Hyperuricemia and Hypertension
A Confluence of Concepts

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Rarely in clinical medicine is it possible to define a distinct laboratory abnormality associated, for unknown reasons, with a specific disease entity and to have one group of tenacious investigators resolve the conundrum of contributing mechanisms. Nonetheless, in this issue of Hypertension such is the case as presented in the investigations of Soletsky and Feig. These investigators have now contributed to a decade or more of animal and human investigation by Feig and Johnson and their coworkers by unraveling the major mechanism that links hyperuricemia to hypertension. This has been a long-standing clinical and basic science quest.

Gout, as the long-term manifestation of hyperuricemia, is a metabolic disease process that has been known from antiquity. Egyptian physicians described the disease some 5000 years ago followed by the astute clinical characterization of the disease, in the fifth century BC, by the Greek physician Hippocrates, as "the unwalkable disease." By the mid-1800s AD Sir Alfred Baring Garod identified that uric acid was the cause of gout and not a consequence of the disease. In addition, this also coincided with the time framework in which several investigators speculated on the linkage of hyperuricemia to the presence of hypertension. However, it was not until the contemporary studies of Feig and Johnson and colleagues that we learned that, in animal models, acute elevation of serum urate induces a prompt elevation of blood pressure and that chronic elevation sustains the abnormal pressure and induces irreversible vascular and glomerular changes that lead to a form of salt-sensitive hypertension.

Hence, the lesson learned from the animal investigations suggested that, in humans, early treatment to reduce hyperuricemia associated with increases in blood pressure might be successful, whereas the years of hyperuricemia attendant with the emergence of gout and contemporaneous hypertension might be a setting in which lowering of serum urate would not lead to resolution of the hypertension.

With respect to the human condition, the early appearance of hyperuricemia is a reliable predictor of later development of hypertension, and in adults with essential hypertension the comorbidity of hyperuricemia is very common. Now enter the studies of Feig and Johnson. A decade ago they identified that some 90% of adolescent hypertension is associated with hyperuricemia and that the threshold for the effect of serum urate in these children is between 5.0 and 5.5 mg/dL. The latter is a range of serum urate concentration that is lower than the supersaturation value of 6.8 mg/dL at core body temperature. It thereby indicated that the mechanism of hyperuricemia-associated increase in blood pressure is independent of the deposition of crystal monosodium urate, which, of course, is the case for the development of gout. Next in the evolution of the scientific quest was the logical, albeit controversial, decision to treat the hyperuricemia of the hypertensive adolescents with allopurinol, a xanthine oxidase inhibitor. This was remarkably successful with some two thirds of the study subjects normalizing their blood pressure.

The sequential vexing question was whether the amelioration of hypertension was because of the reduction of the serum urate itself or a urate-independent biochemical effect of inhibition of xanthine oxidase. Inhibition of xanthine oxidase is associated with several important clinical effects. These activities may be summarized as follows: (1) a reduction in endogenous production of uric acid signaled by reduced systemic concentrations of urate, (2) a reduction in the local consumption of molecular oxygen as used in the production of xanthine and uric acid, (3) a decrease in the production of local reactive oxygen species potentially reducing oxidative stress; (4) a reduction in catabolism of adenosine monophosphate leading to potentially better tissue energetics, and (5) a reduction in the catabolism of vasodilatory nitric oxide. In ischemic and inflammatory vascular tissue, as is often associated with hypertension, the observation that there is a major upregulation of the production of endothelial-associated xanthine oxidase is of relevance. The latter xanthine oxidase is bound to the luminal surface of the endothelial cells, and recent studies have confirmed that endothelial dysfunction, mediated by xanthine oxidase, is an important component of vascular disease, such as coronary artery disease. In patients with chronic stable angina, inhibition of xanthine oxidase by allopurinol results in significant symptomatic improvement, whereas, in similar patients, inhibition of renal proximal transporters by probenecid does not confer clinical benefit.

The next logical approach to resolving the mechanistic issues associated with hyperuricemia-associated hypertension in adolescents was to reduce their serum urate with a therapeutic approach independent of xanthine oxidase inhibition. In this issue of Hypertension that is what is reported by Soletsky and Feig. They present the results of their studies using the uricosuric agent probenecid as the means of reducing serum urate. They demonstrate that reduction of serum urate in their hypertensive subjects, with either xanthine oxidase inhibition...

