COMPARISON OF SPOT URINARY PROTEIN CREATININE RATIO AND 24 HOUR URINARY PROTEIN EXCRETION IN CHILDREN PRESENTING WITH NEPHROTIC SYNDROME IN TERTIARY CARE HOSPITAL OF EASTERN NEPAL

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ABSTRACT

Nephrotic syndrome is an important chronic disorder in children and it's one of the important diagnostic criteria is presence of heavy proteinuria (> 40 mg/m^2/hour).

As 24-hour urinary protein estimation is cumbersome, inconvenient, time consuming and expensive, a more convenient and accurate method of urinary protein estimation is needed.

24-hour urinary protein estimation and urine protein/ creatinine in a child with nephrotic syndrome correlates well but there are very few studies done in Nepal to prove this correlation. Hence, this study is undertaken with objective of evaluating usefulness of urine protein/creatinine (UP/UC) in random sample of urine as a rapid and reliable test for quantification of proteinuria and to know their correlation with 24hour urinary protein excretion.

Objectives

Primary Objective

To evaluate accuracy of urine protein creatinine ratio (UP/UC) in early morning sample in comparison with 24 hours urinary protein excretion in children of nephrotic syndrome having normal Glomerular Filtration Rate.

Secondary Objective

1. To evaluate usefulness of urine protein / creatinine ratio (UP/UC) in random sample of urine as rapid and reliable test for quantification of proteinuria.
2. To evaluate biochemical and other laboratory abnormalities in children with nephrotic syndrome.
3. To study varied clinical presentation of Pediatric nephrotic syndrome

Methodology

This is a descriptive cross-sectional study conducted in pediatric unit, Nobel Medical College Teaching Hospital, Biratnagar for 12 months. In this study, 50 patients of both sexes, ranging from one to fifteen years of age were studied. The modes of presentation, laboratory investigation reports which included urine routine microscopy, 24-hour urine protein estimation, urine protein / creatinine in random sample of urine were documented and data was analyzed by linear regression.

Result

Linear regression revealed that as timed 24-hour urine protein in gm/24 hour increased, Random urine/protein creatinine ratio mg/mg also increased linearly with correlation coefficient of r = 0.56 which was highly significant ($p < 0.001$).

Conclusion

This study concludes that UP/UC ratio in a spot urine reflects the amount of protein in 24-hour urine collection. UP/UC ratio > 2 in patients with normal renal function represents nephrotic range proteinuria.

KEYWORDS

Nephrotic syndrome, Proteinuria, Urine protein/creatinine ratio.

INTRODUCTION

Nephrotic syndrome (NS) is one of the most common renal disorders in children. It is a clinical manifestation involving glomerulus causing heavy proteinuria.[1]

The prevalence worldwide is approximately 16 cases per 100,000 children with an incidence of 2 to 7 per 100,000 children. In children males appear to be more affected than females at ratio of 2:1, but this predominance fails to persist in adolescence.[2]

Without proper treatment, nephrotic syndrome is associated with high risk of mortality. Various phenotypes of nephrotic syndrome are identified that are classified according to responsiveness to steroids.[3]

Nephrotic syndrome is caused by a variety of glomerular and systemic diseases, but the most common type identified in childhood is idiopathic nephrotic syndrome. Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy. These etiologies have different age distributions. Nephrotic syndrome may also be secondary to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria). Drugs like Penicillamine, gold, NSAIDS, pamidronate, interferon, heroin, lithium and sirolimus can cause secondary nephrotic syndrome.[4]

More than two-third of the idiopathic NS are sensitive to oral steroids therapy and have relatively good prognosis. About 10-20% of children with NS show poor response to the steroids therapy. This group of children with Nephrotic syndrome are treated with alternative therapies, which include other immunosuppressants.[5]

Children with NS (particularly SRNS) have a chronic clinical course with multiple hospital admissions, prolonged immunosuppressant therapy and protracted proteinuria.[6]

Assessment of urinary protein excretion is not only diagnostic but also has prognostic value in monitoring of nephrotic syndrome. Traditionally, urinary protein assessments has been done in 24 hours urine collection specimens but this approach is time consuming, cumbersome, and imprecise.[3]

