Distribution of pathologic findings in individuals with nephrotic proteinuria according to serum albumin

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Abstract

Background. Previous studies of the nephrotic syndrome have not carefully examined the relationship between serum albumin and the distribution of pathologic diagnoses found at the time of biopsy. The spectrum of pathologic findings in individuals with nephrotic proteinuria and a normal serum albumin has not been determined. Knowledge regarding the spectrum of findings in nephrotic proteinuria according to serum albumin levels may help nephrologists in the clinical decision making of when to perform a renal biopsy and in determining proper management of these patients.

Methods. Pathologic reports of native kidney biopsies performed for idiopathic proteinuria > 3 g/24 h were reviewed. Clinical characteristics and biopsy findings were compared for individuals with serum albumin < 30 g/L (Group I), 30 to < 35 g/L (Group II) and ≥ 35 g/L (Group III).

Results. There were 57 patients in Group I, 20 in Group II and 35 in Group III. The proportion of individuals with focal and segmental glomerulosclerosis (FSGS) increased according to group: 26% in Group I, 45% in Group II and 74% in Group III. Of 35 patients in Group III, 34 had FSGS or advanced nephrosclerosis from another cause. Seven of 17 Group III patients with follow-up required dialysis after a mean interval of 6 years. Few of these patients received immunosuppressive therapy.

Conclusions. As serum albumin increases in the nephrotic syndrome, the proportion of patients with FSGS increases. Patients with nephrotic proteinuria and a serum albumin > 35 g/L suffer from FSGS, nephrosclerosis and have poor renal survival. When evaluating nephrotic patients, nephrologists should use this knowledge about the spectrum of disease in the clinical decision making of when to perform a biopsy and in providing the patient more precise information regarding risks, benefits and alternatives of the kidney biopsy procedure.

Keywords: focal and segmental glomerulosclerosis; idiopathic nephrotic syndrome; proteinuria; renal biopsy; spectrum of disease

Introduction

While the general characteristics of nephrotic syndrome—proteinuria, hypoalbuminemia, hypercholesterolemia, and edema—are well recognized, there is no precise, generally accepted definition that defines the extent of proteinuria or hypoalbuminemia required for the syndrome [1]. In studies of the nephrotic syndrome, nephrotic proteinuria has been variably defined as > 3 g/24 h or ≥ 3.5 g/24 h. Most studies have relied on edema as a manifestation of nephrotic syndrome and have not strictly defined hypoalbuminemia [2,3]. Based on animal models, edema is thought to characteristically develop when the serum albumin falls below 30 g/L [1]. However, the presence of edema is variable even when the serum albumin is below 30 g/L [4].

The purpose of this investigation was to determine the distribution of disease in individuals with nephrotic proteinuria (> 3 g/24 h) according to the level of serum albumin. It was postulated that the distribution of disease is different in nephrotic individuals according to the level of serum albumin prior to treatment.

Knowledge regarding the spectrum of disease in patients with nephrotic proteinuria according to the level of serum albumin can then be used in the clinical decision making as to when to perform a biopsy and in providing the patient more precise information regarding risks, benefits and alternatives of the kidney biopsy procedure, as well as potential outcome.

Methods

The pathologic reports of native kidney biopsies performed at North Carolina Baptist Hospital and examined by the Department of Pathology of Wake Forest University School of Medicine between 1 September 1987 and 31 July 2005 were reviewed. Patients > 18 years of age with proteinuria > 3 g/day and no obvious cause for proteinuria were identified, and their nephrology clinical charts and hospital records were examined. Charts were reviewed by one of two physicians (A.J.B. and K.G.) for the following information:
name, gender, race, date of birth, height, weight, history of hypertension, diabetes, malignancy or other systemic diseases, history of renal transplant, family history of kidney disease, urine analysis findings of haematuria, proteinuria, red blood cell casts, pyuria, serum albumin, blood urea nitrogen, serum creatinine, serum cholesterol and 24-h urinary protein determination. If more than one set of laboratory values were present, the values at the time closest to the kidney biopsy were used. All available historical information and laboratory tests were reviewed to exclude patients with secondary causes of nephrotic syndrome. Oedema was graded by clinicians from 0 to 4+. This grade was recorded for participants from a time period immediately prior to the kidney biopsy. Information obtained from the pathology report included reason, diagnosis and date of biopsy. All biopsies were interpreted by one renal pathologist (SSI). The biopsies of patients with focal and segmental glomerulosclerosis (FSGS) were reviewed to determine subtypes [5].

