Original Paper

Clinicopathological Characteristics, Role of Immunosuppressive Therapy and Progression in IgA Nephropathy with Hyperuricemia

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Key Words

IgA nephropathy • Hyperuricemia • Characteristics • Therapy • Outcome

Abstract

Background/Aims: The aim of the study was to investigate clinicopathological characteristics, the role of immunosuppressive therapy and renal outcome in IgA nephropathy (IgAN) patients with hyperuricemia. **Methods:** 206 biopsy-proven primary IgAN patients were included between January 2010 and December 2015, and divided into two groups: patients without hyperuricemia (n=122), and patients with hyperuricemia (n=84). The clinicopathological features, response, renal outcome and safety were recorded. In univariate and multivariate models, hyperuricemia-associated pathological factors were analyzed. **Results:** The patients with hyperuricemia presented higher systolic blood pressure, worse kidney function and more severe time-averaged proteinuria. Proportions of glomerulosclerosis, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, lymphocytes and monocytes infiltration were higher, while the proportion of segmental adhesion was lower in patients with hyperuricemia. By multivariate logistic regression analysis, only tubular atrophy/interstitial fibrosis (T1~2) (HR=3.969, 95% CI=1.439–10.945, P=0.008) was significantly associated with hyperuricemia. For hyperuricemic patients, the response rate to therapy and renal survival rate were significantly higher in patients that received RAS blockade in combination with immunosuppressive therapy. After RAS blockade treatment, renal survival in the patients with hyperuricemia was worse compared with the patients without hyperuricemia. **Conclusion:** Hyperuricemic IgAN patients presented more severe clinical features. Tubulointerstitial injury

could be a pathological feature closely related to hyperuricemia in IgAN. Immunosuppressive therapy and RAS blockade could reduce proteinuria and improve renal outcome in IgAN patients with hyperuricemia.

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Introduction

IgA nephropathy (IgAN) is characterized by the predominant deposition of IgA in the glomerular mesangium, which is the most common form of glomerulonephritis worldwide and accounts for nearly half of the primary glomerular diseases in China [1]. Hyperuricemia appears to be common in IgAN patients even with normal glomerular filtration rate (GFR). Besides, end stage renal disease (ESRD) occurs in approximately 15% of IgAN patients within 10 years [2]. Hyperuricemia has been considered as a risk factor for progression of chronic kidney disease as well as IgAN [3, 4]. However, few studies have explored the detailed characteristics of IgAN patients with hyperuricemia.

Recently, the Oxford classification, a new histopathologic classification of IgAN, was developed by the International IgA Nephropathy Network [5-7]. The current classification consisted of five histopathologic features—mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and cellular/fibrocellular crescents (C). The purpose of this classification was to be reliable and simple for predicting clinical outcome, although it required validation in different populations [8]. Renin-angiotensin system (RAS) blockade including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB), even corticosteroids and immunosuppressants, were gradually utilized for treatment of IgAN [9].

Nevertheless, few follow-up trials included pathologic factors and intended to systematically evaluate the association between pathological features (especially the Oxford classification) or treatment and hyperuricemia. In this single-center, retrospective study, we took advantage of our cohort to investigate clinicopathological characteristics, therapeutic effectiveness of immunosuppressive therapy and renal outcome in IgA nephropathy with hyperuricemia from China.

Materials and Methods

Patients

Patients with biopsy-proven IgAN from January 2010 to December 2015 were enrolled in this study, who were in hospital at Fujian Provincial Hospital. Exclusion criteria were as follows: fewer than eight glomeruli on the biopsy; and secondary causes of mesangial IgA deposits, such as Henoch-Schönlein purpura, liver disease and systemic lupus erythematosus.

Measurements

Demographic and clinicopathologic data at biopsy were collected as follow: age, gender, medical history, systolic and diastolic blood pressure, body mass index (BMI), serum creatinine, blood urea nitrogen (BUN), serum albumin, uric acid, serum cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, amount of red blood cell (RBC) in urine and proteinuria, serum IgA and treatment modalities. Information on proteinuria and serum creatinine was obtained during the follow-up period.

