STUDY EVALUATION OF URINE PROTEIN/URINE CREATININE RATIO FOR QUANTIFICATION OF PROTEINURIA IN RAPID AND RELIABLE DIAGNOSIS OF NEPHROTIC SYNDROME

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ABSTRACT

BACKGROUND
Nephrotic syndrome is a common renal disease in 2-6-year-old children characterised by proteinuria, hypoalbuminemia, oedema and hypercholesterolemia. Incidence is 2-3 /1 lakh children per year. Without treatment, nephrotic syndrome in children is associated with significant morbidity and mortality.

Aim of the study is to evaluate the usefulness of urine protein/urine creatinine ratio of (UP/UC) in a random and reliable test for the quantification of proteinuria.

MATERIALS AND METHODS
This is a prospective case control study for a period of one year i.e., from 1st July 2013 to 30th June 2014 carried out in the paediatric wards of King George Hospital, Visakhapatnam, Andhra Pradesh. A case group of 40 children suffering from nephrotic syndrome and a control group of 40 children with proteinuria due to causes other than nephrotic syndrome who fulfilled the inclusion criteria were included in the study.

RESULTS
A case group of 40 children between the ages of 2-12 years who were admitted with nephrotic syndrome during the study period. Males were 24(60%) and 16(40%) females. 24(60%) children presented with first episode and 16(40%) children with relapse at the time of admission. All cases presented with anasarca. 21(52.5%) children also had scrotal oedema. Oliguria was present in 39(97.5%) cases and UTI in 22 (55%) children.

Regarding lab investigations, urine albumin was found to be 4+ in 36 children. Mean values of serum creatine was 0.603 mg/dl. Urine spot protein to urine creatinine ratio was 6.16 in study group, whereas it was 1.01 in control group and the p value was statistically significant (0.0001). Applying tests of significance and kappa statistics, the UP/UC test in comparison with 24-hour urine protein ratio values were found to have a sensitivity of 95%, positive predictive value of 95%, specificity of 95%, positive predictive value of 95% and correlation coefficient r=0.802 and p <0.0001 on linear regression method.

CONCLUSION
In the present study, the UP/UC test is highly reliable and rapid test for quantification of proteinuria, and UP/UC ratio of >3 with normal renal function represents nephrotic range proteinuria.

KEYWORDS
Nephrotic Syndrome, Proteinuria, UP/UC Ratio, Renal Function.

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screen for abnormal protein excretion without the necessity of an accurately timed collection and is especially useful for following children with Proteinuria in whom repetitive 24-hour urine collections are cumbersome and this study helps in children.²

MATERIALS AND METHODS
The present study was conducted out on children admitted to paediatric wards of King George hospital, Andhra medical college, Visakapatnam, Andhra Pradesh during the period of 1st July 2013 to 30th June 2014. This is a prospective case control study comprising of two groups selected by purposive sampling technique.

Group 1 (case group): Number of cases of nephrotic syndrome-40.

Group 2 (control group): Number of patients who are admitted for evaluation of proteinuria secondary to causes other than nephrotic syndrome like acute nephritic syndrome, urinary tract infection-40.

Inclusion Criteria
All cases of nephrotic syndrome in whom steroid therapy is not yet started. All cases satisfied the following criteria:
1. Massive proteinuria >40 mg/m²/hour
2. Hypoalbuminemia <2.5 gm/dl
3. Generalised oedema
4. Hypercholesterolemia >200 mg/dl

Exclusion Criteria
Abnormality of renal function as evidenced by the presence of abnormal biochemical parameters, i.e.
1. Blood urea
2. Serum creatinine

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.

Cases noted down into the proforma with respect to history, examination and investigation.

Following parameters are noted on entry into study as per the proforma.
1. History
2. Examination
3. Investigation

All patients were asked to carefully collect a 24-hour urine protein sample which is measured using Esbach’s Albuminometer.

A random urine sample was obtained, and urine protein/creatinine ratio was calculated. Urine protein was estimated by Biuret method and creatinine is measured by Jaffe’s reaction. The random urine, protein-creatinine ratio was calculated mg/mg.

Comparison of cases and controls was done with respect to a single pertinent variable, i.e. proteinuria.

Statistical Analysis
Data was analysed by linear regression and by calculating the correlation coefficient between urinary protein/creatinine ratio and 24-hour urinary protein. The validity of this test was assessed by sensitivity, specificity and positive predictive value. Also, chi-square test was applied for non-parametric data.

