Serum Uric Acid in Primary Hypertension
From Innocent Bystander to Primum Movens?

Chirag Bavishi, Franz H. Messerli, Stefano F. Rimoldi

See related article, pp 934–940

Over a quarter of a century, primary hypertension has become a rapidly growing health problem in children and adolescents.1 The pathogenesis of primary hypertension remains unclear and is said to involve a complex interplay of genetic, environmental, and behavioral factors. Serum uric acid (sUA) has been implicated in pathogenesis and maintenance of primary hypertension.2 However, insulin resistance, metabolic syndrome, and obesity, that have become highly prevalent in children and adolescents are associated with both elevated sUA and hypertension. Not surprisingly, it has been hotly debated whether sUA is a cause, consequence, or just an innocent bystander in the pathogenesis of hypertension. By analyzing the effect of lifestyle changes on blood pressure (BP), body weight and sUA levels in children, the article by Viazzi et al3 attempts to clarify some of these issues.

Lifestyle changes remain a cornerstone for prevention and treatment of primary hypertension in children and adolescents.4 The authors studied the role of lifestyle modifications such as diet and physical activity on BP, body weight and sUA levels in a cohort of 248 children (55% boys, mean age=10.5 years) at increased cardiovascular risk, defined by elevated BP values and excess of weight and dyslipidemia and a positive family history of cardiovascular disease. Majority of the children in the study had excess weight with 34% children being overweight and 48% obese. In addition, 50% of the children had values of systolic and diastolic BP 290th percentile and ≥21% children had dyslipidemia. After a mean follow-up of 1.5 years, lifestyle changes achieved a significant reduction in mean systolic BP and mean body mass index in the above study. However, in this study, in spite of lifestyle modifications, overall sUA levels were slightly, but statistically significantly increased during the study. More importantly, any decrease in body mass index was associated with a substantial decrease in sUA and systolic BP. Accordingly, in children who had lost weight, sUA was decreased and systolic BP was also reduced. In the context of these results, the next logical question is whether sUA had any role in mediating this weight-related reduction in systolic BP? To answer this, the authors devised a model to calculate systolic BP in response to weight reduction with different baseline sUA values. They documented that the presence of increased sUA levels at baseline significantly blunted the reduction in BP during the subsequent study period.

The interventions used in the study were considerably more lenient than suggested by the 2011 National Heart, Lung, and Blood Institute expert guidelines for cardiovascular health and risk reduction in children and adolescents.5 Viazzi et al3 used structured physical activity of at least 2 hours per week with no more than 1 hour per day of sedentary activities, whereas the National Heart, Lung, and Blood Institute expert guidelines recommend 1 hour per day of moderate to rigorous physical activity and limit sedentary time to <2 hours per day. Although diet and exercise recommendations for an individual child/adolescent may vary depending on age and other factors, adherence to physical activity and dietary modifications are the key for achieving sustained results in this highly vulnerable group. On the basis of their findings, the authors suggest that sUA may play an important role in the stimulation of insulin resistance by inducing endothelial dysfunction, thereby becoming the primum movens for both, metabolic and hemodynamic alterations associated with hypertension.

Although the authors do not claim to have found the holy grail, they do suggest that maintaining relatively low uric acid values over time could be more effective at preventing the onset of hypertension than lowering uric acid to reduce BP levels once hypertension is established. Should we then routinely check for sUA levels in at-risk children? The question is difficult to answer for several reasons: (1) although, sUA could serve as a prognostic marker, lifestyle modifications would have to be initiated in such at-risk children anyhow irrespective of sUA levels, (2) there is lack of firm evidence that lowering elevated sUA in such situations will confer benefits, (3) it is unknown whether pharmacological urate–lowering strategies should be used in at-risk children with elevated sUA, (4) defining the optimal cutoff for sUA to initiate any intervention is challenging because sUA levels increases with age and are influenced by diet and antihypertensive therapy.

Once hypertension develops, there is some evidence that uric acid–lowering therapy reduces BP. In a meta-analysis of 10 clinical studies involving 738 individuals,6 we showed that allopurinol was associated with a small, but significant decrease in systolic and diastolic BP compared with

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controls. Randomized trials have shown that in adolescents with hypertension and elevated sUA, allopurinol resulted in significant reduction of clinic and ambulatory systolic and diastolic BP compared with placebo.6–8 However, these strategies need to be confirmed in larger prospective trials, and specific risk/benefits should be thoroughly investigated in pediatric populations.

The findings of Viazzi et al3 highlight our current understanding of mechanism linking sUA to hypertension. Elevated sUA may lead to hypertension through a 2-step process (Figure). Initially, sUA cause oxidative stress, mediated by the activation of the renin–angiotensin system and inhibition of endothelial nitric oxide, which mediates reversible systemic and renal vasoonstriction. The mechanisms through which sUA activates renin–angiotensin system is not fully understood; however, an increase in sUA induces vasoonstriction by activation of renin–angiotensin system, and subsequently uric acid uptake into vascular smooth muscle leading to cell proliferation.9 Over time, this is followed by irreversible changes in intrarenal vasculature.10 In this study, the impact of lifestyle modifications on BP control was attenuated by elevated baseline sUA suggests that such children might have progressed to the irreversible phase and structural renal damage may have occurred.11 Although appealing, these observations need further scrutiny. Future studies should also focus on additional confounding factors such as consumption of high fructose-rich sugar-sweetened beverages, which have been associated with elevated body mass index, sUA, and hypertension.12

This provocative study by Viazzi et al3 adds to the growing body of literature exploring the complex relationship between sUA, BP, obesity, and insulin sensitivity. Time and again, sUA emerges as one of the key factor modulating primary hypertension. The presence of increased sUA levels at baseline not only predicted development of hypertension but also significantly blunted the decrease in BP associated with lifestyle changes. Further prospective studies should aim at identifying the select group of patients with primary hypertension in whom sUA-lowering strategies would yield benefits not only in lowering BP but also in preventing cardiovascular events. Borghi and Cicero13 recently stated that “plasma uric acid levels require more attention in the evaluation of the metabolic risk profile of children and adolescents”. We thoroughly agree.

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References


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