RESEARCH ARTICLE

Association between hyperuricaemia and clinical pathological characteristics of patients with IgA nephropathy

Ling Lu[1], Bin Li[2], Guohua Dai[3], Yi Feng[4], Huaguo Feng[5]

Abstract

Objective: To study the association of hyperuricaemia with clinical and pathological characteristics of patients with IgA nephropathy, and to clarify adverse effects of hyperuricaemia on the onset and progression of IgA nephropathy.

Methods: A total of 244 patients with IgA nephropathy enrolled in Jiangjin Center Hospital were divided into a group with normal serum uric acid level and a group with elevated level. Age, gender, course of disease, blood pressure, liver function, renal function, blood lipid levels, blood glucose level, 24-hour urine protein level and pathological grades were recorded. The correlations of serum uric acid level with clinical indices and pathological grades were analyzed.

Results: The incidence rate of IgA nephropathy complicated with hyperuricaemia was 25.4%. The two groups had significantly different course of disease, body mass index (BMI), and levels of urea nitrogen, creatinine, triglyceride and urine protein ($p<0.05$). The group with elevated serum uric acid level had higher Lee's grade, tubulointerstitial lesion grade and renal arteriolar lesion grade. Patients with IgA nephropathy were prone to hyperuricaemia, being closely correlated with BMI, course of disease, blood pressure, triglyceride level and renal function. High pathological grades were important indices for poor prognosis.

Conclusion: The serum uric acid levels of patients with IgA nephropathy should be monitored to effectively control hyperuricaemia and to avoid its complications.

Keywords: hyperuricaemia, IgA nephropathy, glomerular disease. (JPMA 71: 1930; 2021)

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Introduction

IgA nephropathy is a group of immune glomerular diseases, primarily induced by IgA deposits in the mesangial area due to multiple etiological factors. This disease is the main pathological type of glomerulonephritis worldwide.[1] In the past, the prognosis of this disease was considered good. However, in recent years, studies have shown that IgA nephropathy was a progressive glomerular disease. About 15-20% of patients with IgA nephropathy develop into end-stage renal disease within 10 years after pathological diagnosis using renal biopsy, hence needing renal replacement therapy.[2] Donadio et al, reported that IgA nephropathy-induced end-stage renal disease accounted for 10% of all kinds of end-stage renal diseases.[3] At present, the pathogenesis of IgA nephropathy remains elusive. The progression of IgA nephropathy is affected by many factors, such as age, severity of proteinuria, and high blood pressure. Recently, with the improvement of living standards and changes in dietary structure, especially the intake of foods rich in purines, the prevalence rate of hyperuricaemia is on the rise, and its pathogenic roles in cardiovascular and kidney diseases have attracted widespread attention.

[1,2]Department of Nephrology, Jiangjin Center Hospital, Chongqing, China; [3-5]Department of Hepatobiliary Surgery, Jiangjin Center Hospital, Chongqing, China.

Correspondence: Huaguo Feng e-mail: fenghuaguojch@yahoo.com

Uric acid, as the final product of human and primate purine metabolisms, is mainly synthesized in the liver and small intestine. About 2/3 of serum uric acid is excreted by the kidney, and the remaining 1/3 is cleared in the intestinal tract. Both excessive serum uric acid production due to purine metabolism disorder and decreased uric acid excretion by the kidney can increase the uric acid level, causing hyperuricaemia. Besides, elevated serum uric acid level can cause gout, high blood pressure, cardiovascular diseases, kidney diseases, etc. Meanwhile, since uric acid is a reducing agent, the decrease of serum uric acid level inhibits the scavenging of considerable oxygen radicals, which may also damage renal function. Niskanen et al, found that uric acid might be an independent risk factor for cardiovascular and renal diseases after many other risk factors were controlled.[4] Syrjänen et al, followed up 223 patients with IgA nephropathy for 10 years, and found that hyperuricaemia increased the risk of disease progression 2.4-fold compared with that of patients with normal uric acid level.[5] Moreover, Filiopoulos et al, found that the damage of hyperuricaemia to kidneys even exceeded that of proteinuria, so particular attention should be paid to patients with Ig A nephropathy and hyperuricaemia simultaneously.[6] We herein studied the correlations between hyperuricaemia and the pathological characteristics of IgA nephropathy, aiming to study the role of hyperuricaemia in the progression of IgA nephropathy.

