

Aggravation of Immunoglobulin A Nephropathy by Hyperuricemia

A Mini-Review on Current Findings and New Concepts

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Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of primary glomerulopathy worldwide. Various investigations have addressed the clinical and morphological risk factors related to the risk of progression. Recently, much attention has been made toward the prognostic implication of serum uric acid in patients with IgAN. It has been observed that treatment of hyperuricemia with allopurinol in chronic kidney failure has resulted in a fall in blood pressure and inhibition of the progression of kidney injury. Recent studies have documented that hyperuricemia is an independent risk factor for IgAN, and appropriate treatment by allopurinol is a reasonable modality in these patient. We believe that allopurinol should routinely be included to the treatment of IgAN patients; however, this hypothesis requires further investigation. Clinical studies are suggested to better understand kidney protective properties of allopurinol in IgAN.

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INTRODUCTION

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of primary glomerulopathy worldwide.^{1,2} Since the first description in 1968, the optimal approach to its treatment has remained a significant contest.^{3,4} It is estimated that 20% to 40% of patients with primary glomerulonephritis have high serum IgA.^{5,6} Regardless of heterogeneity of IgA and a generally slow course of disease progress, IgAN is a significant contributor to progression to end-stage kidney failure.³⁻⁶ In fact, various investigations have addressed the clinical and morphological risk factors related to the risk of progression.⁵⁻⁹ These include initial renal insufficiency, long lasted or heavy proteinuria, high blood pressure, and some morphologic lesions, which recently classified as Oxford classification.⁷⁻⁹ Hence, initial identification of patients at high risk of forthcoming loss of kidney function would simplify timely therapeutic modalities to prevent

progression to end-stage renal disease.^{10,11}

Recently, various investigations have tried to identify these high-risk patients, and these new data can be joined into both the assessment of patients and therapeutic modalities. In pathology point of view, the Oxford classification has recognized 4 morphologic variables as independent prognostic factors: endocapillary hypercellularity, segmental glomerulosclerosis, mesangial hypercellularity, and tubular atrophy/interstitial fibrosis.⁷⁻¹¹ Other pathology variables such as extracapillary proliferation, fibrinoid necrosis of the glomerular tuft, and immunohistological findings have not been proposed to have prognostic significance, yet.⁷⁻¹¹ Of clinical variables, level of proteinuria, blood pressure, and baseline kidney function have been found to have prognostic implication.^{5,6,10} However, inconsistent associations with outcome are observed with sex, age, and isolated macroscopic hematuria, too.^{5,6,10-13}

EPIDEMIOLOGY

Recently, much attention has been drawn toward the prognostic implication of serum uric acid in patients with IgAN.^{14,15} Indeed, an elevated serum uric acid level is found to be a risk factor for progression of kidney disease in Finnish and Japanese populations with IgAN.¹⁴⁻¹⁷ However, elevated serum uric acid level as a definitive risk factor has not been detected for kidney damage in IgAN patients, yet. On the other hand, there is not enough data on whether, treatment of hyperuricemia with allopurinol can improve kidney outcome in nephropathy of IgA.¹⁴⁻¹⁷ About 70% of uric acid is eliminated by the kidneys; thus, hyperuricemia occurs when kidney function worsens. It is not clear yet whether the hyperuricemia, seen in kidney insufficiency, plays a role in the progression of kidney failure.^{4,14-17}

HYPERURICEMIA AND IMMUNOGLOBULIN A NEPHROPATHY

Recent clinical investigations illustrated that serum uric acid level is closely associated with hypertension or beginning of hypertension in hyperuricemic patients.^{4,14-17} Interestingly, it has been observed that treatment of hyperuricemia with allopurinol lowers blood pressure in juvenile essential hypertension patients having hyperuricemia.¹⁴⁻¹⁷ Additionally, it is well understood that hyperuricemia is closely related to chronic kidney failure as a risk factor for kidney insufficiency.¹⁴⁻¹⁸ Likewise, it has been observed that treatment of hyperuricemia with allopurinol in chronic kidney failure has resulted in a fall in blood pressure and inhibition of the progression of kidney injury.¹⁶⁻¹⁸ On the other hand, the cessation of allopurinol treatment in chronic kidney failure was followed by a rise in blood pressure and the development of kidney damage.¹⁴⁻¹⁸