More appropriate quantitative test for proteinuria is spot urine protein: creatinine ratio (UPr: UCr). 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 proteinuria. Ratios <0.5 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 24 hours urine protein excretion. Normal protein excretion in children is defined as <4 mg/m^2/hr.; abnormal proteinuria is defined as 4-40 mg/m^2/hr.; and nephrotic range proteinuria is defined as > 40 mg/m^2/hr. 24-hour urine collection, which is the gold standard used for the estimation of proteinuria, is cumbersome and in older children, 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 protein/creatinine ratio takes into accounts the fact that creatinine remains fairly constant in the presence of a stable GFR.[1]

Hence, this study was done to evaluate the accuracy of urine protein creatinine ratio (UP/ UC) in a spot sample for quantitative measurement of proteinuria in comparison with 24 hours urinary protein excretion in children of nephrotic syndrome having normal Glomerular Filtration Rate and to evaluate the UP/UC ratio as a rapid and reliable test for the estimation of various ranges of proteinuria and its usefulness in the diagnosis of nephrotic syndrome in children.

METHODOLOGY

This was a descriptive cross-sectional study which was conducted in the Department of Pediatrics in Nobel Medical College from Jan 2021 to Dec 2021 after obtaining approval from the Institutional review committee where cases of nephrotic syndrome were recruited.

The sample size of the study was calculated by estimating the sample proportion of 0.886 according to literature review of Navale RA et al with a confidence level of 95% and a precision of ±10 %, the sample size thus calculated was 39.[3] However, during the study period we enrolled 50 cases.

Children with nephrotic syndrome admitted in ward/ pediatric intensive care unit (PICU) of pediatrics department, Nobel Medical College satisfying the criteria of Nephrotic range proteinuria >40 mg/m^2/hour, Hypoalbuminemia <2.5 gm/dl and Generalized Edema were included in the study. Children in renal failure and in those where parents did not give consent were excluded from the study. Exclusion criteria was considered as a necessity for this study since the ratio of urine protein and creatinine in a random sample reflects the protein excretion only in presence of a stable glomerular filtration rate.

Clinical and laboratory parameters of the enrolled children were recorded in a structured proforma. Following clinical parameters were recorded: age, sex, age of onset of nephrotic syndrome, duration of disease, edema, anthropometry (height, weight, body mass index) blood pressure recordings, following laboratory parameters were recorded: Blood urea, serum creatinine, urine protein: urine creatinine ratio, 24-hour urine protein estimation, serum albumin, serum cholesterol.

All patients were asked to carefully collect a 24-hour urine protein sample and Foley's catheterization done for collecting 24hour urine sample in a child below 3 years which was measured using Eshbach's Albuminometer.

Also, a random urine sample was obtained, and urine protein/creatinine ratio was calculated. Urine protein was estimated by Pyrogallol Red-Molybdate method and creatinine was measured by Jaffe's reaction. The random urine, protein-creatinine ratio was calculated mg/mg.

RESULTS

In our study, most of the patient belonged to the age group 1-5 years and 6-10 years with total 23 in each age group followed by 4 patients above 10 years as shown in table below.

Table 1: Age and sex distribution of cases with nephrotic syndrome

Sex	Age			Total
	1-5 years	6-10 years	> 10 years	
Male	16	14	1	31
Female	7	9	3	19
Total	23	23	4	50

In the present study, 66% of patients presented as first attack of nephrotic syndrome and about 34% (24% as frequent relapse and 10% as infrequent relapse) of patients had one or more relapse at the time of admission as shown below in figure 1.

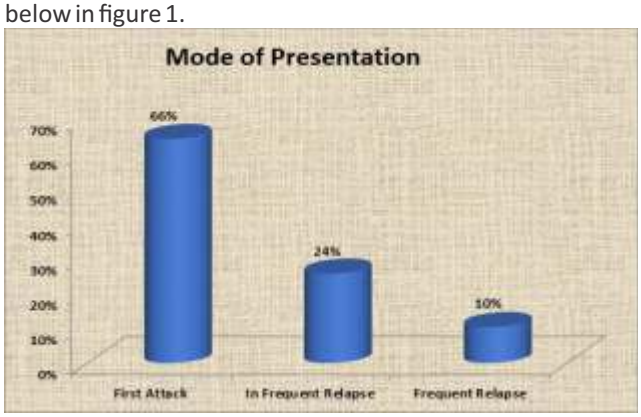

Figure 1: Distribution of patients according to their mode of presentation

In the present study, 18% of the patient presented with hematuria and 16% (8 cases) of the patients presented with hypertension at the onset.

