Int Urol Nephrol (2015) 47:673–678
DOI 10.1007/s11255-015-0939-7

NEPHROLOGY - ORIGINAL PAPER

Hyperuricemia is associated with progression of IgA nephropathy

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Received: 29 October 2014 / Accepted: 23 February 2015 / Published online: 12 March 2015

Abstract
Background and aim IgA nephropathy (IgAN) is one of the world's most common glomerular diseases. Hyperuricemia was recently defined as risk factor for chronic kidney disease. We aimed to investigate the impact of baseline serum uric acid levels on progression of IgAN.
Materials and methods A total of 93 patients with IgAN were screened. Demographic information and biochemical data were recorded. eGFR (using the CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration formula) was used as renal function marker. Baseline and sixth month eGFR values were calculated. Progression of renal disease was defined as the difference between baseline eGFR and sixth month eGFR (delta eGFR).
Results Mean age of the patients was 40 ± 11 years (60 % were males). Baseline mean eGFR was 77.9 ± 30.2 mL/min, and baseline mean serum uric acid was 5.65 ± 1.68 mg/dL. Importantly, baseline serum uric acid levels were found to be associated with the change in eGFR ($r = 0.252$, $p = 0.01$). In multivariate analysis (adjusted $R^2 = 0.171$, $p = 0.031$), adjusting for age, gender, baseline eGFR, blood pressure, baseline albumin concentration and ACEI and/or ARB use revealed that the baseline serum uric acid levels significantly predicted the change in eGFR.
Conclusion Baseline serum uric acid concentration is directly proportional to the rate of decline in renal functions in patients with IgAN. Uric acid-lowering treatments may be beneficial for the prevention of progression of IgAN. However, randomized controlled studies are needed for this purpose.

Keywords Chronic kidney disease · Glomerular filtration rate · Hyperuricemia · IgA nephropathy

Introduction

IgA nephropathy (IgAN) is one of the most common glomerular diseases, accounting for 30 % of primary

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glomerulonephritis, and represents one of the main causes of end-stage renal disease (ESRD) [1]. Risk factors for progression of IgA nephropathy include male gender, early-onset disease, absence of macroscopic hematuria, persistent microscopic hematuria, hypertension, proteinuria, presence of renal dysfunction at the time of diagnosis and unfavorable pathological findings such as presence of endocapillary hypercellularity, mesangial hypercellularity, segmental and global glomerulosclerosis, tubular atrophy, interstitial fibrosis and crescents [2]. Most controlled clinical studies, however, have focused on identifying the relationship between hypertension, hyperglycemia and kidney disease, and few studies have explored the clinical and prognostic significance of serum uric acid in IgA nephropathy.

Hyperuricemia is a well-known independent risk factor for cardiovascular disease and for kidney disease [3]. Hyperuricemia is associated with hypertension in patients with normal renal function, and furthermore, it was associated with a higher reduction in GFR compared to normouricemic individuals [4]. Experimental studies revealed that hyperuricemia activates the renin–angiotensin system, decreases nitric oxide, increases inflammation and oxidative stress and therefore might be a relevant and modifiable risk factor for progression of kidney disease in IgA nephropathy. Indeed, lowering uric acid concentration (with allopurinol therapy) may result in improvement in renal function and blood pressure [4, 5].

A recent study suggested that hyperuricemia may be associated with progressive of IgA nephropathy [6], while Myllymaki et al. [7] found a correlation between hyperuricemia and severity of biopsy findings in IgA nephropathy. However, these data are insufficient and require confirmation by independent larger trials, with longer follow-up. We, therefore, designed this study to investigate the possible relationship between baseline serum uric acid levels and the progression of IgA nephropathy.

