Study on Hyperuricemia in HBV-Associated Glomerulonephritis

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Key Words: HBV-associated glomerulonephritis; Hyperuricemia; Glomerular filtration rate; Tubular interstitial injury

ABSTRACT

Objectives: To determine the prevalence and risk factors for hyperuricemia in hepatitis B virus–associated glomerulonephritis (HBV-GN).

Methods: Univariate and multivariate logistic regression analysis was applied to decide the risk factors of hyperuricemia in HBV-GN, and clinical and pathologic data were compared between HBV-GN patients with hyperuricemia and those with normal serum uric acid.

Results: Among our 227 HBV-GN cases, 31.3% of the patients had hyperuricemia at the time of renal biopsy. Univariate analysis showed that the level of serum creatinine and the severity of glomerular and tubular interstitial injury were significantly related to hyperuricemia. Multivariate logistic regression analysis identified the levels of serum creatinine and tubular interstitial injury as independent factors for hyperuricemia. The incidence of hypertension and lower estimated glomerular filtration rate was significantly higher in hyperuricemic patients with HBV-GN than in normouricemic patients. There were also fewer membranous nephropathy, more proliferative sclerosing glomerulonephritis, and more tubular interstitial injury in hyperuricemic patients with HBV-GN.

Conclusions: Our study results suggest that hyperuricemia is common in HBV-GN, which may facilitate the progression of HBV-GN and renal tubular interstitial injury as well as the development of hypertension.

Hepatitis B virus–associated glomerulonephritis (HBV-GN) is one of the most prevalent secondary glomerular diseases in China and accounts for 0.25% of renal biopsies.1 The natural history of HBV-GN is not completely understood. Although spontaneous regression of nephrotic syndrome was reported in 30% to 60% cases with membranous nephropathy (MN) caused by HBV, these patients still remain symptomatic with active HBV serology for 12 months or longer. Patients who do not clear the virus may have renal insufficiency.2 Isolation of immune complexes from the kidney and expression of HBV viral antigens in kidney tissue suggest that the pathogenesis of HBV-GN has an immunologic basis. However, biosocial studies have detected no correlation between HBV carriage and proteinuria. Genetic studies on human leukocyte antigen class I and II genes have showed only a predisposition to MN and no correlation in those with milder degrees of proteinuria.3 These findings suggest that development of
Hyperuricemia not only is predictive of insidious, chronic, and progressive renal disease, while reduction of serum uric acid by allopurinol treatment has been associated with a slower progression of renal disease. These studies suggest that hyperuricemia not only is a consequence of renal insufficiency but also contributes to the progression of chronic kidney diseases (CKDs). A recent study has shown an independent association of hyperuricemia with the severity of liver damage in patients with nonalcoholic fatty liver disease, including hepatitis C virus. However, an association between hyperuricemia and HBV-GN has not been reported to our knowledge.

This study investigated the prevalence, underlying factors, and significance of hyperuricemia in 227 patients with HBV-GN diagnosed by renal biopsy. Our study demonstrated that hyperuricemia is common and parallels the level of serum creatinine and the degree of renal tubular interstitial injury. Hyperuricemia may facilitate the development of hypertension, can aggravate renal tubular interstitial injury, and is one of the risk factors for the progression of HBV-GN.

Materials and Methods

Patients

Of the 5,157 patients who were hospitalized in Fuzhou General Hospital of Nanjing Military Command and underwent renal biopsy from January 1999 through July 2007, 227 were diagnosed with HBV-GN, accounting for 4.4% of all renal biopsy patients in the same period. Percutaneous renal biopsy was performed by using an automatic biopsy gun that was guided by ultrasound. The diagnostic criteria for HBV-GN used in China are as follows: (a) hepatitis B surface antigen (HBsAg)-positive serum; (b) the presence of glomerular nephritis, excluding lupus nephritis and other secondary glomerular diseases; and (c) positive HBV antigens, including HBsAg or hepatitis B core antigen, or HBV DNA determined by polymerase chain reaction in kidney tissue. Approval of the study was obtained from the ethics committee of Fuzhou General Hospital of Nanjing Military Command, China.

