in remission, defined as protein free urine (urine protein negative/trace; or 4 mg/m²/hr) for 3 consecutive days. The data were presented as mean, standard deviation, and percentage. The data

was analysed by linear regression by using Pearson's Correlation of Coefficient (r-value). A *P* value of < 0.05 was considered as significant.

Results

The majority of the patients belonged to 0-5 years age group (45%) and 42.5% were between 6-10 years. Only 12.5% of patients were >10 years of age. The mean age was 6.31 ± 2.99 (range 1.5-12 years). There were 27 males (67.5%) and 13 females (32.5%). There were 15 cases (37.5%) with first episode, 5 (12.5%) with 1 episode, 9 (22.5%) with 2 episodes, 4 (10%) with 3 episodes, 3 (7.5%) with 4 episodes and 4 (10%) with 5 episodes in the past. Mean episodes of all the patients was 1.77. Routine laboratory investigations was carried out in all the patients as shown in Table 1. Mean urinary protein was 1.85 ± 0.94 (gm/L); creatinine 38.08 ± 14.34 (mg/dl) and the protein: Creatinine ratio 5.32 ± 3.08 in the spot urine collections done in the first week. Mean urine volume was 922.0 ± 288.29 ml, protein was 1.54 ± 0.85 gm/day, protein excretion in mg/m²/hr was 80.87 ± 37.25 , protein excretion in gm/l was 1.78 ± 1.00 and creatinine 38.9 ± 12.48 mg/dl. In the third week, a total of 7 out of 19 patients who did not achieve remission were analyzed. Mean protein was 0.855 ± 0.168 gm/l; creatinine 24.52 ± 4.07 mg/dl and ratio was 3.37 ± 0.71 . Mean urine volume was 1300 ± 466.36 ml, protein gm/day was 0.981 ± 0.327 , protein mg/m²/day was 48.28 ± 5.43 , protein gm/l 0.803 ± 0.176 and creatinine was 26.57 ± 3.59 mg/dl. On statistical analysis by using Pearson's Correlation of coefficient for correlation of spot urine ratio versus protein urea at first week, r value (0.833, *P* < 0.01) was observed and found to be statistically significant. Mean spot urine ratio was found to be 5.30 ± 3.13 and protein urea was 80.87 ± 37.72 .

Discussion

In the present study 40 children of either sex, aged less than 14 years presenting as primary nephrotic syndrome either during the first episode or relapse were studied. Majority of the patients belonged to 1-5 years age group i.e. 45% between 0-5 years and 42.5% between 6-10 years. Only 12.5% cases belonged to >10 years of age. Mean age of study population was 6.31 ± 2.99 years ranging from 1.5-12 years. Similar observations were made by Navale *et al.*,^[11] Chahar OP, *et al.*^[12] and Shastri NJ, *et al.*^[13] Routine laboratory investigation was

Table 1: Laboratory investigations

Parameter	Mean \pm SD
Hb (g/dl)	10.99 \pm 1.84
ESR (mm)	36.02 \pm 15.93
Blood urea (mg/dl)	31.72 \pm 10.17
S. creatinine (mg/dl)	0.63 \pm 0.23
S. uric acid (mg/dl)	4.52 \pm 1.89
S. protein (g/dl)	3.98 \pm 0.604
TGL (mg/dl)	422.77 \pm 87.26
Cholesterol (mg/dl)	325.12 \pm 81.55
Creatinine clearance	16.04 \pm 10.11

carried out in all the patients. Mean hemoglobin of cases was 10.99 ± 1.83 , ESR 36.02 ± 15.93 , blood urea 31.72 ± 10.17 , serum creatinine 0.63 ± 0.23 , serum uric acid 4.52 ± 1.89 , serum protein 3.98 ± 0.604 , TGL 422.77 ± 87.26 and cholesterol 325.12 ± 81.55 . Mean serum cholesterol observed in the present study was 325.12 which is close to another study like Navale *et al.*^[11] which showed mean cholesterol as 320 and a similar observation which was done by Appel GB^[14] *et al.* showing a mean cholesterol of 302 mg/dl. Pedal edema was found to be positive in 37.5% of patients with (+) though 25 had (++) edema. In distribution of cases according to urinary dipstick method we found a total of 9 cases with 2+, 21 with 3 + and 10 cases with 4 + proteinuria. Mean urinary protein was found to be 1.85 ± 0.94 (gm/L); creatinine 38.08 ± 14.34 (mg/dl) and ratio 5.32 ± 3.08 when spot urine investigations was done at first week. Mean urine volume was 922.0 ± 288.29 , protein gm/day was 1.54 ± 0.85 , protein mg/m²/hr was 80.87 ± 37.25 , protein gm/l was 1.78 ± 1.00 and creatinine was 38.9 ± 12.48 . According to study done by Iyer RS, *et al.*^[15] the ratio was found to be 5.55 which are very similar to our study. But a study done by Navale *et al.*^[11] and Chahar OP, *et al.*^[12] showed a slightly lower ratio of 3.28 and 2.52 respectively. In the present study it was found that there was a decreasing trend of protein (gm/l), creatinine (mg/dl) and their ratio from first week onwards to second week and third week. Protein (gm/l) at first week was 1.85 ± 0.94 which decreased to 0.855 ± 0.168 after 3rd week. Similarly, creatinine (mg/dl) was 38.08 ± 14.34 at first week which reduced to 25.42 ± 4.07 at the end of third week. In the present study, increasing trend of urine volume (ml) at first week 922.0 ± 288.29 to 1300 ± 466.36 at end of third week was recorded. This is consistent with the fact that as patient is started on steroids, proteinuria settles and edema begins to reduce. On statistical analysis by using Pearson's Correlation of coefficient, r-value (0.833, $P < 0.01$) was observed and found to be statistically significant. Mean spot urine protein/creatinine ratio was found to be 5.30 ± 3.13 and protein urea was 80.87 ± 37.72 . Correlation was very consistent as observed in other similar studies like Iyer *et al.*^[15] and Wahbeh AM, *et al.*^[16] which showed a $r = 0.81$ and $r = 0.83$ respectively. Much higher correlation was found in another similar study by Siwach SB, *et al.*^[17] where $r = 0.88$. Creatinine excretion varies among individuals according to age, sex and body size but still it shows good accuracy and correlation with urinary proteins. This is probably because the index is independent of errors in urine collection. Creatinine index and ratio in random urine provided the same information about proteinuria Thus the uniformly high correlation coefficients were sufficiently strong evidence to the creatinine proteins index for assessment of persistent proteinuria. The main limitation of protein: creatinine index is a wide daily variation in the urinary proteins excretion rate associated with changes in posture, physical activity, protein intake and haemodynamic factors. The proteins: creatinine index and ratio in random urine provided the same information about proteinuria status and was more convenient for clinical usage.

Conclusion

24-hour urine collection which is the gold standard used to estimation proteinuria is cumbersome and in older children may be socially unacceptable. Hence, a spot urine examination would be more acceptable and less time consuming. It would also help school going children from missing an extra day of school. Therefore the ratio will be of great value to primary care physicians in early diagnosis of nephritic syndrome in children thereby helping in early initiation of treatment. The usefulness of spot urine sampling using the protein/creatinine ratio and protein dipstick was thus tested against the 24, hour urine protein excretion, which is the gold standard for estimation of protein excretion.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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