Patients who presented with idiopathic proteinuria >3 g/day were included in a further analysis. All patients with a prior history of diabetes mellitus, connective tissue disease, obstructive uropathy, human immunodeficiency virus infection or malignancy were excluded. One participant with glucocorticoid-induced diabetes mellitus that resolved after 4 days of glucocorticoid treatment was included. Patients with an antinuclear antibody titre >1:128 were excluded. Patients with acute renal failure (rise in serum creatinine of >1 mg/dL/week) or haematuria (>3 RBC/hpf) were also excluded. The purpose of the study was to examine pathologic findings in patients who presented in an ambulatory care setting for evaluation of idiopathic proteinuria >3 g/day, including patients with all values of serum albumin.

ANOVA testing was performed to compare continuous variables between the three groups. Chi-squared testing was done to compare discrete variables. Estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease formula [6]. This study was approved by the Institutional Review Board of Wake Forest University School of Medicine.

### Results

Over the 18-year period, native renal biopsies were performed at North Carolina Baptist Hospital on 1045 patients >18 years of age. Of these, 112 (10.7%) underwent a kidney biopsy for urinary protein excretion >3 g/24 h. These patients were further divided into three groups based on their serum albumin values. 57 (51%) patients having a serum albumin ≤29 g/L formed Group I, 20 (17.8%) patients having a serum albumin value between 30 and 34 g/L formed Group II and 35 (31.3%) patients with serum albumin ≥35 g/L formed Group III. Clinical characteristics of patients in each group are presented in Table 1. The mean value for proteinuria was lower in Group III than the other two groups. Patients in Group I were much more likely to have oedema and worse oedema than individuals in Groups II or III. Of interest, 36% of patients in Group I did not have oedema.

### Biopsy findings according to group

In Group III, there were 19 patients with a serum albumin >40 g/L and 13 patients with a serum albumin between 35 g/L and 40 g/L. Of the 19 patients with a serum albumin ≥40 g/L, 12 suffered solely from FSGS, 1 had focal global glomerulosclerosis and 1 had pathologic changes consistent with end-stage kidney disease/severe nephrosclerosis. Five had FSGS associated with other conditions: two with IgA nephropathy, one with FSGS and C1q nephropathy, one with FSGS and early diabetic nephropathy (no clinical signs of diabetes at the time of biopsy) and one with FSGS and a necrotic glomerulus. In the latter case, there was one necrotic glomerulus in a wedge biopsy with >100 glomeruli showing scarring ranging from segmental sclerosis and hyalinosis to global obsolescence; the clinical course was consistent with FSGS. In one case of IgA nephropathy, the biopsy was found to represent subclass 2 as designated by Haas [7]: focal and segmental glomerular sclerosis without active cellular proliferation. In the other case of IgA nephropathy, the biopsy represented subclass 5, with >40% globally sclerotic glomeruli and >40% estimated cortical tubular atrophy or loss. In summary, all individuals with a

### Table 1. Comparison of clinical characteristics between Group I (serum albumin ≤29 g/L), Group II (serum albumin 30–34 g/L) and Group III (serum albumin ≥35 g/L)