Hyperuricemia was defined as a serum uric acid concentration greater than 420 $\mu\text{mol/L}$ in males and 360 $\mu\text{mol/L}$ in females. Hypertension referred to a blood pressure $\geq 140/90$ mmHg; blood pressure measurements were repeated twice in a patient in a sitting position and in the patient's right arm. Mean arterial pressure (MAP) was defined as a diastolic pressure plus one-third of the pulse pressure. Proteinuria was measured by a 24-h urine protein collection. The average of proteinuria every 6 months was calculated, which represented the time-averaged proteinuria. Renin-angiotensin system (RAS) blockade included angiotensin-

converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or both. Immunosuppressive therapy was defined as receiving corticosteroids with or without an immunosuppressant. Corticosteroid therapy indicated use of oral prednisone (started at 1.0 mg/kg per day for 6 to 8 weeks and then tapered to 5 to 10 mg every 2 weeks) for 6 months at least. Immunosuppressants indicated cyclophosphamide (used at a total dosage of 6 to 8 g). RAS blockade combined with immunosuppressive therapy was called combination therapy. Response was defined as $\geq 50\%$ reduction in proteinuria during follow-up, with a stable kidney function (serum creatinine within the normal range or not increased by 30% more than baseline values). Non-response was defined as $< 50\%$ reduction in baseline proteinuria or progression to renal survival end point (ESRD or doubling of creatinine level).

All renal biopsy specimens were divided routinely for immunofluorescence microscopy, light microscopy and electron microscopy. The paraffin-embedded sections were stained with hematoxylin and eosin, periodic acid-Schiff, silver methenamine, and Masson's trichrome. All renal biopsy results were reviewed independently by two renal pathologists according to the Oxford and Lee's classifications [5, 6]. Five pathologic features of the Oxford classification were defined as follows: mesangial score of ≤ 0.5 (M0) or > 0.5 (M1); segmental glomerulosclerosis absent (S0) or present (S1); endocapillary hypercellularity absent (E0) or present (E1); tubular atrophy/interstitial fibrosis $\leq 25\%$ (T0), 26–50% (T1) or $> 50\%$ (T2); and cellular/fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in $> 25\%$ of glomeruli (C2). Pathological features also included global glomerulosclerosis, segmental adhesion, interstitial inflammation, vascular lesions and IgA glomerulus immunofluorescence.

Outcome

The time of renal biopsy was used as the starting point, and the study end point was defined as: 1) End-stage renal disease (ESRD); or 2) doubling of creatinine level. ESRD was defined as an estimated glomerular filtration rate (eGFR) of < 15 ml/min per 1.73 m², using the modified Modification of Diet in Renal Disease equation for the Chinese population or initiation of dialysis or transplantation [10].

Statistical analysis

Continuous variables were expressed as the means $\pm$ standard deviation or medians with the 25th and 75th percentiles and analyzed by *t*-test, Mann-Whitney U-test or Kruskal-Wallis H-test. Categorical variables were presented as frequency with percentages and analyzed using Fisher and χ^2 test. The occurrence of response and renal survival times were analyzed with the Kaplan-Meier method compared by Log rank test. Univariate followed by multivariate logistic regression were used to determine the independent correlative factors for hyperuricemia. All pathologic features were included in univariate logistic regression and only pathologic features significantly associated with hyperuricemia were considered in multivariate logistic regression. The results were expressed as hazard ratio (HR) with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. All statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

The mean age of 206 patients included in the study was 33.2 ± 10.0 years at the time of biopsy. Mean eGFR was 88.4 ± 41.1 ml/min per 1.73 m². According to the Kidney Disease Outcomes Quality Initiative classification, 94 (45.6%), 56 (27.2%), 43 (20.9%) and 13 (6.3%) patients had stages 1 to 4 chronic kidney disease separately. Mean uric acid concentration was 373.0 ± 112.3 μ mol/L, and 84 (40.8%) patients had hyperuricemia. All patients received RAS blockade. 125 (60.7%) patients received RAS blockade alone; 81 (39.3%) patients received corticosteroids which included 25 patients (12.1%) combined with cyclophosphamide. There was no patient treated with urate lowering therapy, such as xanthine oxidase inhibitor at the time of onset and during follow-up.

