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Association between serum uric acid and kidney disease with pediatric focus

Myung Hyun Cho[1]

[1]Department of Pediatrics, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea

Hyperuricemia is a global medical issue. Kidney disease and hyperuricemia are clearly related. Whether uric acid is a disease bystander or a therapeutic target in chronic kidney disease (CKD) remains controversial. Uric acid is involved in various mechanisms that worsen kidney function, and many epidemiological and animal studies have shown an association between hyperuricemia and kidney deterioration. However, several confounding variables limit this interpretation of the relationship. Two recent large well-designed studies failed to show that allopurinol, a uric acid-lowering agent, slows the decline in glomerular filtration rate. Nevertheless, this conclusion remains premature. The role of uric acid-lowering agents in delaying disease progression in patients with early-stage CKD, such as pediatric patients, requires further study.

Keywords: Child; Hyperuricemia; Renal insufficiency, chronic; Uric acid

Introduction

Uric acid is the final product of the endogenous and exogenous purine metabolism (adenine and guanine). It is not only a byproduct of metabolism but also a necessary component for the human body. As a powerful antioxidant that accounts for approximately half of all naturally occurring antioxidants in humans, uric acid was beneficial for human survival long ago [1]. It was important when consuming fruits and vegetables decreased dramatically due to climate change [2]. Uric acid also maintained blood pressure when salt intake was insufficient [3]. However, nowadays, nobody talks about the need for uric acid in our bodies.

Hyperuricemia is a global medical issue. The prevalence of hyperuricemia has become high [4]. According to a paper published in 1924, only 39% of adults with even hypertension had serum uric acid levels ≥3.5 mg/dL, in contrast, the mean level of adults in the United States in 2015 and 2016 was 5.39 mg/dL [5,6]. A shift to a Westernized diet contributes to the increasing prevalence of hyperuricemia [3]. Hyperuricemia causes gout or nephrolithiasis. In addition, it is associated with chronic kidney disease (CKD), hypertension, cardiovascular disease, metabolic syndrome, and type 2 diabetes [7]. It is unclear whether uric acid is a disease bystander or a therapeutic target for these chronic diseases [3]. Particularly in CKD, studying the role of uric acid is difficult because it is excreted mainly by the kidneys. Hence, reduced kidney function leads to increased serum uric acid levels. The role of uric acid in CKD and the effectiveness of serum uric acid-lowering treatments in patients with CKD and asymptomatic hyperuricemia remain controversial. Herein, I discuss this issue, particularly in pediatric patients.

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Correspondence to
Myung Hyun Cho
Department of Pediatrics, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Republic of Korea
E-mail : dong82dong82@naver.com

Definition of hyperuricemia

Consensus is lacking on the definition of hyperuricemia [8], which makes it impossible to compare multiple studies directly. The average serum uric acid level is reportedly higher in men than women. The cutoff levels for hyperuricemia can be set according to sex: for men, they are usually 7.0–7.7 mg/dL; for women, they are 5.7–6.6 mg/dL [4,9]. However, based on the level at which uric acid forms crystals, the cutoff levels for men and women can be equal at 6.8 or 7.0 mg/dL [8]. It is more difficult to establish a definition of hyperuricemia in children because of differences in serum uric acid levels according to age as well as gender. The average uric acid level increases with age, especially in boys in their early teen years [10,11]. Different upper normal limits were set in the textbook according to age and sex: 5.0 mg/dL for 1–3 years, 4.7 mg/dL for 4–6 years, 5.0 mg/dL for 7–9 years, 5.4 mg/dL for 10–11 years (boys), 4.7 mg/dL for 10–11 years (girls), 6.7 mg/dL for 12–13 years (boys), 7.8 mg/dL for 14–15 years (boys), 5.8 mg/dL for 12–15 years (girls), 8.6 mg/dL for 16–19 years (boys), 5.9 mg/dL for 16–19 years (girls) [12].

Mechanisms by which uric acid induces kidney injury

Uric acid is involved in various mechanisms that impair kidney function. First, uric acid crystallopathy damages the kidneys [13]. Uric acid forms monosodium urate crystals at concentrations >6.8 mg/dL [14]. Urate crystals are deposited in the kidney interstitium and induce damage. Second, it acts as a prooxidant in cells [13]. Uric acid becomes a prooxidant, which increases the production of reactive oxygen species when the concentration in the cell is high. Oxidative stress leads to DNA damage, enzyme inactivation, production of inflammatory cytokines, and cell apoptosis [15]. Third, uric acid upregulates the expression of angiotensinogen, angiotensin-converting enzyme, and angiotensin II receptors [13]. The activation of renin-angiotensin-aldosterone system increases blood pressure, inflammation, cellular apoptosis, kidney fibrosis, and endothelial dysfunction. Fourth, uric acid downregulates nitric oxide production and endothelial nitric oxide synthase activity and thus promotes vasospasm in afferent arterioles [16].