Hyperuricemia was defined as a condition when the blood uric acid level was more than 7.0 mg/dL for male patients and more than 6.0 mg/dL for female patients. Of the 227 HBV-GN cases, 71 were hyperuricemic (group A), and the blood uric acid level was normal in the other 156 cases (group B).

Clinical Definitions

Clinical data were collected from medical records by the time of renal biopsy, including age, sex, weight, course of disease, blood pressure, serum uric acid, creatinine, triglycerides, cholesterol, serum albumin, hematuria, and 24-hour urinary protein.

The Schwartz formula was used for patients younger than 18 years—that is, estimated glomerular filtration rate (eGFR) = \(0.55 \times \text{Height (cm)} \times [\text{Serum Creatinine (mg/dL)}/88.4]^{-1}\). The simplified Modification of Diet in Renal Disease formula was used for patients older than 18 years—that is, eGFR = \(186 \times \text{(Serum Creatinine/88.4)} – 1.154 \times \text{Age} – 0.203 \times \text{(Female × 0.742)}\). Patients were grouped into different stages by CKD standards according to their eGFR (mL/min) level: stage 1 (≥90 mL/min), stage 2 (≥60 to <90 mL/min), stage 3 (≥30 to <60 mL/min), stage 4 (≥15 to <30 mL/min), and stage 5 (<15 mL/min).

The 227 HBV-GN cases were classified into four clinical categories: hematuria only, proteinuria only, proteinuria accompanied with hematuria, and nephrotic syndrome.

Pathologic Classification

Pathologic categories were sorted according to the Pathological Categories of Renal Glomerular Diseases amended by the World Health Organization in 1995. Among the 227 HBV-GN cases, eight different pathologic types were found: MN, membranoproliferative glomerulonephritis (MPGN), immunoglobulin A nephropathy, mesangial proliferative glomerulonephritis (MsPGN), minimal change disease, focal segmental proliferative GN, focal segmental glomerulosclerosis, and proliferative sclerosing glomerulonephritis (SGN; 50%-75% of glomerulus showed sclerosis, and remnant showed proliferation and segmental sclerosis).

The presence of Bowman capsule adhesion, crescent formation, glomerulosclerosis, and immune complex deposit was also examined. Mesangial proliferation and tubular interstitial injury were classified into four levels: 0 (no injury), 1 (mild injury, injury area <25%), 2 (moderate injury, injury area 25%-50%), and 3 (severe injury, injury area >50%).

Statistical Analysis

Statistical analyses were performed using SPSS 11.5 (SPSS, Chicago, IL). Continuous variables were expressed as mean ± SD, while categorical variables were shown as frequency and percentage. Categorical data were tested using the Pearson \(\chi^2\) test. Differences in the continuous variables between the groups were compared using the \(t\) test or one-way analysis of variance. Univariate and multivariate logistic regression analyses were used to examine the potential...
predisposing factors for hyperuricemia. In univariate and multivariate analyses, variables were expressed as a binary scale or multiple scales, such as absence/presence (coded as 0/1) or no/mild/moderate/severe (coded as 0/1/2/3). The results of the univariate and multivariate analyses were expressed as odds ratio (ORs) and their 95% confidence intervals. The Pearson $\chi^2$ test was one-tailed while all other tests were two-tailed, and factors with a $P$ value less than .05 were considered statistically significant.

Results

Prevalence of Hyperuricemia in Patients With HBV-GN

Seventy-one of the 227 patients who had HBV-GN had hyperuricemia. The incidence of hyperuricemia was not significantly different ($P > .05$) between males (33.7%) and females (24.6%). However, the occurrence of hyperuricemia among children (age <15 years) was significantly lower than among adults (6/50 vs 65/177; $P < .01$).