The patients were divided into two groups according to level of uric acid, namely, without hyperuricemia and with hyperuricemia. At the time of renal biopsy, patients with

Table 1. Clinical characteristics of IgA nephropathy patients without or with hyperuricemia. ^ap value: comparison between two groups. p<0.05 was considered significant. HUA, hyperuricemia; BP, blood pressure; MAP, mean arterial pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; RBC, red blood cell; RAS, renin-angiotensin system; ESRD, end-stage renal disease

Parameter	Without HUA (n=122)	With HUA (n=84)	p value ^a
Age (years)	32.7±10.2	34.0±10.0	0.364
Male (n, %)	48, 39.3%	38, 45.2%	0.399
Interval between presentation and biopsy (months)	3 (1, 12)	6 (1, 12)	0.147
Tonsillitis (n, %)	10, 8.2%	2, 2.4%	0.128
BMI (kg/m ²)	21.7±3.3	22.0±3.1	0.484
Hypertension (n, %)	26, 21.3%	26, 31.0%	0.118
Systolic BP (mmHg)	119.6±16.5	127.0±16.5	0.002
Diastolic BP (mmHg)	77.5±13.6	81.0±11.7	0.056
MAP (mmHg)	91.5±13.9	96.3±12.6	0.012
Uric acid (μmol/L)	299.9±61.5	479.2±79.9	<0.001
Serum creatinine (μmol/L)	79.7±29.2	136.6±62.5	<0.001
Serum creatinine >133μmol/L (n, %)	7, 5.7%	35, 41.7%	<0.001
eGFR (ml/min/1.73 m ²)	106.4±37.4	62.3±31.3	<0.001
BUN (mmol/L)	5.1±1.6	8.1±3.5	<0.001
Proteinuria (g/day)	1.7±0.6	1.8±0.7	0.650
Serum albumin (g/L)	37.4±5.2	37.3±4.8	0.948
Cholesterol (mmol/L)	5.4±1.4	5.8±1.4	0.065
Triglycerides (mmol/L)	1.6±1.2	1.9±1.2	0.055
HDL-C (mmol/L)	1.3±0.4	1.2±0.4	0.093
LDL-C (mmol/L)	3.4±1.2	3.6±1.2	0.140
Hemoglobin (g/L)	127.6±16.6	123.8±20.7	0.166
RBC in urine ≥ 2+ (n, %)	41, 33.6%	26, 31.0%	0.689
Serum IgA (g/L)	3.0±0.9	2.9±1.0	0.441
Follow-up			
Length of follow-up (months)	29±15	33±17	0.101
Time-averaged proteinuria (g/day)	1.0±0.6	1.4±0.8	0.001
Time-averaged proteinuria (n, %)			
≤0.3	5, 4.1%	1, 1.2%	
0.3–1.0	63, 51.6%	37, 44.0%	
1.0–2.0	46, 37.7%	24, 28.6%	0.008
2.0–3.0	8, 6.6%	19, 22.6%	
≥3.0	0, 0%	3, 3.6%	
Treatment			
RAS blockade	75, 61.5%	50, 59.5%	
RAS blockade+Immunosuppressive therapy	47, 38.5%	34, 40.5%	0.778
Response (n, %)			
RAS blockade	33, 44.0%	14, 28.0%	0.070
RAS blockade+Immunosuppressive therapy	33, 70.2%	18, 52.9%	0.112
ESRD or doubling serum creatinine (n, %)			
RAS blockade	2, 2.7%	13, 26.0%	<0.001
RAS blockade+Immunosuppressive therapy	0, 0%	3, 8.8%	0.039