RESULTS
Present study was conducted in the department of paediatrics, King George hospital from July 2013 to June 2014. A total of 40 children with nephrotic syndrome who fulfilled the inclusion criteria were included in the study.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0-1</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2-5</td>
<td>13</td>
<td>8</td>
<td>61.9%</td>
</tr>
<tr>
<td>6-12</td>
<td>11</td>
<td>8</td>
<td>57.9%</td>
</tr>
<tr>
<td>&gt;12</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>16</td>
<td>60%</td>
</tr>
</tbody>
</table>

Table 1. Age and Sex Distribution of Cases (n=40)

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First attack</td>
<td>24</td>
</tr>
<tr>
<td>Relapse</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 2. Mode of Presentation in Cases (n=40)

![Figure 1. Distribution of Symptoms and Complications among Cases (n=40)](image)

![Figure 2. Table 3. Distribution of Urine Albumin Levels among Cases and Controls](image)

<table>
<thead>
<tr>
<th>Urine Albumin</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>0</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>2+</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>3+</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4+</td>
<td>36</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 3. Distribution of Urine Albumin Levels among Cases and Controls

Chi square value=80.000, df=3, P value=0.0001 (significant).
On unpaired t test, the difference of means between the two groups was found to be statistically significant.

\[ t = 33.913, df = 78, P \text{ value} = 0.001 \]

On applying the tests of significance, chi square value was found to be 64.800, with df = 1 and P value of 0.001, which is statistically highly significant. Further analysis was done by applying kappa statistics, to see the percentage of agreement between urine protein/creatinine ratio and 24-hour proteinuria and it was found that kappa value was 0.9 which shows a strong agreement between the two tests.

- Sensitivity = \( \frac{a}{a+c} \times 100 = 95\% \)
- Specificity = \( \frac{d}{b+d} \times 100 = 95\% \)
- Positive predictive value = \( \frac{a}{a+b} \times 100 = 95\% \)
- Negative predictive value = \( \frac{d}{c+d} \times 100 = 95\% \)
- Percentage of false negative = \( \frac{c}{a+c} \times 100 = 5\% \)
- Percentage of false positive = \( \frac{b}{b+d} \times 100 = 5\% \)

In the present study, out of 40 cases, 21 cases were in the age group of 2-5 years and 19 cases were in the age group of 6-12 years. None of the nephrotic syndrome patients were below 2 years and above 12 years. There was male preponderance in this study. 24 (60\%) were males and 16 (40\%) were females in the present study. While 60\% of the patients presented for the first time, about 40\% of the patients had relapse at the time of admission. All the cases presented with generalised oedema. About half of the cases i.e., 52.5\% had presented with scrotal oedema. A significant history i.e., history of decreased frequency and volume of urine output was observed in 39 (97.5\%) cases. Respiratory complications were reported in few cases. Shortness of breath was reported in four (10\%) of cases. Seven (17.5\%) cases had pneumonia. Five (12.5\%) cases had upper respiratory tract infection. One case (2.5\%) developed pleural effusion. None of the cases developed pulmonary tuberculosis. Ascites was observed in 37(92.5\%) of the cases. Whereas fever was observed in 35(87.5\%) of the cases. Most of the cases had 3+, 4+ urine albumin levels whereas most of the controls had 1+, 2+ levels of urine albumin. This difference was found to be statistically significant.
DISCUSSION

This study on evaluating the utility of random urine protein/creatinine ratio was conducted between 1st July 2013 to 30th June 2014 on the cases of nephrotic syndrome admitted in the paediatric wards of king George hospital, Andhra medical college, Visakhapatnam.

Age Distribution

In the present study the age distribution of cases ranged from 2 years to 12 years. The mean age in the present study was 6.02 years.

Similar observations were made by Chahar OP et al.\(^3\) and Shastri NG et al.\(^4\)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>40</td>
<td>2-12 years</td>
<td>6.02 years</td>
</tr>
<tr>
<td>Chahar OP et al.(^3)</td>
<td>30</td>
<td>2.5-14 years</td>
<td>6.7 years</td>
</tr>
<tr>
<td>Shastri NJ et al.(^4)</td>
<td>79</td>
<td>1.5-12 years</td>
<td>7.3 years</td>
</tr>
</tbody>
</table>

Eventhough commonly nephrotic syndrome is seen in pre-school children, in our study the mean age was 6.02 years as majority of cases (60%) were first attacks.

Mode of Presentation

In the present study, 60% of cases who had nephrotic syndrome for the first time and 40% got admitted with relapse.

Duration of Symptoms Prior to Presentation

In the present study, the duration of symptoms prior to the presentation ranged from 3 days to 20 days.

Symptomatology

Oedema

Present study showed face and limbs as the commonest site to be involved i.e. in 100% whereas oedema involving genital area was least i.e. in 52.5% cases. Only 5 patients presented with respiratory distress due to massive oedema. (pleural effusion and massive ascites).

Micturition

All most all cases i.e. 97.5% presented with history of decreased frequency and volume of micturition. 55% of cases had burning micturition and all of them had UTI.

Other Symptoms

87.5% of cases had fever.

Other Signs

Oedema

Pitting type of oedema was noticed in all patients in the present study. Ascites was present in 92.5% of cases.

Infections and/or Complications Associated with Nephrotic Syndrome

Present study (n=40) showed UTI and pneumonia to be present in 55% and 17.5% of cases respectively.