<table>
<thead>
<tr>
<th></th>
<th>Group I (mean ± SD)</th>
<th>Group II (mean ± SD)</th>
<th>Group III (mean ± SD)</th>
<th>Significance (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 17.6</td>
<td>54.2 ± 22.4</td>
<td>44.4 ± 17.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>47.4</td>
<td>50.0</td>
<td>60.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Race (% African American)</td>
<td>35.1</td>
<td>30.0</td>
<td>31.4</td>
<td>0.72</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.4 ± 21.5</td>
<td>81.2 ± 20.6</td>
<td>90.5 ± 28.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.4 ± 10.2</td>
<td>166.4 ± 12.7</td>
<td>174.2 ± 10.2</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 ± 5.7</td>
<td>29.3 ± 6.9</td>
<td>32.3 ± 7.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Oedema (mean of 0 to 4+)</td>
<td>1.5 ± 1.5</td>
<td>0.77 ± 1.3</td>
<td>0.41 ± 0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion with oedema (%)</td>
<td>64.0</td>
<td>33.0</td>
<td>28.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>25 ± 19.3</td>
<td>29.5 ± 22.9</td>
<td>20.7 ± 17.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>159.1 ± 114.9 (µmol/L)</td>
<td>167.9 ± 114.9 (µmol/L)</td>
<td>150.3 ± 79.5 (µmol/L)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>1.8 ± 1.3 (mg/dL)</td>
<td>1.9 ± 1.3 (mg/dL)</td>
<td>1.7 ± 0.9 (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>EGFR (mL/min)</td>
<td>64.3 ± 50.2</td>
<td>60.7 ± 39.8</td>
<td>56.4 ± 26.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Urine protein (g/day)</td>
<td>8.4 ± 4.7</td>
<td>5.7 ± 2.7</td>
<td>5.0 ± 2.2</td>
<td>0.00</td>
</tr>
</tbody>
</table>
between groups, likely due to the relatively small number of patients in the study, and the small proportion that suffers from specified FSGS subtypes.

**Characteristics of individuals in Group III**

As there is little information in the literature on individuals with nephrotic proteinuria and normal serum albumin values, further analyses were performed on individuals in Group III. Patients were stratified based on body weight or body mass index (BMI) and eGFR. Height and weight values were missing in 9 and 2 patients, respectively. Seventeen out of 35 patients (49%) had an eGFR <60 mL/min/1.73 m². Eighteen of 35 patients (51%) weighed >86 kg (190 lb) or had a BMI >30 kg/m². Seven (19.4%) had both.

Treatment patterns could be determined in 22 out of the 36 patients in Group III. Two patients out of the 22 received glucocorticoids, and one was treated with both glucocorticoids and immunosuppressive drugs. The remaining 19 (52.7%) patients were treated with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and did not receive any glucocorticoid or immunosuppressive therapy. Out of the 19 individuals who were not treated with any immunosuppressive or glucocorticoid medication, 12 individuals had a decrease in their eGFR at an average rate of 4.4 mL/min/year and 4 patients were lost to follow-up. Out of these 22 individuals, 7 went on haemodialysis (HD) over a mean of 6.8 ± 4 years. The mean follow-up was 6.9 ± 4.1 years with a range of 6 months to 17 years.

Of the two treated with glucocorticoids, proteinuria improved significantly in one individual while his eGFR essentially remained unchanged (patient remained off dialysis). The other individual was being evaluated for renal transplantation as per the last follow-up data (no data on follow-up urinary protein). In one patient who was treated with both glucocorticoids and immunosuppressive drugs, the eGFR essentially remained unchanged with no noticeable effect on his proteinuria while on drug therapy, although his proteinuria did decrease on stopping the immunosuppressive drugs.

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**Table 2. Distribution of disease according to group**

<table>
<thead>
<tr>
<th>Group</th>
<th>FSGS (%)</th>
<th>Minimal change disease (%)</th>
<th>Membranous GN (%)</th>
<th>Other (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (serum albumin &lt;30 g/L)</td>
<td>15 (26.3%)</td>
<td>3 (5.3%)</td>
<td>16 (28.1%)</td>
<td>23 (40.4%)</td>
<td>57</td>
</tr>
<tr>
<td>II (serum albumin ≥30 g/L and &lt;35 g/L)</td>
<td>9 (45.0%)</td>
<td>3 (15.0%)</td>
<td>4 (25.0%)</td>
<td>4 (20.0%)</td>
<td>20</td>
</tr>
<tr>
<td>III (serum albumin &gt;35 g/L)</td>
<td>26 (74.2%)</td>
<td>0</td>
<td>1 (2.9%)</td>
<td>8 (22.9%)</td>
<td>35</td>
</tr>
</tbody>
</table>

P < 0.01 for comparison of the statistical difference between all groups.