hyperuricemia presented with higher systolic blood pressure (127.0±16.5 mmHg vs. 119.6±16.5 mmHg, P=0.002), higher MAP (96.3±12.6 mmHg vs. 91.5±13.9 mmHg, P=0.012), higher levels of serum creatinine (136.6±62.5 μmol/L vs. 79.7±29.2 μmol/L, P<0.001), higher levels of BUN (8.1±3.5 mmol/L vs. 5.1±1.6 mmol/L, P<0.001) and lower eGFR (62.3±31.3 ml/min/1.73m² vs. 106.4±37.4 ml/min/1.73m², P<0.001) than patients without hyperuricemia. There were no significant differences in age, gender, interval between presentation and biopsy, BMI, diastolic blood pressure, occurrence of hypertension and tonsillitis, proteinuria, serum albumin, lipid, hemoglobin, hematuria and serum IgA between the patients in both groups. During follow-up period, the time-averaged proteinuria was significantly higher in patients with hyperuricemia (1.4±0.8 g/day vs. 1.0±0.6 g/day, P=0.001). Despite of similar length of follow-up, treatment modalities and response to treatment between two groups, more patients with hyperuricemia progressed to ESRD or doubling serum creatinine than patients without hyperuricemia, no matter which treatment modality these patients received (in patients that received RAS blockade, 26.0% vs. 2.7%, P<0.001; in patients that received RAS blockade and immunosuppressive therapy, 8.8% vs. 0%, P=0.039) (Table 1).

Pathological characteristics

As shown in Table 2, pathological features including glomerulosclerosis (95.2% vs. 79.5%, $P=0.001$), segmental glomerulosclerosis (S1) (69.0% vs. 51.6%, $P=0.013$), tubular atrophy/interstitial fibrosis (T1~2) (54.8% vs. 13.1%, $P<0.001$), lymphocytes and monocytes infiltration $>25\%$ (41.7% vs. 9.0%, $P<0.001$), Lee's classification (Grade IV 63.1% vs. 27.9%, $P<0.001$) were more severe in patients with hyperuricemia. Segmental adhesion was more prevalent in patients without hyperuricemia (73.8% vs. 59.5%, $P=0.031$). There was no difference in mesangial hypercellularity (M1), endocapillary hypercellularity (E1), crescents (C1~2), vascular lesions and IgA glomerulus immunofluorescence between two groups (Table 2).

Hyperuricemia-associated pathological factors

When analyzing associations between hyperuricemia and various pathologic parameters, univariate logistic regression analysis showed that glomerulosclerosis (HR=5.155, 95% CI=1.722–15.427, $P=0.003$), segmental glomerulosclerosis (S1) (HR=2.089, 95% CI=1.166–3.743, $P=0.013$), tubular atrophy/interstitial fibrosis (T1~2) (HR=8.020, 95% CI=4.067–15.813, $P<0.001$), lymphocytes and monocytes infiltration $>25\%$ (HR=7.208, 95% CI=3.383–15.355, $P<0.001$), segmental adhesion (HR=0.523, 95% CI=0.289–0.947, $P=0.032$) were positively correlated with hyperuricemia. Then by multivariate logistic regression analysis, only tubular atrophy/interstitial fibrosis (T1~2) (HR=3.969, 95% CI=1.439–10.945, $P=0.008$) remained to be significantly associated with hyperuricemia (Table 3). For patients with CKD stage 1 and 2, in univariate logistic regression analysis, only tubular

Table 2. Pathologic features of IgA nephropathy patients with or without hyperuricemia at the time of biopsy. ^a p value: comparison between two groups. $p<0.05$ was considered significant. HUA, hyperuricemia