Table 2: Urine microscopy for hematuria

Hematuria		
	Frequency	Percent
Yes	9	18
No	41	82
Total	50	100

In the present study, 92% of patient presented with swelling of limbs and 82% presented with puffiness of face followed by decreased urine output and abdominal distension. The least common manifestation was genital oedema which was seen in only 28% of cases.

Table 3: symptoms of patients presenting with nephrotic syndrome

S. N.	Symptoms	Frequency (n)	Percentage (%)
1	Swelling Of Limb	46	92
2	Puffiness Of Face	41	82
3	Decreased Urine Output	18	36
4	Abdominal Distension	18	36
5	Genital Oedema	14	28

We found the mean hemoglobin of patient presented with nephrotic syndrome to be 11.18gm/dl, mean serum albumin was 1.90gm/dl, mean blood urea was 29.76mg/dl, mean serum creatinine was 0.59mg/dl, mean serum cholesterol was 340.68mg/dl, mean urine protein/ creatinine was 7.97 and mean 24-hour urinary protein excretion was 119.79mg/m^2/hr.

Table 4: Analysis of investigative parameters of patients with Nephrotic syndrome

Parameters	Range		Mean	Std. Error	Std. Deviation
Age (Year)	2.00	13.00	6.20	0.3749	2.6515
Hemoglobin (gm/dl)	7.70	18.20	11.18	0.2423	1.7135
Serum Albumin (gm/dl)	1.00	2.40	1.90	0.0528	0.3737
Blood Urea (mg/dl)	13.00	56.00	29.76	1.2495	8.8353
Serum Creatinine (mg/dl)	0.20	1.10	0.59	0.0289	0.2045
Serum Cholesterol (mg/dl)	230.0	659.00	340.68	12.0051	84.8889
Urine Protein: Creatinine Ratio	2.90	21.00	7.97	0.6521	4.6111
24 Hour Urinary Protein Excretion (mg/m^2/hr)	52.00	246.00	119.79	7.5297	53.2433

We found the correlation coefficient between Urine Protein: Creatinine Ratio and 24-Hour Urinary Protein Excretion (mg/m^2/hr) to be 0.566 which was highly significant ($p < 0.001$).

Table 5: Correlation between 24-hour urinary protein and urine protein: creatinine ratio

	Correlation	P Value
Urine Protein: Creatinine Ratio 24 Hour Urinary Protein Excretion (mg/m^2/hr)	0.566	0.000

In the linear regression equation, $Y = 2.903 + 0.046(X)$ is the random urine protein creatinine ratio and X is total protein (grams in 24 hours) and it revealed that as X increased Y also increased linearly. The correlation coefficient between these values was 0.56 and this was highly significant ($p < 0.001$).

Table 6: Hypertension at the onset

	Number	Percentage of the case with Hypertension
Present Study	50	16.00
Struss et al.[9]	52	20.7

In the present study, hypertension was noted in 8 cases (16%). As there were no other associated features like hematuria or renal insufficiency to suggest significant glomerular lesion, these children were not investigated further and they responded to steroid therapy.

In a review of ISKDS study by Struss J.et al9, hypertension was found to be present in 20.7% of cases with minimal change nephrotic syndrome.