**Table 3. FSGS subclassification by group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Perihilar</th>
<th>Collapsing</th>
<th>Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>3/15 (20%)</td>
<td>2/9 (22%)</td>
<td>3/26 (12%)</td>
</tr>
<tr>
<td>Group II</td>
<td>4/15 (27%)</td>
<td>0/9 (0%)</td>
<td>1/26 (3.8%)</td>
</tr>
<tr>
<td>Group III</td>
<td>0/15 (0%)</td>
<td>0/9 (0%)</td>
<td>2/26 (7.7%)</td>
</tr>
</tbody>
</table>

P = 0.15 for comparison of the statistical difference between groups.

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Fig. 1. Percentage of individuals with focal and segmental glomerulosclerosis (FSGS) according to serum albumin.
Table 4. Percentage of individuals in each group with FSGS or sclerosis according to BMI and serum albumin

<table>
<thead>
<tr>
<th>Serum albumin (g/L)</th>
<th>&lt;24.9</th>
<th>25.0–29.9</th>
<th>30.0–34.9</th>
<th>≥35</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤29</td>
<td>2/4 (50%)</td>
<td>1/3 (33%)</td>
<td>1/7 (14%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>30–34</td>
<td>2/4 (50%)</td>
<td>1/1 (100%)</td>
<td>1/3 (33.3%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>≥35</td>
<td>4/5 (80%)</td>
<td>6/6 (100%)</td>
<td>6/9 (67%)</td>
<td>8/8 (100%)</td>
</tr>
</tbody>
</table>

Of the large body weight group, 8 out of 20 individuals weighing >86 kg in whom follow-up was available (40%) went on to dialysis over a mean of 7.25 ± 3.6 years. In the group with an eGFR <60 mL/min, 9 of 17 individuals (53%) with follow-up went on dialysis over a mean of 5.4 ± 3.5 years.

Relationship between serum albumin, obesity and FSGS

The possibility existed that normal serum albumin was present predominantly in obese individuals and that these individuals had obesity-related FSGS, which is more likely to be associated with a normal serum albumin [8]. Further analysis was therefore performed to determine the relationship between serum albumin, BMI and FSGS (Table 4). At least 15% of the individuals in each group had a BMI >30 kg/m². Only 3 out of 13 individuals with a BMI >25 kg/m² and a serum albumin <30 g/L had FSGS versus 20/23 individuals with a BMI >25 kg/m² and a serum albumin >35 g/L.

Discussion

The current investigation reveals that patients with nephrotic proteinuria and a serum albumin >35 g/L have a markedly different distribution of disease than individuals with nephrotic proteinuria and a serum albumin <30 g/L, with a markedly increased rate of FSGS. Individuals with a serum albumin between 30 and 35 g/L form an intermediate group with regard to the proportion of individuals with FSGS.

Nephrotic proteinuria with a normal serum albumin is a common clinical problem: almost one-third (34%) of patients undergoing renal biopsy for proteinuria in our study had this condition. This condition may be even more common, given the fact that these patients are frequently asymptomatic and do not present for evaluation, or they do not undergo biopsy because of their benign clinical history.

While nephrotic syndrome is generally recognized as consisting of proteinuria, hypoalbuminaemia, oedema and hypercholesterolaemia; from the time of its initial description [9], the term has not been specifically defined. As described by Heptinstall [10], ‘...most accounts of the condition either deliberately or inadvertently avoid a rigid definition.’ Nephrology textbooks frequently do not provide a specific definition as to the amount of proteinuria or the degree of hypoalbuminaemia required for the syndrome [1,11]. In a study of the clinical and histologic spectrum of nephrotic syndrome, Berman and Schreiner [4] noted the inconsistent presence of oedema, hypercholesterolaemia and hypoalbuminaemia. These authors described nephrotic syndrome as >3.5 g of protein/24 h with a ‘variable tendency toward oedema, hypoproteininaemia and hyperlipaemia’. In a study of idiopathic nephrotic syndrome [12], Churg included individuals with serum albumin values from 10 to 36 g/L and urinary protein excretion from 1.5 to 10 g/24 h. In epidemiologic studies [2,3], Haas and Korbett included individuals with urinary protein >3.5 g/24 h but did not define hypoalbuminaemia. Rivera defined nephrotic syndrome as >3.5 g/d/1.73 m² with a serum albumin <25 g/L [13]. Various investigations regarding the nephrotic syndrome have not provided the definition used [14–16]. Physiologic studies have suggested that oedema occurs when serum albumin levels fall below 30 g/L [1], though Smith noted that while the decreased colloid osmotic activity of the plasma influences the development of oedema, other factors may also be important [17].