Parameter	Without HUA (n=122) (n, %)	With HUA (n=84) (n, %)	p value ^a
Global glomerulosclerosis	97, 79.5%	80, 95.2%	0.001
Segmental adhesion	90, 73.8%	50, 59.5%	0.031
Mesangial hypercellularity M0/M1	57, 46.7%/65, 53.3%	41, 48.8%/43, 51.2%	0.768
Endocapillary hypercellularity E0/E1	81, 66.4%/41, 33.6%	61, 72.6%/23, 27.4%	0.343
Segmental glomerulosclerosis S0/S1	59, 48.4%/63, 51.6%	26, 31.0%/58, 69.0%	0.013
Tubular atrophy/interstitial fibrosis T0/T1~2	106, 86.9%/16, 13.1%	38, 45.2%/46, 54.8%	<0.001
Crescents C0/C1~2	56, 45.9%/66, 54.1%	36, 42.9%/48, 57.1%	0.666
Lymphocytes and monocytes infiltration			
0–25%	111, 91.0%	49, 58.3%	<0.001
$>25\%$	11, 9.0%	35, 41.7%	
Arteriolar wall thicken	59, 48.4%	47, 56.0%	0.284
Arteriolar hyaline degeneration	40, 32.8%	36, 42.9%	0.141
IgA glomerulus immunofluorescence			
+ / ++	78, 63.9%	55, 65.5%	0.840
+++ / ++++	44, 36.1%	29, 34.5%	
Lee's classification			
II	10, 8.2%	3, 3.6%	<0.001
III	78, 63.9%	28, 33.3%	
IV	34, 27.9%	53, 63.1%	

Table 3. Associations between pathologic features and hyperuricemia analyzed by logistic regression. ^a Multivariate model: All pathologic features significantly associated with hyperuricemia were included. CI, confidence interval. $p<0.05$ was considered significant

Parameter	Univariate analysis			Multivariate analysis ^a		
	HR	95% CI	p value	HR	95% CI	p value
Global glomerulosclerosis	5.155	1.722–15.427	0.003	2.586	0.805–8.308	0.111
Segmental adhesion	0.523	0.289–0.947	0.032	0.559	0.275–1.138	0.109
Mesangial hypercellularity M1	0.920	0.527–1.604	0.768			
Endocapillary hypercellularity E1	0.745	0.405–1.370	0.343			
Segmental glomerulosclerosis S1	2.089	1.166–3.743	0.013	1.906	0.948–3.832	0.070
Tubular atrophy/interstitial fibrosis T1~2	8.020	4.067–15.813	<0.001	3.969	1.439–10.945	0.008
Crescents C1~2	1.131	0.646–1.980	0.666			
Lymphocytes and monocytes infiltration $>25\%$	7.208	3.383–15.355	<0.001	1.918	0.608–6.051	0.267
Arteriolar wall thicken	1.356	0.776–2.370	0.285			
Arteriolar hyaline degeneration	1.537	0.866–2.370	0.142			
IgA glomerulus immunofluorescence $\geq+++$	0.935	0.522–1.673	0.820			

atrophy/interstitial fibrosis (T1~2) (HR=3.483, 95% CI=1.322–9.177, P=0.012) was strongly associated with hyperuricemia.

Response to immunosuppressive therapy and renal outcome

Mean follow-up period for these patients was 31±16 months. The patients with and without hyperuricemia could be divided into 2 groups, respectively, according to whether they received immunosuppressive therapy in addition to RAS blockade (or called combination therapy). Duration of follow-up among these 4 groups was similar (P=0.093). For the patients with hyperuricemia, response rates to RAS blockade alone at 1, 2 and 3 years were 56.9%, 35.9% and 25.1%, respectively, but response rates to combination therapy at 1, 2 and 3 years were 86.9%, 63.5% and 51.3%, respectively; the rates were significantly higher in patients that received combination therapy. For the patients without hyperuricemia, response rates also were significantly higher in patients that received combination therapy. For the patients that received the same treatment, there was no significant difference in response to treatment between patients with and without hyperuricemia.