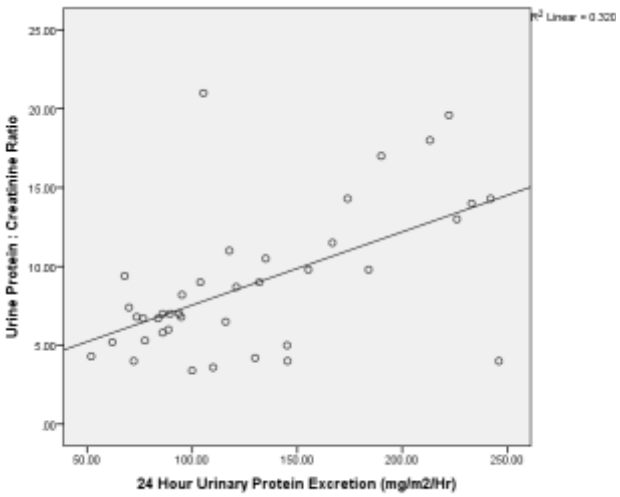

Figure 2: Linear regression of random urine protein creatinine ratio against 24-hour urine protein of patients with nephrotic syndrome

DISCUSSIONS

In our study, the age distribution of cases ranged from 2 years to 13 years. The mean age in the present study was 6.2 years which was similar to the observations made by Navale RA et al3 and Shastri NG et al.[7]

In the present study 66% of patient had first attack, 10% had infrequent relapse and 24% of cases who presented to the hospital had frequent relapse. The similar observation was made by Navale RA et al where 54% of patients had first attack and 46% had relapsed.[3]

In our study, 18% of cases showed hematuria and similar observation made by Siegal et al.[8] Also 16% of cases had hypertension at the onset of disease which was similar to the observation made by Strauss J et al.[9]

Present study showed face and limbs as the commonest site to be involved i.e., in 92% whereas edema involving genital area was least i.e., in 28% of cases. 36% patient presented with abdominal distension due to massive edema (pleural effusion and ascites). Similar observations were made by Navale RA et al.[3] where 86.66% of patient presented with edema.

36% of cases presented with history of decreased frequency and volume of micturition. Similar observations were made by Navale RA et al.[3]

In the present study, the value of Hb ranged from 7.7 gm/dl to 18.2 gm/dl and the mean Hb (gm/dl) observed in the study was 11.18 gm/dl. The value of blood urea ranged from 13-56 mg/dl with mean value of 29.76 mg/dl and the value of serum creatinine ranged from 0.20-1.10 mg/dl with the mean value of 0.59 mg/dl, similar to observations made by Navale RA et al.[3] Serum albumin ranged from 1.0 gm to 2.40 gm/dl with the mean of 1.92 gm/dl comparable to observations made by Hiraoka et al.[10] The range of serum cholesterol was 230-659 mg/dl with the mean value of 340.68 mg/dl comparable to observations made by Appeal GB et al.[11]

In our study, the range of 24 hours urinary proteinuria observed was 52-246mg/m^2/ hour with a mean value of 119.79 mg/m^2/ hour in contrast to a study done by Navale RA et al.[3] where timed 24 hours urine total protein was found to be 41-114.36 mg/m2/hour, mean was 64.76 mg/m2/hour. The range of values observed for spot urinary protein: creatinine ratio was 2.92-21 with a mean of UP/UC 7.97 similar to a study conducted by Iyer RS et al.[12]

In our study, correlation coefficient obtained was 0.566 and value obtained was statistically significant (P <0.01) which is similar to the studies conducted by Navale RA et al and Wahbeh AM et al.[3,13]

CONCLUSION

We conclude that random urine protein-creatinine ratio is highly reliable and rapid test for quantification of proteinuria in children. It reflects the amount of protein in a 24-hour collection and UP/UC ratio > 2 in patients with normal renal function represents nephrotic range proteinuria.

RECOMMENDATIONS

Spot urine examination for proteinuria and urine protein /creatinine ratio should be considered as a first line investigation for diagnosis and treatment outcome of nephrotic syndrome in children as it is more acceptable and is less time consuming and for older children. This study showed good accuracy and correlation between 24-hour urinary protein estimation and urine protein/creatinine ratio. Therefore, the urine protein/creatinine ratio will be of great value in early diagnosis of nephrotic syndrome in children thereby helping in early initiation of treatment and preventing from future complications.

LIMITATIONS OF THE STUDY

This is a hospital-based study so the actual clinical presentation and the biochemical parameter of patient with nephrotic syndrome in the community level cannot be determined.

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CONFLICT OF INTEREST

None.

FINANCIAL DISCLOSURE

None.

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