Gorensek MJ et al.\(^6\) (n=214) in a 20-year retrospective study observed 17.3% cases of peritonitis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Percentage of Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Gorensek MJ et al.(^6)</td>
<td>214</td>
<td>17.3</td>
</tr>
</tbody>
</table>

No cases were observed in our study because of small number of sample size and short duration of study whereas Gorensek et al.\(^6\) studied for a period of 20 years.

Investigative Parameters

1. Haemoglobin (HB gm/dl): in the present study (n=40), 75% of cases showed presence of anaemia. The value of HB ranged from 8 gm/dl to 13 gm/dl.
2. Total leucocyte count (TLC): in the present study (n=40), the total leucocyte count ranged from 3500-14,500 cells/mm\(^3\).
3. Blood urea: in the present study the value of blood urea ranged from 12-33 mg/dl. The mean value of blood urea was noted to be 22.98 mg/dl.
4. Serum creatinine: in the present study the value of serum creatinine ranged from 0.4-0.8 mg/dl. The mean value of serum creatinine observed was 0.603 mg/dl.
5. Serum albumin: in the present study, serum albumin ranged from 1.6 gm to 2.4 gm/dl. The mean serum albumin level observed was 2.01 gm/dl. Similar observations were made by Hiraoka et al.\(^7\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Serum Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>2.01 g/dl</td>
</tr>
<tr>
<td>Hiraoka et al.(^7)</td>
<td>1.8 g/dl</td>
</tr>
</tbody>
</table>

Serum Cholesterol

The range of serum cholesterol in the present study was 246-804 mg/dl and the mean serum cholesterol was noted to be 352 mg/dl. Similar observations were made by Appeal GB et al.\(^7\)

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Mean (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>40</td>
<td>352</td>
</tr>
<tr>
<td>Appeal GB et al.(^7)</td>
<td>20</td>
<td>302</td>
</tr>
</tbody>
</table>

Urine Analysis

Urine Culture: UTI was noted in 55% of cases in the present study. E. coli, proteus, klebsiella were the organisms grown in 50%, 8%, 41% of cases respectively.

Urine protein by sulphosalicylic acid method (random sample): all cases showed urine protein to be > 3+ in the present study.
Urine Total Protein in a Timed 24-Hour Sample

In the present study, the range observed was 3.11-3.98 g/24-hours with a mean value of 3.32g/24-hour. Iyer RS et al. found the range of timed 24-hours urine protein to be 0.8-7 gm/24-hour and a mean value of 4.6g/24-hour was observed.

The following table shows comparison of validity indicators of random urine protein/creatinine ratio in cases of nephrotic syndrome in various studies.

**Validity Indicators of Random Urine Protein/Creatinine Ratio in Cases of Nephrotic Syndrome**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity Value</th>
<th>Specificity Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>40</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Abitbol C et al.</td>
<td>64</td>
<td>95%</td>
<td>93%</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>Iyer RS et al.</td>
<td>50</td>
<td>97%</td>
<td>97%</td>
<td>95%</td>
<td>93%</td>
</tr>
<tr>
<td>Chahar OP et al.</td>
<td>30</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Shastri NJ et al.</td>
<td>79</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Table 20

*details not mentioned; **log converted

Correlation Coefficient (r) between Values of 24-Hour Urine Protein and Random UP/UC Ratio

In the present study, correlation coefficient obtained in cases was 0.802, in control 0.891 and in the both groups combined value obtained was 0.753 and in all three groups value obtained was statistically significant (p<0.001).

The correlation coefficient obtained in the other studies is mentioned below and, in their studies, also values obtained were highly significant (p<0.001).

<table>
<thead>
<tr>
<th>Studies</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>r=0.80</td>
</tr>
<tr>
<td>Abitbol C et al.</td>
<td>r= 0.97</td>
</tr>
<tr>
<td>Shastri NJ et al.</td>
<td>r=0.95</td>
</tr>
</tbody>
</table>

Table 22

CONCLUSION

Urine total protein in timed 24-hour sample of nephrotic syndrome patients was in the range of 3.11-3.98 gms with the mean value of 3.32 gms while as UP/UC ratio ranged from 2.54-18.30 with the mean value of 6.16.

Urine total protein in a 24-hour sample- proteinemia secondary to causes other than nephrotic syndrome (like AGN, UTI) was in the range of 0.14-2.85 gms with the mean value of 0.37 gms while as UP/UC ratio ranged from 0.32-3.89 with the mean value of 1.01. A significant correlation was found between times 24-hour urinary protein and UP/UC ratio in both the groups, i.e. as timed 24-hour urinary protein increased UP/UC ratio also increased linearly.

Thus, we conclude that random urine protein-creatinine ratio is highly reliable and rapid test for qualification of proteinuria in children. It reflects the amount of protein in a 24-hour collection and UP/UC ratio >3 in patients with normal renal function which represents nephrotic range proteinuria. Thus, it avoids all the drawbacks which are associated with time collection method.
REFERENCES