Doubling of serum creatinine or ESRD occurred in 18 patients (8.7% of all patients). No death was reported in all patients. For the patients with hyperuricemia, the 3-year renal survival rate was significantly higher in patients that received combination therapy (85.8% vs. 75.2%, log-rank P=0.047). Renal survival rate in the patients that presented hyperuricemia and received RAS blockade alone was worse compared with each one of the other three groups. For the patients that received combination therapy, there was no significant difference in renal survival between patients with and without hyperuricemia in the follow-up (log-rank P=0.067) (Fig. 1).

Safety

The side effects of the drugs were mild during follow-up. Two patients that received ACEI experienced tolerable cough that was controlled after ACEI dose was reduced. Two patients treated with corticosteroids experienced common cold that was controlled quickly

Fig. 1. Kaplan-Meier renal survival for patients with IgA nephropathy. All patients were divided into 4 groups according to whether patients presented hyperuricemia and received combination therapy. Combination therapy included RAS blockade and immunosuppressive therapy. Compared with the patients that presented hyperuricemia and received RAS blockade alone, the renal survival rate in each one of the other three groups was significantly higher (a: log-rank test, p=0.001; b: log-rank test, p=0.003; c: log-rank test, p=0.047). There was no significant difference in renal survival between any two groups of group a, b and c (a vs. b: log-rank test, p=0.237; b vs. c: log-rank test, p=0.328; a vs. c: log-rank test, p=0.067). HUA, hyperuricemia; RAS, renin-angiotensin system. p<0.05 was considered significant.

after symptomatic treatment. None of the patients that received immunosuppressive therapy developed diabetes mellitus. Serious adverse events such as serious infections and hyperkalemia were not observed in all patients.

Discussion

To date, only few studies have investigated clinicopathological characteristics, therapeutic effectiveness of treatment and renal outcome after treatment in IgA nephropathy with hyperuricemia from China. However, studies investigating clinicopathologic features, response to treatment, especially immunosuppressive therapy, and prognosis can contribute to better understanding about the association between clinicopathological features and hyperuricemia and also provide meaningful evidence for intervention strategies. In this study, we found that for patients with hyperuricemia, systolic blood pressure, serum creatinine, BUN, time-averaged proteinuria, proportions of glomerulosclerosis, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, lymphocytes and monocytes infiltration, grade IV according to Lee's classification were all significantly higher, while eGFR and the proportion of segmental adhesion were significantly lower. Then we found that by multivariate logistic regression analysis, only tubular atrophy/interstitial fibrosis was the hyperuricemia-associated pathological factor for IgAN patients and even for patients with normal eGFR. Moreover, immunosuppressive therapy combined with RAS blockade, rather than RAS blockade therapy alone, was more effective in reduction of proteinuria and improved renal outcome in IgAN patients with hyperuricemia. Therapeutic effectiveness of immunosuppressive therapy and renal outcome after RAS blockade treatment and immunosuppressive therapy in patients with hyperuricemia was similar to that in those without hyperuricemia.

Our study showed that elevated blood pressure and impaired kidney function were more common in hyperuricemic IgAN patients. A recent clinical investigation by Shu et al. illustrated the similar results [11]. However, several studies reported no significantly difference in blood pressure, proteinuria or serum creatinine between patients with and without hyperuricemia, possibly because populations with different clinical characteristics were included in these studies [12, 13].

In our study, glomerulosclerosis, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, lymphocytes and monocytes infiltration were more prevalent in IgAN patients with hyperuricemia and therefore these pathological features might explain a higher proportion of grade IV according to Lee's classification in these patients. Similarly, two recent studies found that prevalence of segmental glomerulosclerosis and tubulointerstitial fibrosis were greater in patients with hyperuricemia in comparison to the patients without hyperuricemia [11, 14]. Two studies from China and Japan, respectively, showed that glomerulosclerosis was also more common in hyperuricemic IgAN patients [13, 15]. However, these studies indicated several different results. Patients with hyperuricemia presented with more severe mesangial hypercellularity in the study conducted by Shu et al. and more vascular lesions as reported by Cheng et al. [11, 15]. This might be explained by diversity of disease severity in patients enrolled from different centers and should be explored by more clinical trials. Furthermore, by multivariate logistic regression analysis, we found that only tubular atrophy/interstitial fibrosis was independently associated with hyperuricemia in IgAN patients and the result was similar even in patients with normal eGFR. Intriguingly, these results implied that tubulointerstitial injury could be closely related to elevated level of uric acid and might be an early stage pathological feature caused by hyperuricemia. Several studies demonstrated that plasma uric acid levels correlated strongly with tubular interstitial lesions in IgAN and hyperuricemia might be a marker for tubulointerstitial lesions [16, 17]. The study by Kang DH et al. showed that hyperuricemic rats had more tubulointerstitial fibrosis and provided direct evidence that uric acid might be a true mediator of kidney