Subjects and Methods

This case control study has been approved by the ethics committee of our hospital, and written consent was obtained from all patients. Between January 2016 and December 2017, 244 patients with primary IgA nephropathy diagnosed by percutaneous renal biopsy in Jiangjin Center Hospital were selected. They were then divided into a group with normal serum uric acid level (n=182) and a group with elevated level (n=62). IgA nephropathy was diagnosed in accordance with the WHO classification criteria for pathological diagnosis of primary glomerular diseases in 1995.[7] Exclusion criteria: Patients with IgA nephropathy caused by Henoch-Schonlein purpura, hepatitis B virus infection, systemic lupus erythematosus, cirrhosis and tumours; complication with other kidney diseases such as diabetic nephropathy, obesity-related nephropathy and interstitial nephritis; with systemic diseases that might affect renal physiology and pathology.

Age, gender, course of disease, body mass index (BMI), blood pressure, liver function, renal function, and levels of blood lipids, blood glucose and 24-hour urine protein were recorded. Fasting elbow vein blood was collected on the morning of the next day after grouping for routine blood and biochemical index tests. Procedure for 24-Hour urine protein excretion test was explained to all patients. Each patient was told to clear the bladder from 7 am from when timing was started and all urine discharged within 24 h was stored in a container (including the urine sample at 7 am) and mixed.

Criteria for clinical indices:

1) Age: The patients were divided into five age groups, i.e. ≤20 years old, 21-30 years old, 31-40 years old, 41-50 years old, and >50 years old.

2) BMI was calculated as weight in kgs divided by height in meter squared and obesity was defined in these subjects as BMI ≥28 kg/m^2.[8]

3) Hyperuricaemia: Men and postmenopausal women with serum uric acid level of >7 mg/dl (420 µmol/L) and premenopausal women with level of >6 mg/dl (350 µmol/L) were defined as hyperuricaemia.[9]

4) Hypertension: According to the JNC 8 Hypertension Guidelines from JAMA Network, a blood pressure of ≥140/90 mmHg during the course of disease or the physical examination upon hospital admission was defined as hypertension.[10]

5) Renal dysfunction: Serum creatinine level was ≥1.19 mg/d (105 µmol/L).

A Tru-Cut biopsy needle was used to rapidly perform one-time percutaneous puncture under the guidance of ultrasonic B-scan, and living renal tissue samples were collected. A portion of the samples were embedded in paraffin, prepared into 2 µm-thick sections, and subjected to HE, PAS, PASM and Masson staining, respectively. Then Lee's grade for IgA nephropathy[11] and tubulointerstitial lesion (TIL) grade[12] were evaluated under light microscope. The remaining samples were frozen, sectioned and stained with isothiocyanate-labeled goat anti-human IgG, IgA, IgM, C3, C4, C1q and fibrinogen. The deposition site, distribution characteristics and intensity of the kidney were observed with direct fluorescence staining. Indirect immunofluorescence assay was performed to detect hepatitis B, HBsAg and HBcAg. Then the degree of renal arteriolar lesions was assessed. Grade 0: Without lesions; grade 1: with mild thickening of the vascular wall, and without changes such as fibrinoid necrosis; grade 2: with moderate thickening of the vascular wall, accompanied by fibrin deposition, necrosis and mild luminal stenosis; grade 3: with obvious thickening of the vascular wall, hyaline degeneration, sclerosis, and obvious luminal stenosis.

All data were analyzed by SPSS 17.0 software. The continuous data were expressed as mean±standard deviation (X±SD), and inter-group comparisons were performed with t test. The categorical data were expressed as case number and/or percentage, and inter-group comparisons were conducted with Chi-square test. P<0.05 was considered statistically significant, and p<0.01 was considered strongly statistically significant.

Results

There were 244 patients with Ig A nephropathy, including 132 males and 112 females (ratio: 1.18:1). The age group who underwent renal biopsy ranged from 12 to 70 years old, with the largest portion in the 21-30 years group (39.3%). This group also had the highest male/female ratio (2:1) (Table-1).

Of the 244 patients with IgA nephropathy, 62 (25.4%) had elevated serum uric acid levels, including 34 males and 28 females, and 182 (75.6%) had normal levels, including 98 males and 84 females. The average age of normal serum uric acid level group was 31±13 years old, and that of elevated serum uric acid level group was 34±11 years old,

Table-1: Gender and age of patients with IgA nephropathy.

	≤20 years	21-30 years	31-40 years	41-50 years	>50 years	Total
Case No. (%)	36 (14.8)	96 (39.3)	52 (21.3)	44 (36.0)	16 (6.6)	244 (100)
Male	20 (55.6)	64 (66.7)	22 (42.3)	18 (40.9)	8 (50.0)	132 (54.1)
Female	16 (44.4)	32 (33.3)	30 (57.7)	26 (59.1)	8 (50.0)	112 (45.9)
Male/female ratio	1.25:1	2:1	0.73:1	0.69:1	1:1	1.18:1

Table-2: Relationships between baseline clinical data and serum uric acid level.