Materials and methods

In this retrospective study, the patients for the study were selected among patients with IgA nephropathy who were being followed at our outpatient clinics and diagnosed based on renal biopsy. Inclusion criteria were (1) diagnosis of IgA nephropathy based on renal biopsy and (2) a follow-up period of at least 6 months;

Exclusion criteria were (1) absence of six-month follow-up; (2) diabetes mellitus; (3) presence of chronic organ dysfunction such as heart failure, hepatic cirrhosis and hepatitis; (4) treatment with uric acid-lowering therapy (allopurinol therapy) or history of gout disease; (5) previous immunosuppressive therapy due to the rapidly progressive glomerulonephritis; and (6) presence of malignancy or chronic infection.

Hyperuricemia was defined >7 mg/dL for man and 6.5 mg/dL for woman as defined in previous studies [4].

A total of 145 patients with IgA nephropathy were assessed in this study. A total of 52 patients were excluded from the study; 15 patients had crescentic glomerulonephritis and received immunosuppressive therapy, 10 patients had short follow-up period <6 months, ten patients were treated with uric acid-lowering therapy (allopurinol), four patients had type two diabetes mellitus without retinopathy, six patients had chronic hepatitis or hepatic cirrhosis, two patients had heart failure, five patients were using losartan (because of the losartan decreases the serum uric acid level) and two patients had malignancy. A total of 93 patients that met the inclusion/exclusion criteria were screened. Demographic information and biochemical data were recorded. eGFR (estimated glomerular filtration rate) was used as renal function marker. Baseline and sixth month eGFR creatinine values were calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula using the parameters of age, race and gender. Progression of renal disease was defined as the difference between baseline eGFR and sixth month eGFR (delta eGFR).

Statistical analysis

The data were analyzed using the SPSS 16.0 for Windows software (SPSS Inc., Chicago, IL). Categorical variables are reported as frequencies and group percentages. Differences between the groups were analyzed by Mann–Whitney *U* test and Scheffé's *F* test with ANOVA. Correlation between two variables was analyzed by Spearman's rank correlation test. All data are shown as mean ± SD, except for the data in Table 2. A multivariate regression model with a stepwise backward method was applied to evaluate the independence of factors, using logarithmic transformed values of non-normally distributed variables. A p value <0.05 was considered to show a statistically significant result.

Results

Baseline clinical characteristics and laboratory parameters of all study participants and both hyperuricemic and normo-uricemic patients are shown in Table 1. The mean age of the patients was 40 ± 11 years; 60 % (56 patients) were males; baseline mean serum creatinine was 1.2 ± 0.52 mg/dL, mean eGFR 77.9 ± 30.2 mL/min and the mean serum uric acid level 5.65 ± 1.68 mg/dL. Hyper-uricemic patients were older (44.3 ± 12.4 vs 37.9 ± 10.2 years, $p = 0.01$). At the time of diagnosis,

