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# Hyperuricemia; a warning sign of future cardiovascular events and chronic kidney disease

Farahnak Assadi\*

Department of Pediatrics, Section of Nephrology, Rush University Medical Center, Chicago, IL, USA

## ARTICLE INFO

**Article Type:**  
Editorial**Article History:**  
Received: 8 September 2017  
Accepted: 1 November 2017  
ePublished: 12 November 2017**Keywords:**  
Uric acid  
Hypertension  
Microalbuminuria  
Chronic kidney disease  
Cardiovascular disease**Implication for health policy/practice/research/medical education:**

Strategies to lower the incident of hypertension associated-cardiovascular disease should include monitoring serum uric acid level, and if its level is higher than 5.5 mg/dL, treatment with allopurinol should be initiated.

**Please cite this paper as:** Assadi F. Hyperuricemia; a warning sign of future cardiovascular events and chronic kidney disease. J Nephroarmacol. 2018;7(1):1-2. DOI: 10.15171/npj.2018.01.

## Introduction

Obesity-related hypertension (HTN) in children and adolescents is frequently associated with elevated serum uric acid (UA) levels, high sensitivity C-reactive protein (CRP), and microalbuminuria (MA) (1-3). More than 70% of children with essential HTN have elevated serum UA levels above 5.5 mg/dL (4). Obese children with elevated uric acid (UA) have a higher prevalence of cardiovascular disease (CVD) risk factors (5). Elevated UA is also independent risk factors for faster progression of chronic kidney disease (CKD) in both children and adolescents (6).

The UA-induced HTN is mediated through the activation of the renin-angiotensin system (RAS), down regulation of nitric oxide, and vascular endothelial dysfunction (7-9). In a recent study, Feig et al reported on 30 adolescent aged 11-19 years with newly diagnosed essential HTN and serum UA level of >6 mg/dL. The participants were treated with allopurinol and placebo for 4 weeks with 2 weeks washout periods between treatments (10). Twenty of 30 patients achieved normal blood pressure (BP) while taking allopurinol compared to one patient while taking placebo ( $P < 0.01$ ).

More recently, Assadi sought to investigate whether UA-lowering agent in combination with angiotensin converting enzyme inhibitor (ACEI) can reduce BP more effectively in children with essential HTN than the ACEI (11). In this randomized clinical trial 44 adolescents,

aged 12-19 years, received either enalapril alone or enalapril plus allopurinol for 8 weeks. Baseline serum UA level ( $\geq 5.5$  mg/dL), mean BP, age, and body mass index (BMI) were similar between the 2 groups. After 8 weeks, treatment, mean BP and serum UA level were lower in the combination treatment group compared with enalapril group. The results suggest that lowering serum UA level with allopurinol should be considered in hypertensive children with elevated UA greater than 5.5 mg/dL (8). In another study, Assadi examined the therapeutic effect of microalbuminuria (MA) lowering on regression of left ventricular hypertrophy (LVH) in 54 hypertensive children and adolescents between 11-19 years old (12). All participants were receiving concomitant treatment with hydrochlorothiazide and ACEI. Baseline and 12-month follow-up assessment of left ventricular mass index (LVMI) and urine MA/creatinine ratio (MA/Cr), were obtained. MA was expressed as MA/Cr  $> 30$  ug/mg. Weight, body surface area BMI, mean arterial pressure, and MA were all univariate correlates of LVMI. In a multiple regression analysis, a significant relationship was found between LVMI and MA, BMI and mean arterial pressure. MA had the most significant correlation with LVMI at follow-up, suggesting that MA-lowering agents may halt or slow the progression of LVH in children and adolescent with essential HTN (10).

In a more recent clinical trial, Lauren and colleagues reported on 49 hypertensive children, aged 3-19 years

\*Corresponding author: Prof. Farahnak Assadi, Email: fassadi@rush.edu

with hyperuricemia who had completed both baseline and 12-month evaluations. At baseline, 24% had serum UA greater than 5.5 mg/dL, 52% were either overweight or obese, and 39% had LVH (13).

High-sensitivity CRP, low high-density lipoprotein, and LVMI were all significantly associated with elevated serum UA levels at baseline. Each 1 mg/dL increase in baseline UA was associated with a 2.5 g/m<sup>2</sup>.7 increase in the LVMI overtime. However, this association was no longer significant after adjustments for changes in serum UA, BP and medication use at 1-year follow-up. These findings suggest that hypertensive children with elevated serum UA have a higher prevalence of obesity-related CVD risk factors and that UA may be a marker of obesity and not an independent CVD risk factor (7).

Rodenbach et al assessed the impact of hyperuricemia on progression of CKD on over 600 children and adolescent with a median age of 12.3 years (6). They reported, older age, male gender, lower GFR and BMI >95th percentile were associated with higher serum UA levels and faster progression to CKD. High BP, CKD, and raised urine protein-creatinine ratio were also associated with faster times to the CKD progression. Authors concluded that hyperuricemia is an independent risk factor for faster progression of CKD in children and adolescents.

### Conclusion

These studies demonstrate a new potential therapeutic approach, which, require confirmation in larger clinical trials. In the meanwhile, strategies to lower the incident of HTN associated-CVD should include monitoring serum UA level, and if its level is higher than 5.5 mg/dL, treatment with allopurinol should be initiated. Further, it is highly likely that UA-lowering therapy in children with CKD could also slow the disease progression.

To date, no published studies have evaluated the therapeutic effects of allopurinol to retard disease progression among children and adolescents with CKD. Thus, controlled, randomized, and longitudinal clinical trials are warranted to examine this hypothesis.

### Author's contribution

FA is the single author of the manuscript.

### Conflicts of interest

The author declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

### Funding/Support

None.

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