Index	Normal serum uric acid level group (n=182)	Elevated serum uric acid level group (n=62)	t/χ^2	*p*-value
Gender			0.018	0.892
Male	98 (53.8)	34 (54.8)		
Female	84 (46.2)	28 (45.2)		
Age (year)	31±13	34±11	1.629	0.105
Disease course (month)	8.96±1.61	21.90±3.12	41.987	<0.001
BMI (kg/m^2)	22.32±2.83	23.81±3.70	3.298	0.001
Blood pressure			13/614	<0.001
Normal	114 (62.6)	20 (32.3)		
Hypertension	68 (37.4)	42 (67.7)		
Age (year)			0.118	0.739
≤20	32 (17.6)	4 (6.5)		
21-30	76 (41.8)	20 (32.3)		
31-40	36 (19.8)	16 (25.8)		
41-50	30 (16.5)	14 (22.6)		
>50	8 (4.3)	8 (12.8)		

Table-3: Relationships between serum uric acid level and biochemical indices.

Index	Normal serum uric acid level group (n=182)	Elevated serum uric acid level group (n=62)	t/χ^2	*p*-value
Renal function			45.511	<0.001
Normal	162 (89.0)	30 (48.4)		
Dysfunction	20 (11.0)	32 (51.6)		
Urea nitrogen (mg/dl)	15.12±3.83	23.912 ±3.6	15.558	<0.001
Creatinine (mg/dl)	0.93±4.08	1.73±6.78	97.690	<0.001
Serum total protein (g/L)	60.10±4.52	59.86±4.77	0.356	0.722
Serum albumin (g/L)	35.35±1.45	35.33±1.07	0.100	0.921
Triglyceride (mg/dl)	146.91± 27.4	193.85 ±27.43	10.129	<0.001
Total cholesterol (mg/dl)	201.87±11.96	203.422 ±12.74	0.863	0.389
High-density lipoprotein-cholesterol (mg/dl)	67.95±11.96	67.95 ±12.35	0.000	1.000
Low-density lipoprotein-cholesterol (mg/dl)	136.644 ±10.81	138,96±10.8	1.521	0.130
Blood glucose (mg/dl)	90.64±5.4	91.54±5	1.152	0.250
Urine protein (mg/24 h)	3885.10±388.25	5558.89±334.34	30.322	<0.001

Table-4: Pathological characteristics of patients with IgA nephropathy.

Index	Normal serum uric acid level group (n=182)	Elevated serum uric acid level group (n=62)	χ^2	*p*-value
Lee's grade			16.869	<0.001
I + II	50 (27.5)	6 (9.7)		
III	102 (56.0)	32 (51.6)		
IV + V	30 (16.5)	24 (38.7)		
TIL grade			127.222	<0.001
I	18 (9.9)	1 (1.6)		
II	150 (82.4)	11 (17.7)		
III + IV	14 (7.7)	50 (80.7)		
Renal arteriolar lesion grade			73.520	<0.001
0	110 (60.4)	8 (12.9)		
1	48 (26.4)	12 (19.4)		
2	10 (5.5)	16 (25.8)		
3	14 (7.7)	26 (41.9)		

without a significant difference (p=0.105). The disease course of normal serum uric acid level group (8.96±1.61 months) was significantly shorter than that of the elevated serum uric acid level group (21.90±3.12 months) (p<0.05). The normal level group had a significantly lower BMI (22.32±2.83 kg/m^2) than that of elevated level group (23.81±3.70 kg/m^2) (p<0.05). Of the patients with normal serum uric acid levels, 114(62.6%) had normal blood pressures and 68 (37.4%) had hypertension. In the elevated serum uric acid level group, 20 patients (32.3%) had normal blood pressures and 42(67.7%) suffered from hypertension. The two groups had significantly different proportions of hypertensive cases (p<0.05).

The serum uric acid levels of patients with IgA nephropathy were not significantly related with gender or age (p=0.892, 0.739), but were significantly related with disease course, BMI and hypertension (p<0.05) (Table-2).

IgA nephropathy accounted for 32.7% of the primary renal glomerular diseases diagnosed by renal biopsy during the same period. The incidence rate of IgA nephropathy complicated with hyperuricaemia was 25.4%. The normal serum uric acid level group had significantly lower BMI as well as levels of urea nitrogen, creatinine, triglyceride and urine protein than those of the elevated serum uric acid level group (p<0.05) (Table-3).