Table 1 Baseline demographic and laboratory characteristics of the patients

IgA nephropathy ($n = 93$)	IgA nephropathy ($n = 93$) Mean ± SD or (%)	Hyperuricemic ($n = 30$) Mean ± SD or (%)	Normouricemic ($n = 63$) Mean ± SD or (%)	p
Age (years)	40 ± 11	44.3 ± 12.4	37.9 ± 10.2	**0.017**
Male/female	56/37	19/11	37/26	
Systolic BP (mmHg)				0.850
Median	120	126	128	
Interquartile range	113–138	100–180	95–200	
Mean diastolic BP (mmHg)	82.1 ± 11.1	83.7 ± 12.6	81.2 ± 10.2	0.471
Medications				
ACEI	70 (75.3 %)	24 (80 %)	46 (73 %)	0.543
ARB	48 (51.7 %)	10 (33 %)	38 (60 %)	0.725
Combination of ACEI and ARB	34 (36.5 %)	9 (30 %)	25 (40 %)	0.668
Ca^{+}-channel blocker	11 (11.8 %)	5 (16.6 %)	6 (9 %)	0.177
Beta blockers	6 (6.5 %)	1 (3 %)	5 (7 %)	0.064
Diuretics	8 (8.6 %)	5 (16.6 %)	3 (4 %)	0.102
Statins	11 (11.8 %)	4 (13 %)	7 (11 %)	0.313
Smoking	8 (8.6 %)	3 (10 %)	5 (8 %)	0.847
Body mass index (kg/m^2)	28.9 ± 5.2	30.8 ± 4.5	28.5 ± 5.4	0.399
Total cholesterol (mg/dL)	206.5 ± 60.4	199.7 ± 34.5	210.1 ± 70.7	0.545
LDL-cholesterol (mg/dL)	130.7 ± 45.5	127.9 ± 33.5	131.8 ± 50.0	0.810
HDL-cholesterol (mg/dL)	42.3 ± 9.7	40.8 ± 7.9	43 ± 10.7	0.489
Triglyceride (mg/dL)	178.2 ± 83.4	209.4 ± 122.5	163.2 ± 53.2	0.233
Glucose (mg/dL)	89.2 ± 9.6	90.5 ± 14.6	88.7 ± 6.9	0.695
Creatinine (mg/dL)	1.2 ± 0.52	1.25 ± 0.53	1.18 ± 0.5	0.513
eGFR (mL/dk/1.73 m^2)	77.9 ± 30.2	73.1 ± 28.7	80.2 ± 30.9	0.282
Uric acid (mg/dL)	5.65 ± 1.68	7.6 ± 0.76	4.7 ± 1.04	**<0.001**
Urine protein (mg/day)				
Median	62	48	100	0.669
Interquartile range	16–345	14–360	22–289	
Calcium (mg/dL)	9.3 ± 0.6	9.3 ± 0.57	9.3 ± 0.61	0.922
Phosphorus (mg/dL)	3.4 ± 0.64	3.4 ± 0.78	3.4 ± 0.58	0.795
Total protein (g/dL)	6.8 ± 0.79	6.8 ± 0.49	6.9 ± 0.9	0.642
Albumin (g/dL)	4.04 ± 0.57	4.1 ± 0.33	4.0 ± 0.7	0.665
Hemoglobin (g/dL)	13.8 ± 1.64	13.5 ± 1.4	14.0 ± 1.8	0.295

ACEI angiotensin-converting-enzyme inhibitors, *ARB* angiotensin receptor blockers, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Bold represents statistically significant values

89 % of the patients were using angiotensin-converting-enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) treatment. Only 8.6 % of the patients were on combination treatment with a diuretic, and their serum baseline uric acid and delta GFR values were similar to those without diuretics ($p = 0.12$ and $p = 0.64$, respectively). After diagnosis of IgAN, all patients received either ACEI or ARB.

Serum uric acid concentration was found to be significantly correlated with serum cholesterol, triglyceride, creatinine, urine protein excretion (UPE) and mean arterial pressure (MAP) ($p < 0.001$ for all correlations). Correlation analyses of delta eGFR with the other biochemical values are presented in Table 2. There was no significant correlation between baseline eGFR and delta eGFR ($r = 0.181$, $p = 0.08$). Although the correlation was not quite strong, baseline serum uric acid levels were found to be associated with the change in eGFR ($r = 0.252$, $p = 0.01$; Fig. 1) Delta eGFR was higher in patients with high uric acid level ($p = 0.003$; Fig. 2). A multivariate analysis was performed to investigate factors such as age, gender, baseline eGFR, blood pressure, baseline albumin concentration, proteinuria and ACEI and/or ARB use that are known to be associated with a decline in GFR; baseline serum uric acid levels