Clinical and Histopathologic Risk Factors for Hyperuricemia in Patients With HBV-GN

Univariate analysis showed that the prevalence of hyperuricemia was significantly higher in patients with HBV-GN with a serum creatinine of 1.50 mg/dL or higher, a moderate to severe degree of mesangial proliferation, glomerular sclerosis of 50% or more, crescent formation, and moderate to severe degree of tubular interstitial damage of the kidney. Among the clinical and pathologic factors, OR analysis showed that an increase of serum creatinine and the degree of renal tubular interstitial damage were associated with hyperuricemia in HBV-GN (Table 1), which were proven as independent risk factors by multivariate logistic regression analysis (Table 2).

We observed that the decrease of eGFR was associated with serum uric acid (Figure 1). To further examine the effect of renal function on hyperuricemia, we divided patients into three groups according to the level of the glomerular filtration rate (GFR). When the eGFR was below 60 mL/min, the prevalence of hyperuricemia increased to 60.5%, which was significantly higher than that in patients with stage 1 and stage 2 CKD ($P < .05$) (Table 3).

To further detect the effect of tubular interstitial injury on hyperuricemia, we compared the serum uric acid level of patients with different levels of tubular interstitial injury. Compared with patients with no renal tubular interstitial injury, the level of serum uric acid was significantly higher in patients who had HBV-GN with moderate or severe renal tubular interstitial injury (Figure 2).

<table>
<thead>
<tr>
<th>Factors</th>
<th>$\chi^2$</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine ≥1.50 mg/dL</td>
<td>18.81</td>
<td>5.04 (2.31-10.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glomerulosclerosis</td>
<td>8.73</td>
<td>2.97 (1.41-6.25)</td>
<td>.003</td>
</tr>
<tr>
<td>Crescent formation</td>
<td>4.43</td>
<td>2.14 (1.04-4.40)</td>
<td>.035</td>
</tr>
<tr>
<td>Mesangial proliferation (≥2)</td>
<td>5.69</td>
<td>2.08 (1.13-3.80)</td>
<td>.017</td>
</tr>
<tr>
<td>Tubular interstitial injury (≥2)</td>
<td>10.78</td>
<td>3.91 (1.66-9.22)</td>
<td>.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; HBV-GN, hepatitis B virus–associated glomerulonephritis; OR, odds ratio.

$\geq 2$ Indicates moderate or severe level of mesangial proliferation or tubular interstitial injury.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Exp(β) (SE)</th>
<th>$\chi^2$</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr ≥1.50 mg/dL</td>
<td>1.400 (0.435)</td>
<td>10.355</td>
<td>4.053 (1.728-9.506)</td>
<td>.001</td>
</tr>
<tr>
<td>Tubular interstitial injury (≥2)</td>
<td>0.532 (0.271)</td>
<td>3.862</td>
<td>1.702 (1.001-2.893)</td>
<td>.049</td>
</tr>
</tbody>
</table>

CI, confidence interval; HBV-GN, hepatitis B virus–associated glomerulonephritis; OR, odds ratio; Scr, serum creatinine.

$\geq 2$ Indicates moderate or severe level of mesangial proliferation or tubular interstitial injury.
Clinical and Histopathologic Parameters in Hyperuricemic Patients With HBV-GN

We divided 227 cases of HBV-GN into a hyperuricemic group (n = 71) and a normouricemic group (n = 156). No significant difference was observed when variables, including sex, body weight, course of disease, serum triglycerides, serum cholesterol, and serum albumin, were compared between the two groups (P > .05). There was also no significant difference in the type of clinical manifestations. However, the mean ± SD age of the patients in the hyperuricemic group was 28.2 ± 11.6 years, which was older than that of the normouricemic group. The prevalence of hypertension in the hyperuricemic group was 29.6% (21/71), which was significantly higher than that of the normouricemic group (18.0%) Table 4.