disease by increasing renal renin and COX-2 expression [18]. Therefore, serum uric acid level could possibly affect the pathophysiology in IgAN patients. It was possible that high serum uric acid might independently cause the damage of tubulointerstitium in IgAN even in early stage. Because of the important role of tubulointerstitial damage in progression of IgAN, the significance of hyperuricemia may be quite considerable. In addition, interstitial inflammation often occurred with tubulointerstitial injury, so it could explain why lymphocytes and monocytes infiltration was prevalent in IgAN patients with hyperuricemia [6]. A lower proportion of segmental adhesion was found in IgAN patients with hyperuricemia possibly because of a higher proportion of segmental glomerulosclerosis [5, 6].

Finally, in our study, hyperuricemia possibly had no influence in therapeutic effectiveness, but affected prognosis in IgAN patients despite RAS blockade treatment. There was an increasing interest on the association between hyperuricemia and chronic kidney disease. Many studies found that hyperuricemia was closely associated with poor prognosis and an independent predictor of renal outcome in IgAN [3, 11-13, 15, 19, 20]. Serum uric acid level could affect prognosis of chronic kidney disease by directly mechanical damage or indirectly chronic interstitial inflammation and fibrosis [21, 22]. Furthermore, it was suggested that in the follow-up, immunosuppressive therapy may have a positive effect for therapeutic effectiveness in patients with hyperuricemia, which have a similar effect in patients without hyperuricemia. Although the role of immunosuppressive therapy including corticosteroids was still controversial because of uncertainty about effectiveness and safety [23, 24], it was notable that compared with RAS blockade alone in our study, immunosuppressive therapy in addition to RAS blockade had a positive effect not only on reduction of proteinuria, but also on improvement of renal outcome in IgAN patients with hyperuricemia, and proved to be acceptably safe. Nevertheless, further study was needed to figure out whether immunosuppressive therapy, especially corticosteroids, could reduce or even reverse the tubulointerstitial damage resulting from uric acid. Besides, with respect to urate lowering therapy like allopurinol, although no patient accepted it in our study, only a few studies indicated allopurinol did not significantly change kidney progression or proteinuria [20, 25]. However, Shi Y et al. found that allopurinol might improve the control of hypertension [20].

Several limitations of this study should be recognized. First, our study was a single-center retrospective cohort study with a small sample size, which might result in some bias. For instance, the effects of therapeutic interventions could not be accurately assessed in current study and needs to be researched by further prospective studies. Second, the follow-up time was not long enough, so we possibly missed a significant difference in the renal survival, such as a possible difference between patients that received combination therapy with hyperuricemia and without hyperuricemia and also, we could not figure out the independent influence and predictive value of hyperuricemia in prognosis after adjustment for renal function. Thirdly, all patients received RAS blockade so it was difficult to assess its value for therapeutic effectiveness and renal outcome. Further well-designed multicenter cohort studies with larger sample sizes and longer regular follow-up are still needed to confirm these results.

Conclusion

Hyperuricemic IgAN patients presented elevated blood pressure, severe kidney dysfunction and time-averaged proteinuria. Tubulointerstitial injury could be a pathological feature closely related to hyperuricemia in IgAN. Immunosuppressive therapy and RAS blockade could reduce proteinuria and improve renal outcome in IgAN patients with hyperuricemia.

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Disclosure Statement

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