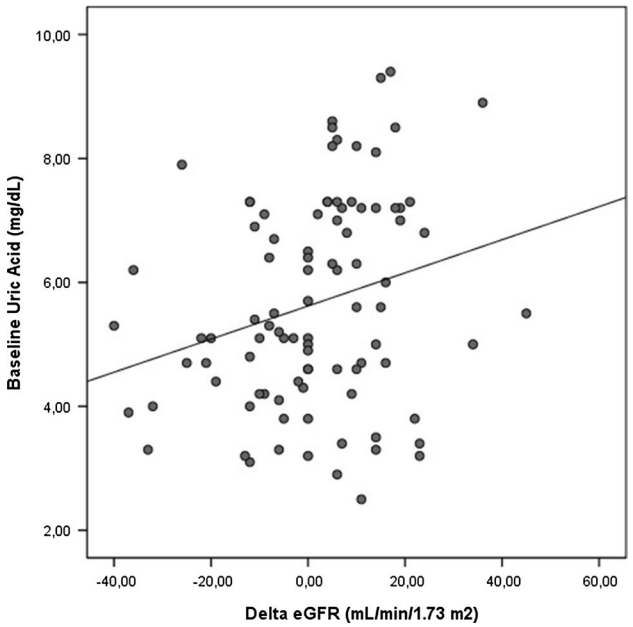

Fig. 1 Correlation between serum uric acid levels and delta eGFR

Table 2 Correlation analysis of delta eGFR with other biochemical parameters (*R* correlation coefficient)

	R	*p*
Age (years)	0.12	0.24
Total cholesterol (mg/dL)	0.008	0.96
LDL-cholesterol (mg/dL)	−0.104	0.59
HDL-cholesterol (mg/dL)	−0.041	0.81
Triglyceride (mg/dL)	0.271	0.10
Glucose (mg/dL)	−0.073	0.66
Creatinine (mg/dL)	−0.137	0.19
eGFR (mL/dk/1.73 m^2)	0.181	0.08
Uric acid (mg/dL)	**0.252**	**0.01**
Urine protein (mg/day)	0.109	0.53
Calcium (mg/dL)	0.137	0.21
Phosphorus (mg/dL)	0.007	0.94
Total protein (g/dL)	−0.141	0.37
Albumin (g/dL)	−0.12	0.93
Hemoglobin (g/dL)	0.033	0.81

Bold represents statistically significant values

remained a significant independent predictor for the change in eGFR (adjusted $R^2 = 0.171$, $p = 0.031$; Table 3).

Discussion

The salient finding of the present study is that baseline high serum uric acid concentration is independently associated

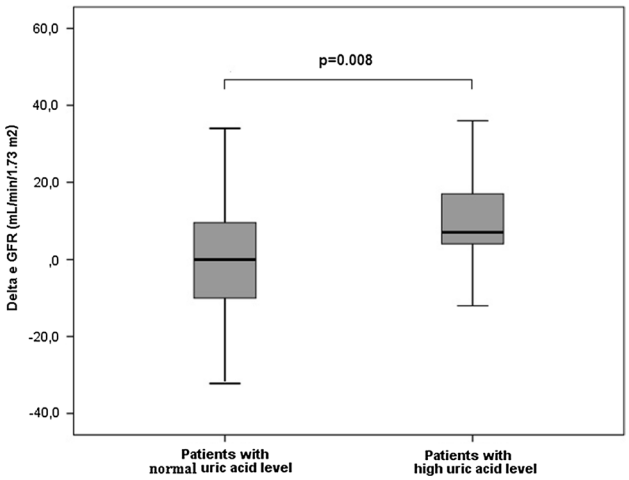

Fig. 2 Delta eGFR in patients with normal uric acid levels and patients with high uric acid level

with the rate of decline in renal function (eGFR) in patients with IgA nephropathy.

IgA nephropathy is one of the major causes of ESRD. Clinically recognized important risk factors for IgAN progression to ESRD are older age, absence of macroscopic hematuria, persistent microscopic hematuria, hypertension, proteinuria, and presence of renal dysfunction at the time of diagnosis. In addition some histologic features such as presence of endocapillary hypercellularity, mesangial hypercellularity, segmental and global glomerulosclerosis, tubular atrophy, interstitial fibrosis and crescents are important risk factors for progression to ESRD, particularly when organized and quantified in histological risk scores [2].