Analysis on the HBV-GN pathologic categories between the hyperuricemic and normouricemic groups revealed that most normouricemic patients with HBV-GN had MN (n = 69; 44.2%), while there was a near even distribution of MN (n = 21; 29.6%), MsPGN (n = 16; 22.5%), and MPGN (n = 15; 21.1%) in hyperuricemic patients with HBV-GN. The percentage of MN was significantly lower (P < .05), while SGN was higher (P < .01), in the hyperuricemic HBV-GN cases Table 5.

Comparisons of pathologic indices between hyperuricemic and normouricemic groups showed that the prevalence of glomerulosclerosis (>50%), crescent formation, saccus adhesion, moderate to severe mesangial proliferation, and renal interstitial tubular injury in hyperuricemic patients with HBV-GN was significantly higher than that in the normouricemic patients with HBV-GN (P < .05) Table 6.

Table 3
Relationship Between Prevalence of Hyperuricemia and Stage of CKD in HBV-GN

<table>
<thead>
<tr>
<th>CKD Stages</th>
<th>Prevalence of Hyperuricemia, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1, eGFR &gt;90 mL/min</td>
<td>132 (21.2)</td>
</tr>
<tr>
<td>Stage 2, eGFR 60-89 mL/min</td>
<td>57 (35.1)</td>
</tr>
<tr>
<td>Stages 3-5, eGFR &lt;60 mL/min</td>
<td>38 (60.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>227 (31.3)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBV-GN, hepatitis B virus–associated glomerulonephritis.

Figure 2 Effect of the degree of renal tubular interstitial injury (TIL) on serum uric acid (SUA) level in hepatitis B virus–associated glomerulonephritis. Circles represent outliers that extend between 1.5 and 3.0 times the interquartile range. Asterisks indicate extreme outliers beyond 3.0 times the interquartile range.

Table 4
Comparisons of Clinical Features Between Hyperuricemic vs Normouricemic Patients With HBV-GN

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperuricemic (n = 71)</th>
<th>Normouricemic (n = 156)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>28.2 ± 11.6</td>
<td>24.6 ± 12.7</td>
<td>.041&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex, M/F, No.</td>
<td>56/15</td>
<td>110/46</td>
<td>.188</td>
</tr>
<tr>
<td>Disease course ≥3 y, No.</td>
<td>16</td>
<td>35</td>
<td>.987</td>
</tr>
<tr>
<td>Clinical category, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria only</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Proteinuria only</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Proteinuria with hematuria</td>
<td>33</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>35</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>21 (29.6%)</td>
<td>28 (18.0%)</td>
<td>.048&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Laboratory values, mean ± SD&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h Urinary protein, g/dL</td>
<td>4.12 ± 4.06</td>
<td>3.39 ± 3.27</td>
<td>.148</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>299.61 ± 142.47</td>
<td>272.97 ± 117.76</td>
<td>.139</td>
</tr>
<tr>
<td>Serum triglyceride, mg/dL</td>
<td>184.96 ± 121.24</td>
<td>169.03 ± 140.71</td>
<td>.513</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>2.73 ± 1.06</td>
<td>2.87 ± 1.07</td>
<td>.346</td>
</tr>
<tr>
<td>Scr ≥1.50 mg/dL, No.</td>
<td>21</td>
<td>12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Scr, mg/dL</td>
<td>1.87 ± 2.34</td>
<td>0.98 ± 1.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>80.50 ± 44.31</td>
<td>110.35 ± 41.70</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>eGFR</sup>, estimated glomerular filtration rate; HBV-GN, hepatitis B virus–associated glomerulonephritis; Scr, serum creatinine.

<sup>a</sup> P < .05 between hyperuricemic and normouricemic HBV-GN.