The current investigation suggests that from a clinicopathologic perspective, limiting the diagnosis of nephrotic syndrome to individuals with a serum albumin <30 g/L is appropriate and clinically advantageous. These individuals appear to have a different spectrum of disease, and this knowledge may be useful in guiding the clinician toward further diagnosis and treatment. Oedema measurement reflects a qualitative judgment that is affected by sodium intake, diuretic usage and renal function. Oedema was not present in one-third of individuals with a serum albumin <30 g/L and appears to be a less valuable criterion to be used in the definition of the nephrotic syndrome.

Individuals with a serum albumin >40 g/L invariably had FSGS or significant glomerular sclerosis on kidney biopsy. A number of these patients were obese, and others have shown that proteinuric individuals with obesity-associated FSGS are more likely to have normal serum albumin values [8,18]. However, obese individuals with the nephrotic syndrome did not suffer exclusively from FSGS (Table 4). Moreover, almost all individuals with a serum albumin >35 g/L had FSGS, regardless of weight.

The vast majority of individuals in Group III with FSGS did not undergo therapy with immunomodulating medications. There were several likely reasons for this: (1) patients did not have the complete nephrotic syndrome and were less likely to have severe oedema which may have prompted therapy. (2) Many of the patients were obese, and therapy with prednisone may have been less likely to be attempted due to the potential for increased side effects. (3) Conservative therapy of FSGS was more common in our practice area during the time course of the study. The patients also had a very poor outcome, with 7/17 individuals proceeding to dialysis over a mean course of follow-up of 6 years. It is uncertain if more aggressive treatment may have changed this outcome.

The results of this study may help to explain the perception of an increasing frequency of FSGS in patients undergoing a kidney biopsy. As kidney biopsy becomes easier to perform and more frequent over time, individuals with normal serum albumin, some degree of renal insufficiency, or obesity may be more likely to be biopsied than in the past. Epidemiologic studies looking at changes in the incidence of FSGS have not commented on serum

Whether there was a difference in the proportion of individuals with various FSGS subtypes could not be determined in this study. The number of cases in our study was relatively small, and the percentage of individuals suffering from a particular FSGS subtype is small, as has been documented [20]. Stokes et al. have shown a statistically higher serum albumin in FSGS patients with subtype not otherwise specified, while the serum albumin was similar between cellular, collapsing and glomerular tip lesion in their series [5].

Unsurprisingly, the results of this study will likely change the approach to kidney biopsy at our center. Previously, it was considered that all individuals with nephrotic proteinuria might benefit from a kidney biopsy. Individuals with obesity and mild to moderate renal insufficiency were included as having a potential to benefit. Based on this study, it would appear that nephrotic individuals with obesity or renal insufficiency who have a serum albumin >35 g/L are overwhelmingly likely to have FSGS and unlikely to receive immunomodulating therapy. Obese individuals who have the nephrotic syndrome may have other underlying diagnoses and may have a better chance of benefiting from kidney biopsy.

A weakness of this study is that the results are from only one institution. Geographic bias in the patients who undergo a kidney biopsy might affect the spectrum of disease. Results from larger pathologic databases would be valuable in this regard. In addition, the vast majority of individuals with FSGS were not treated, and it is unclear if treatment of these individuals would have affected kidney function. Others have noted a distinction in response to therapy between individuals with FSGS and the complete nephrotic syndrome versus individuals with FSGS and nephrotic proteinuria without hypoalbuminemia, with the latter having a better prognosis [21].

An important, general principle that can be derived from this study is that a computerized database can easily be analyzed to determine the distribution of disease for distinct clinical settings. A database containing both clinical and pathologic information is especially helpful. Nephrologists should create and explore databases at their medical centers to identify their kidney biopsy patterns and what the results of these patterns are.

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Conflict of interest statement. None declared.

References

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