As shown in this study, hyperuricemia is well known to be associated with hypertension. Hyperuricemia is also related to endothelial dysfunction and development of cardiovascular and kidney diseases [4, 8–11]. Previous studies detected hyperuricemia in 25 % of hypertensive patients, while hypertension was detected in 50–70 % of patients with hyperuricemia [12]. It was suggested that uric acid induces proliferation of vascular smooth muscle cells and activates the renin–angiotensin–aldosterone system [10, 11, 13]. Hyerperuricemia was also found to reduce the synthesis of nitric oxide, at the same time increasing inflammation and oxidative stress. All of these changes may also have role in the pathogenesis and progression of IgA nephropathy [14]. In animal studies, hyperuricemia was demonstrated to cause renal injury by leading to Th1/Th2 cell polarization and extracellular matrix gene expression [15]. Myllymaki et al. [7] investigated the relationship between histopathological findings and serum biochemical values of 202 patients with IgA nephropathy and found hyperuricemia as an independent risk factor for tubular atrophy, interstitial fibrosis and inflammation. Zhou et al.

Table 3 Multiple backward linear regression analysis of delta eGFR (Adjusted $R^2 = 0.171$, $p = 0.031$)

Parameter	Partial regression coefficient (β)	Standard error (S.E.)	p value
Age (years)	−0.044	−0.264	0.79
Gender (M:1)	−0.073	0.439	0.66
Baseline eGFR	0.170	1.036	0.31
Proteinuria (log)	−0.261	1.632	0.38
Baseline uric acid	**3.051**	**1.335**	**0.03**
Dual blockage with ACEI and ARB	0.146	0.873	0.39

M male, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin receptor blockers

Bold represents statistically significant values

[20] showed that higher plasma uric acid levels are associated with more severe tubulointerstitial lesions in 258 IgAN cases with normal baseline eGFR (eGFR ≥ 90 mL/min/1.73 m^2).

In humans, several studies described associations between serum uric acid concentration and progression of CKD [16, 17]. Data from a cohort of 3499 subjects, who had been followed for 12 months in Southeastern Asia, revealed that hyperuricemia was an independent risk factor for the progression of kidney disease [18]. Furthermore, lowering serum uric acid with allopurinol improves kidney function [4, 19]. Most importantly, in two previous studies, it was shown that the serum uric acid levels are associated with the progression of IgA nephropathy [1, 5].

Hyperuricemia may be a marker to predict tubular atrophy/interstitial fibrosis in IgAN, especially in those with normal eGFR [20]. In fact, tubular excretion of uric acid plays a major role of removal uric acid from the body. Therefore, hyperuricemia could be considered a secondary consequence of the tubular damage and thus a biomarker of disease severity. Although in numerous studies it was shown that hyperuricemia is an independent risk factor for progression of CKD including IgAN [4–7], a clear causative role/interaction remains to be established.

Our group previously showed that treatment of hyperuricemia with allopurinol in CKD resulted in a fall in blood pressure and reduction in progressive deterioration of renal function [4]. In light of previous studies, we speculate that treatment of hyperuricemia may be tested in trials as a part of treatment in IgAN [21, 22].

The limitations of the study have to be mentioned. Firstly, the follow-up period was relatively short, and sample size was also limited. Secondly, we included IgAN patients of which were not received immunosuppressive medications to elucidate the role of serum uric acid level independently. We also did not correlate the severity of biopsy findings of IgAN with serum uric acid level.

Conclusion

Baseline high serum uric acid concentration might be risk factor for decline in kidney function in IgA nephropathy patients. Uric acid-lowering treatments may be beneficial for the prevention of progression of IgA nephropathy. Further randomized controlled studies are needed to elucidate the effect of treatment of hyperuricemia on decline in kidney function in IgA nephropathy.

Conflict of interest The authors declare that they have no conflict of interest.

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