<sup>b</sup> Laboratory values are given in conventional units; conversions to Système International units are as follows: serum cholesterol (mmol/L), multiply by 0.0259; serum triglyceride (mmol/L), multiply by 0.0113; serum albumin (g/L), multiply by 10; Scr (μmol/L), multiply by 88.4.
Discussion

Our study showed that the prevalence of hyperuricemia in patients with HBV-GN is 31.3%, which is similar to other GN. We did not find that liver function and HBV titer affected blood uric acid level. However, when the serum creatinine level was 1.50 mg/dL or higher—an indicator of impaired renal function—and when the GFR decreased by more than 50%, the prevalence of hyperuricemia in HBV-GN was four times higher than in patients with HBV-GN with a normal serum creatinine level (OR, 5.04), which is consistent with other studies. This suggests that reduced glomerular filtration and decreased uric acid excretion from tubules contribute to the development of hyperuricemia in HBV-GN. It was believed that long-term hypertension leads to benign arteriosclerosis in the kidney glomerulus and that lack of oxygen and blood supply to the kidney tubules causes lactic acidosis, which challenges the excretion of uric acid and causes retention of uric acid and subsequent hyperuricemia.10

Hyperuricemia may also promote the progression of HBV-GN. An earlier study by Syrjanen et al11 indicated that hyperuricemia increased the risk of progression of immunoglobulin A (IgA) nephropathy by 2.4-fold compared with the IgA nephropathy associated with a normal level of blood uric acid. In the Japanese population, the relative risk of developing high serum creatinine in people with a serum uric acid level of 8 mg/dL or higher was 2.91 in men and 10.39 in women, which is much higher than those with a serum uric acid level less than 5.0 mg/dL.12 It has been reported that, in cisplatin-induced acute kidney injury, hyperuricemia results in more severe kidney injury without significant formation of uric acid crystals.13 Tomita et al14 reported that once blood uric acid levels rose, the risk of renal failure increased significantly. Data from our study showed that hyperuricemic patients with HBV-GN had more severe hypertension and more severe glomerular and renal interstitial tubular injury than those with normal levels of blood uric acid. The incidence of an eGFR less than 60 mL/min in hyperuricemic patients with HBV-GN was 32.4%, which was significantly higher than that in patients with HBV-GN who had a normal uric acid level (9.6%; \( P < .01 \)).

The mechanism of how hyperuricemia influences the progression of renal diseases is not clear. It has been postulated that uric acid can promote the expression of chemotactic factors and cytokines, activate the renin-angiotensin system, increase C-reactive protein expression in blood vessels, facilitate proliferation of vascular smooth muscle cells, and promote hypertension and atherosclerosis. Hence, uric acid has been one of the most important factors to cause inflammation, endothelial dysfunction, and vascular diseases.15 In addition, uric acid can also directly activate antigen presentation and increase CD70 expression of T lymphocytes and thus is involved in the development of immunologic diseases.16 Even mild hyperuricemia can increase transforming growth factor-\( \beta \) excretion into the urine and aggregate hypertension and renal dysfunction.17 It has been found that an increase of...
blood uric acid level by 1.0 mg/dL. heightens the relative risk of developing hypertension by 23%. A high blood uric acid level also increases renin secretion and hence promotes hypertension. In our study, the prevalence of hypertension was 29.6% in hyperuricemic patients with HBV-GN, which was significantly higher than that found in normouricemic patients with HBV-GN (18.0%; P < .05).

Control of serum uric acid level can theoretically benefit HBV-GN therapy. A control study had shown that in patients with diabetic nephropathy (serum creatinine <3 mg/dL), lowering the serum uric acid level with allopurinol treatment for four months caused a significant attenuation of proteinuria.

Due to the concerns of liver impairment caused by HBV and the side effects of allopurinol, the effectiveness of allopurinol to treat proteinuria needs to be further investigated. It will also be of interest to investigate gene polymorphisms potentially involved in the development of hyperuricemia as well as the therapeutic responses to uric acid–lowering reagents in patients with HBV-GN.

In conclusion, our study results showed that around 30% of patients with HBV-GN have hyperuricemia. Hypertension, elevated serum creatinine (≥1.50 mg/dL), severity of glomerular damage (mesangial expansion, glomerulosclerosis, and crescent formation), and renal tubular interstitial injury are associated with hyperuricemia in HBV-GN. Our results from this retrospective case control study may shed light on the necessity of future therapeutic regimens to control hyperuricemia in patients with HBV-GN.

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References