Epidemiologic and animal studies of association between hyperuricemia and kidney deterioration

The findings of many epidemiological studies have generally supported the role of hyperuricemia as an independent predictor of a future decline in kidney function. In large prospective studies, elevated baseline serum uric acid levels independently predicted the development of CKD [17,18]. Long-term studies (>25 years) demonstrated the association between hyperuricemia and end-stage kidney failure [19,20]. Epidemiological studies revealed similar results in pediatric patients with CKD [21,22]. In a prospective cohort study of children and adolescents with CKD, a high baseline uric acid level was an independent risk factor for faster progression of CKD [21]. Even if the baseline uric acid level is not high, patients whose uric acid levels rise over time tend to quickly lose their kidney function [22].

In an animal experiment, kidney function deteriorated when uric acid was increased [23]. Rats with partially resected kidneys with high serum uric acid induced by oxonic acid, a uricase inhibitor, demonstrated higher serum creatinine, blood pressure, and proteinuria than rats with partially resected kidneys without increasing uric acid. Histologically, rats with hyperuricemia showed a marked increase in glomerular anterior artery thickness as well as muscle cell proliferation. Rats with partially resected kidneys and treated with oxonic acid and allopurinol displayed similar serum uric acid levels, proteinuria, blood pressure, and histological changes to those of controls.

Clinical trials of the effectiveness of uric acid-lowering agents on kidney function in patients with CKD

Several studies aimed to determine whether uric acid-lowering agents can alleviate kidney disease exacerbation. Some studies have reported that xanthine oxidase inhibitors, a type of uric acid-lowering agent, delay the progression of kidney dysfunction [24-26]. The FREED study is representative [24]. It was a large (n=1,070) randomized study with a follow-up period of 36 months. Febuxostat reduced the incidence of kidney impairment, such as the development of microalbuminuria or proteinuria, worsening overt albuminuria, doubling serum creatinine levels, or progression to end-stage kidney disease. The participants were elderly, but many had early-stage kidney disease. The mean estimated glomerular filtration rate (eGFR) was

55 mL/min/1.73 m^2, and the mean urine albumin-creatinine ratio was 18 mg/g. A clinical study of pediatric patients with CKD showed similar results [25]. Ghane Sharbaf and Assadi [25] sought to determine whether allopurinol treatment reduced the risk of CKD progression in children. Seventy patients with CKD stage I-III and a uric acid level >5.5 mg/dL were enrolled. Although it was a small (n=70) and short-term (4 months) study, allopurinol treatment increased the eGFR, whereas no difference was observed in the control group.

However, in 2020, two large, well-designed studies, the PERL, and the CKD-FIX, published in the *New England Journal of Medicine* showed this trend has changed [27,28]. These studies failed to show that allopurinol treatment decreased the decline in GFR compared with placebo. PERL enrolled 530 adult patients with type 1 diabetes mellitus, with a mean age of 51 years, a mean eGFR 68 mL/min/1.73 m^2, and evidence of diabetic kidney disease (urine albumin-creatinine ratio, 20–3,333 μg/min or a decrease in GFR ≥3 mL/min/1.73 m^2 per year over the previous 3–5 years) [27]. Allopurinol dose was titrated from 200 to 400 mg daily based on GFR. After 3 years of follow-up, the mean serum uric acid level decreased from 6.1 to 3.9 mg/dL with allopurinol and remained at 6.1 mg/dL with placebo. The mean decrease in measured GFR was −3.0 mL/min/1.73 m^2 per year with allopurinol and −2.5 mL/min/1.73 m^2 per year with placebo (between-group difference, −0.6 mL/min/1.73 m^2 per year; 95% confidence interval, −1.5 to 0.4). CKD-FIX enrolled 369 of 620 intended patients because of slow recruitment [28]. Patients were adults with a mean age of 62 years, with CKD stage 3 or 4 with decreased eGFR by more than 3 mL/m/1.73 m^2 in the preceding year and no history of gout. The allopurinol dose started at 100 mg daily and increased to 300 mg if safe. The mean serum uric acid level decreased from 8.2 to 5.3 mg/dL with allopurinol and remained at 8.2 mg/dL with placebo. After 2 years of follow-up, there were no differences in eGFR change between groups (allopurinol −3.33 mL/min/1.73 m^2 per year and placebo −3.23 mL/min/1.73 m^2 per year; mean difference −0.10 mL/min/1.73 m^2 per year [95% confidence interval, −1.18 to 0.97]).