Among the 244 patients with IgA nephropathy, most cases had Lee's grade III (54.9%). The incidence rates of hyperuricaemia in patients with grades IV and V were significantly higher than those of cases with grades I and II (p<0.05). The tubulointerstitial damage in the normal serum uric acid level group was mostly TIL grade II (150 cases, 82.4%), and that of the elevated level group was mostly grade III + IV (25 cases, 80.6%). The incidence rate of hyperuricaemia in patients with TIL grades III and IV was significantly higher than that of cases with grades I and II (p<0.01). The renal arteriolar lesion in the normal serum uric acid level group was mainly grades 0 and 1 (86.8%), and that of the elevated level group was mainly grades 2 and 3 (67.7%). The incidence rates of hyperuricaemia in patients with grades 2 and 3 significantly exceeded those of cases with grades 0 and grade 1 (p<0.01).

The group with elevated serum uric acid level had higher Lee's grade, TIL grade and renal arteriolar lesion grade (Table-4).

Discussion

IgA nephropathy accounted for 32.7% of primary renal glomerular diseases diagnosed by renal biopsy in our hospital, which was lower than the reported incidence rate in literature.[13] IgA nephropathy could occur at any age, but 80% of patients were 16-35 years old in one of the studies, which was consistent in our study.[14] IgA nephropathy is more common in males. The male/female ratio was 2:1 to 6:1,[15] and about 3:1 to 1:1 in China.[16] Similarly, the ratio in this study was 1.18:1.

Uric acid is the end product of human purine metabolism. Recently, the incidence rate of hyperuricaemia has increased evidently. Hyperuricaemia is closely related to obesity, lipid metabolism disorder, blood pressure and impaired glucose tolerance, as a risk factor for the onset and progression of atherosclerosis, coronary heart disease and hypertension.[17,18] At present, there are few reports regarding the incidence of hyperuricaemia in patients with IgA nephropathy, or the influence of hyperuricaemia on their clinical indices and pathological changes. Herein, the incidence rate of hyperuricaemia in patients with IgA nephropathy was 25.4%. The patients with elevated serum uric acid level had a longer disease course than that of patients with normal level, being consistent with previous literature.[19,20]

Hypertension is a common clinical manifestation of IgA nephropathy, which can accelerate the disease progression. A large number of animal and clinical studies have confirmed that hyperuricaemia was an independent risk factor for the onset and progression of hypertension.[21-23] Voruganti et al, reported that basal serum uric acid level was the strongest independent predictor of hypertension. With a 1 mg/dl elevation in this level, the risk of developing hypertension increased by 23%.[24] This study showed that the incidence rate of hypertension in elevated serum uric acid level group was significantly higher than that of normal level group ($p<0.05$), suggesting a correlation between hyperuricaemia and hypertension. Hyperuricaemia is closely related to dyslipidaemia, and serum uric acid level is positively correlated with triglyceride level.[25] Obese patients undergo elevation of serum uric acid due to high-fat and purine-rich diets. In this study, patients with elevated serum uric acid level had significantly higher BMI and triglyceride level than those of normal level group, suggesting that hyperuricaemia was correlated with obesity and dyslipidaemia. We also found that patients with elevated serum uric acid level had more severe renal impairment and higher urine protein level than those of normal level group, indicating that serum uric acid level was closely related to renal damage and dysfunction. When renal function is impaired, serum uric acid excretion decreases, so its level increases. It is well-documented that the severity of proteinuria in patients with chronic kidney disease was significantly correlated with the degree of renal impairment.[26,27]

Renal biopsy for pathological grading is of great value in evaluating the prognosis of kidney disease. Patients with high grades often have poor prognosis. Herein, compared with patients having normal serum uric acid level, the proportions of Lee's grades IV and V as well as TIL grades III and IV in patients with elevated level were significantly larger, being in accordance with literature.[28] This study revealed that the proportion of renal arteriolar lesion grade 3 in patients with elevated serum uric acid level was significantly higher than that of patients with normal level. The incidence rate of hyperuricaemia in patients with renal artery lesion grades 2 and 3 was significantly different from that of patients with grades 0 and 1. Hence, this lesion might be associated with high serum uric acid level and blood pressure.

Conclusion

In conclusion, patients with IgA nephropathy were prone to hyperuricaemia. Hyperuricaemia complicated with IgA nephropathy had more frequent clinical manifestations such as massive proteinuria, hypertension and renal dysfunction. The pathological grade of patients with elevated serum uric acid level was higher than that of patients with normal level, as a crucial index for poor prognosis.