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or renal proximal tubular inhibition of urate reabsorption, results in mitigation of hyperuricemia-associated increases in blood pressure. Nonetheless, caution in the interpretation of the reported data is necessary. The number of studied subjects is very limited, with only 20 adolescents per treatment limb. In addition, the majority of the study subjects were significantly obese, with a body mass index and body weight of ≈36 (kg/m²) and 100 kg, respectively. This makes generalizability of the data to a typical adolescent population questionable. The studied subjects were not controlled for sodium balance and the modest weight loss noted in the allopurinol- and probenecid-treated groups compared with the ≈2 kg weight gains in the placebo group is problematic. Allopurinol and probenecid are not known to possess a natriuretic effect. However, in contrast to the serum urate-lowering effects of allopurinol and probenecid, thiazide diuretics induce volume contraction with modest weight loss and a reduction in blood pressure while elevating serum urate. Clearly, a robust well-powered multicenter study, with adequate sodium balance control, is required to characterize the clinical applicability of the observations of Soletsky and Feig.¹

Basic science questions remain to be resolved. It is reasonable to question the hierarchical importance of extracellular urate concentrations versus intracellular urate concentrations as the primary driver associated with blood pressure disturbance. Active transport of urate into vascular smooth muscle cells and endothelial cells has been described but further characterization of the transporters relevant to human hyperuricemia-associated hypertension will be desirable.² The ability to block such urate transport by existing pharmacological means or by drugs in development represents a future chapter in the story.

What remains then is an examination of the clinical implications of these blood pressure-related findings in clinical practice. Loeffler et al³ recently informed us that in the National Health and Nutrition Examination Survey of 1999–2006, adolescents aged 12 to 17 years who had an obesity rate of 17.0% and 3.3% had elevated blood pressure.⁴ These are alarming statistics and are a matter of public health importance. Relevant professional pediatric societies need to continue their tireless efforts to educate the public and to develop innovative preventative programs for our current epidemic of childhood obesity and adolescent hypertension.

In adults with hyperuricemia and hypertension, there is a dearth of investigative information to characterize the therapeutic advisability of serum urate reduction in the management of hypertension. This stems from the fact that, in previous decades, there has been little clinical interest in hyperuricemia or gout. However, in recent years, we have seen a renascence of interest in hyperuricemia and gout. It is possible to estimate the current prevalence of hyperuricemia in the US population as being ≈66.0 million and the prevalence of gout as being 8.3 million based on the US Census Bureau POPClock and the epidemiologic data, reported by Zhu et al, derived from the National Health and Nutrition Examination Survey of 2007–2008.⁵ Despite the fact that many millions of hyperuricemic adults in the United States have the comorbid complication of hypertension, there are no prospective study data to guide therapeutic decisions with respect to the advisability of reducing elevated serum urate in addition to the implementation of standard hypertension management. This clinical circumstance will require adequately powered studies with hard clinical end points. Such studies will need evaluation of the comparison of combined reduction of serum urate and blood pressure versus primary antihypertensive therapy alone.

In addition to hypertension, hyperuricemia is inexorably linked to cardiovascular disease, stroke, and decline of renal function.⁶ It is fortuitous that, in gout patients with known cardiovascular disease, a large well-powered study is underway, designed to quantify the occurrence of major adverse cardiovascular events emerging during long-term management with either of the xanthine oxidase inhibitors allopurinol or febuxostat (Clinicaltrials.gov identifier NCT01101035). The study includes an algorithm to treat to a biochemical serum urate target of <6.0 mg/dL if clinically feasible. The results of the latter study should presumably clarify the angst that exists with respect to the appearance of major adverse cardiovascular events during xanthine oxidase inhibition in gout therapy. For ethical reasons there is no control placebo limb in this trial; nonetheless, by the use of historic controls, the investigation may clarify the hypothesis that xanthine oxidase inhibition for control of hyperuricemia, attendant with gout, may be beneficial for cardiovascular and renal health.

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References

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