It is possible that renin-angiotensin system has an important role in the development of hypertension and kidney damage from hyperuricemia.^{4,11,16-18} Previous studies have shown that activation of the renin-angiotensin system is mediated by various mechanisms such as decreasing neuronal nitric oxide synthase in the juxtaglomerular apparatus or by decreasing kidney perfusion by stimulating the afferent arteriolar vascular smooth cell proliferation and through the induction of cyclooxygenase-2 in the macula densa and arterioles.¹⁹⁻²⁵ In an attempt to

evaluate the prognostic consequences of serum uric acid on patients with IgAN, Cheng and colleagues found that prevalence of glomerular sclerosis, vasculopathy, and tubulointerstitial fibrosis were greater in patients with high serum uric acid in comparison to the patients with normal serum uric acid.¹⁸ They concluded that serum uric acid level in IgAN patients affects the pathophysiology and prognosis of the IgAN. Indeed, they observed that increased serum uric acid experimentally incites kidney vasoconstriction and activation of the renin-angiotensin system.¹⁸

In 46 non-nephrotic IgAN patients and 15 controls with a glomerular filtration rate of 86.7 ± 17.4 mL/min and 118.1 ± 17.2 mL/min, respectively, Sulikowska and coworkers observed a greater renal vasoconstriction in IgAN.²⁵ To analyze the correlation between the level of serum uric acid and the clinical and pathological features of IgAN, Cui and associates conducted a study on 148 patients with IgAN from January 2007 to December 2010. They found that the level of serum uric acid had correlated with 24-hour proteinuria amount, blood pressure and kidney function in IgAN. They also found that tubulointerstitial lesions grade and morphologic lesions of renal artery were severe in hyperuricemic group.²⁶ Likewise, in an investigation on 223 patients with IgAN (107 with and 116 without metabolic syndrome), Kovács and colleagues observed that the metabolic syndrome recognized at the diagnosis or during follow-up of IgAN patients significantly correlated with the primary renal endpoint. They found that hyperuricemia is an independent risk factor of progression of IgAN.²⁷ Accordingly, to identify the long-term kidney survival rate and related risk factors of progression to kidney failure in Chinese adult patients with immunoglobulin A nephropathy, Le and colleagues investigated 1155 patients. They found that 36% of IgAN patients progressed to end-stage kidney failure within 20 years.¹⁶ They observed that some clinical features such as hyperuricemia, hypoproteinemia, high amount of proteinuria, hypertension, and impaired kidney function are independent predictors of harmful kidney outcome.¹⁶

More recently, Shi and coworkers conducted a retrospective cohort study on 353 IgAN patients to find the association of serum uric acid and the progression of kidney disease over a mean

period of 5 years.²⁸ Of 353 IgAN patients, 40 hyperuricemic IgAN patients were randomized to receive allopurinol (100 mg/d to 300 mg/d) or usual therapy for a period of 6 months. The outcomes were kidney disease progression or blood pressure rising. They found that hyperuricemia independently predicted kidney survival at 1, 3, and 5 years after adjustment for various baseline estimated glomerular filtration rates. In their trial, allopurinol did not significantly alter kidney progression or proteinuria.²⁸ However, they found that the antihypertensive drug dosage was reduced in 7 of 9 cases with in the allopurinol group compared to none of 9 cases in the control group. Moreover, serum uric acid level associated with mean arterial pressure in normotensive patients. They concluded that hyperuricemia predicts the progression of IgAN independently of baseline estimated glomerular filtration rate. Also, allopurinol might improve the control of blood pressure. They finally suggested further studies on this subject.²⁸ Indeed, with respect to the primary outcome of the clinical trial and change in kidney function, they found no advantage of allopurinol therapy on kidney function at the end of the 6-month period. This is most probably due to the short duration of the investigation.²⁹

Similarly, Siu and coworkers have shown that allopurinol can slow the progression of kidney disease in subjects with chronic kidney disease and asymptomatic hyperuricemia despite the fact that the majority of their patients were being treated with angiotensin-converting-enzyme inhibitors.²⁹ Likewise in the study by Goicoechea and coworkers in which individuals with stage three of chronic kidney disease were randomized into receiving allopurinol (100 mg/d) or control group for 1-year follow-up. They found kidney function decreased in the control group and improved in the allopurinol group.³⁰

CONCLUSIONS

It is well documented that hyperuricemia is an independent risk factor for IgAN, and appropriate treatment by allopurinol is a reasonable modality in these patient.³¹⁻³⁷ We believe that this drug should routinely be included to the treatment of IgAN patients; however, this hypothesis requires further investigation by larger studies. Clinical studies are suggested to better understand the

allopurinol kidney protective properties in IgAN.

CONFLICTS OF INTEREST

None declared.

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