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References

1. Renfrow MB, Novak J. What insights can proteomics give us into IgA nephropathy (Berger's disease)? Expert Rev Proteomics 2017; 14: 645-7.
2. Shu D, Xu F, Su Z, Zhang J, Chen C, Zhang J, et al.Risk factors of progressive IgA nephropathy which progress to end stage renal disease within ten years: a case-control study. BMC Nephrol 2017; 18: 11-16.
3. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med 2002; 347: 738-48.
4. Niskanen L, Laaksonen DE, Lindström J, Eriksson JG, Keinänen-Kiukaanniemi S, Ilanne-Parikka P, et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. Diabetes Care 2006; 29: 709-11.

5. Syrjänen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 2000; 15: 34-42.
6. Filiopoulos V, Hadjiyannakos D, Vlassopoulos D. New insights into uric acid effects on the progression and prognosis of chronic kidney disease. Renal Fail 2012; 34: 510-20.
7. Churg J, Bernstein J, Glassock RJ. Renal disease: classification andatlas of glomerular diseases. New York: Igaku-Shoin Medical Publishers,Inc., 1995.
8. Tan K, Consultation WE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363: 157-63.
9. Lu ZY, Zhong NS. Internal Medicine. Beijing: People's Medical Publishing House Co., Ltd., 2008.
10. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311: 507-20.
11. Lee SM, Rao VM, Franklin WA, Schiffer MS, Aronson AJ, Spargo BH, et al. IgA nephropathy: morphologic predictors of progressive renal disease. Hum Pathol 1982; 13: 314-22.
12. Zhang Q, Jiang C, Tang T, Wang H, Xia Y, Shao Q, et al.Clinical Significance of Urinary Biomarkers in Patients with Primary Focal Segmental Glomerulosclerosis. Am J Med Sci 2018; 355: 314-21.
13. Dower K, Zhao S, Schlerman FJ, Savary L, Campanholle G, Johnson BG, et al. High resolution molecular and histological analysis of renal disease progression in ZSF1 fa/faCP rats, a model of type 2 diabetic nephropathy. PloSOne 2017; 12: e0181861.
14. Raghavan R, Eknoyan G. What Is Chronic Kidney Disease? In: Management of Chronic Kidney Disease. Berlin, Heidelberg: Springer, 2014; 3-13.
15. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2017; 69: A7-8.
16. Liu BC, Tang TT. [Inspiration of development of nephrology in China by precision medicine]. Chin J Nephrol 2016; 32: 64-7.
17. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med 2016; 54: 7-15.
18. Wan Q, Gao YX, Wu YS, Shi LQ, Huang D, Gao JD. [Correlations between IgA nephrology complicated with hyperuricemia and clinicopathological characteristics]. Chin J IntegrTradi West Nephrol 2017; 18: 971-4.
19. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, et al.Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial.Kidney Blood Press Res 2012; 35: 153-60.
20. Bakan A, Oral A, Elcioglu OC, Takir M, Kostek O, Ozkok A, et al. Hyperuricemia is associated with progression of IgA nephropathy. Int Urol Nephrol 2015; 47: 673-8.
21. Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, et al. Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33: 1729-41.
22. Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. Eur J Intern Med 2016; 29: 3-8.
23. Liang J, Pei Y, Gong Y, Liu XK, Dou LJ, Zou CY, et al. Serum uric acid and non-alcoholic fatty liver disease in non-hypertensive Chinese adults: the Cardiometabolic Risk in Chinese (CRC) study. Eur Rev Med Pharmacol Sci 2015; 19: 305-11.
24. Voruganti VS, Laston S, Haack K, Mehta NR, Cole SA, Butte NF, et al. Serum uric acid concentrations and SLC2A9 genetic variation in Hispanic children: the Viva La Familia Study. Am J Clin Nutr 2015; 101: 725-32.
25. Zhang Y, Wei F, Chen C, Cai C, Zhang K, Sun N, et al. Higher triglyceride level predicts hyperuricemia: A prospective study of 6-year follow-up. J Clin Lipidol 2018; 12: 185-92.
26. Cheong M, Lee J, Lee TY, Kim SB. Prevalence and risk factors of baclofen neurotoxicity in patients with severe chronic kidney disease. Nephrol Dial Transplant 2019; 14.
27. Dobrowolski C, Clark EG, Sood MM. Venous thromboembolism in chronic kidney disease: epidemiology, the role of proteinuria, CKD severity and therapeutics. J ThrombThrombolysis 2017; 43: 241-7.
28. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int 2014; 86: 828-36.