However, making this conclusion is premature. Some aspects must be considered in both studies. First, some participants in both studies had serum uric acid levels within the normal range. The inclusion criteria of the PERL study was a serum uric acid ≥4.5 mg/dL, which is a very low cutoff, and the mean serum uric acid level was 6.1 mg/dL [27]. In the CKD-FIX study, the mean uric acid level was relatively high at 8.2 mg/dL; however, since no serum uric acid cutoff was included in the inclusion criteria, patients with normal uric acid levels were also included [28]. The effects of the uric acid-lowering agents cannot be expected in participants with normal uric acid levels. Second, the late stage of the participants' kidney disease could limit the ability of allopurinol to prevent a decrease in GFR. The participants in the PERL study had a long duration of type 1 diabetes (34.6 years) [27]. In the CKD-FIX study, the mean eGFR was 31.7 mL/min/1.73 m^2 [28]. After kidney lesions become established, they are irreversible and the protective effect of urate-lowering agents may be weakened [29]. The FEATHER study and its post hoc study showed differences in the treatment effects of uric acid-lowering agents in early- and late-stage kidney disease [30,31]. On the contrary, it did not demonstrate that febuxostat, another xanthine oxidase inhibitor, prevented kidney dysfunction [30]. In fact, the results differed only when patients without proteinuria were analyzed. Febuxostat inhibited the eGFR decline in patients without proteinuria [31].

Effect of diet control to low uric acid on kidney function in patients with CKD and hyperuricemia

Hyperuricemia is associated with a purine-rich food intake. To date, there has been no direct study on whether reducing the intake of foods with high purine content delays the decline in kidney function in CKD. However, I suggest restricting the intake of fructose-rich beverages in patients with CKD with hyperuricemia. Fructose results in the conversion of adenosine triphosphate to inosine monophosphate, and leads to uric acid production [32]. Fructose-rich beverage consumption also increases serum uric acid levels in adolescents [33]. It also has a strong effect on obesity [34], an important risk factor for CKD worsening [35]. In adolescents, limiting meat intake to lower their uric acid levels should be careful because it has a negative effect on growth.

Guidelines for treatment of asymptomatic hyperuricemia in patients with CKD

Many clinical guidelines suggest not using uric acid-lowering agents to delay CKD progression in patients with CKD and asymptomatic hyperuricemia [36,37]. However, the Japanese guidelines conditionally recommend the use of uric acid-lowering agents in patients with CKD and asymptomatic hyperuricemia with uric acid ≥8.0 mg/dL [38]. They also considered the

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use of uric acid-lowering agents in patients with asymptomatic hyperuricemia with uric acid ≥9.0 mg/dL without complication. However, this guideline was based on data up to 2017; therefore, the findings of the PERL and CKD-FIX studies were not included. The Kidney Disease: Improving Global Outcomes CKD Work Group recently updated its CKD guidelines [36]. It now suggests that uric acid-lowering agents should not be used by patients with CKD and asymptomatic hyperuricemia to delay CKD progression. However, the certainty of the evidence was very low and the strength of the recommendation was low, meaning that different choices would be appropriate for different patients. Meanwhile, the Korean guidelines released in 2023, it was not formulated to use a uric acid-lowering agent to protect kidney function in CKD stage 3 or 4 patients with asymptomatic hyperuricemia because the profile of benefit/harm was not clear [39].

Uric acid and CKD in childhood

The role of uric acid in pediatric patients may differ from that in adults. The magnitude of serum uric acid role may vary depending on the severity and duration of CKD. This may be especially important in the setting of very early stage and mild kidney damage. Many pediatric patients with CKD are in the early disease stage; therefore, it is not yet known whether a uric acid-lowering agent alleviates kidney disease exacerbation. Large clinical trials should evaluate whether pediatric patients with CKD may benefit from urate-lowering agents in terms of nephroprotection. In hypertension, a similar hypothesis was proposed that the effect of lowering uric acid differs depending on the progression of disease [40]. Studies in elderly patients have shown more diverse results in the relationship between uric acid and hypertension, while uric acid is more likely to be important for hypertension in young people [40]. In the early (young) phase of the disease, increased serum uric acid levels can negatively impact endothelial function by reducing the activity of endothelial nitric oxide synthase and activating the renin-angiotensin-aldosterone system [40]. Addressing potential hypertensive triggers during this phase can lead to a stable decrease in blood pressure. In the later (adult) phase, the structural effects of uric acid on kidney function are characterized by the proliferation of vascular smooth muscle cells, injury to periglomerular vessels, glomerular hypertension, and ultimately interstitial fibrosis [40]. Once kidney damage has occurred, lowering serum uric acid levels becomes ineffective.

Conclusions

Kidney disease and hyperuricemia are clearly related. However, several confounding variables limit the interpretation of this relationship. Although interventional studies have been conducted, it has not yet been concluded that uric acid-lowering agents are ineffective in delaying CKD progression in CKD patients. Well-designed clinical trials of their therapeutic effects in subjects with very early stages of kidney damage, such as in children and adolescents, are warranted.

Conflicts of interest

Myung Hyun Cho is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contributions

All the work was done by MHC.

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