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Uric Acid: A Clearer Focus

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EDITORIAL

Uric Acid: A Clearer Focus

Plasma phosphorus and uric acid/urate levels were removed from clinical laboratories' metabolic panels nearly 3 decades ago. There was insufficient evidence for their continued measurement. Moreover, fears of treating asymptomatic hyperuricemia with allopurinol, with its risk of side effects and hypersensitivity, contributed to uric acid's removal from the metabolic panel. Subsequently, the evidence base for both of these nephrocentric molecules developed. This issue of Advances in *Chronic Kidney Disease* converges on uric acid/urate, which gained preeminence in hominoids by virtue of the loss of the *uricase* gene during evolution through the Miocene Epoch.

The guest editors, Drs. Anthony J. Bleyer and Stanislav Kmoch have, like a large reflecting telescope, collected an impressive amount of information from their respective contributors and concentrated it, producing a much clearer image of this purine-derived metabolic end-product's role in human physiology and pathophysiology. Their enhanced picture clarifies our knowledge regarding normal uric acid/urate physiology and pathophysiology (Fig 1). Greater insight is provided not only for gout and uric acid stone formation but also for hypertension and CKD, as they relate to genetic tubulointerstitial disorders, including hyperuricemic mutations of the *UMOD* (*uromodulin*),[1] *REN* (*renin*),[2,3] and *HNF-1b* (*hepatocyte nuclear factor-1 beta*) genes.[4]

Once a highbrow disease of the genteel, gout has seen a resurgence in the past 2 decades in the United States. The consequence of hyperuricemia, gout, and uric acid nephrolithiasis may result from perturbations of renal handling of uric acid. Although approximately 90% of the ultrafiltered uric acid undergoes reabsorption, the kidneys excrete only about 60% to 70% of the body's uric acid; the rest is secreted by the bowel. Recent investigations have overturned the previously held conception of renal urate handling. This end-product of purine metabolism is filtered, reabsorbed, and secreted by specific proximal tubule organic anion transporters, such as URAT1 (uric acid transporter-1 protein)[5] and GLUT9a (glucose transporter-like protein 9a), now referred to simply as GLUT9.[6] It is now clear that urate is not reabsorbed and secreted, contradicting the classic model of presecretory reabsorption, secretion, and postsecretory reabsorption. Also, it is now appreciated that the uricosuric agents losartan, furosemide, probenecid, and benzbromarone inhibit apical URAT1, whereas pyrazinamide stimulates this transporter. On the basolateral aspect, GLUT9 is inhibited by losartan, probenecid, and benzbromarone, thereby inducing uricosuria.[5]

The incidence and prevalence of gout and uric acid stones have risen concomitantly with the ongoing epidemic of obesity, metabolic syndrome, and type 2 diabetes. The culprit for gout is likely endogenous uric acid overproduction fueled by the exogenously introduced high fructose corn syrup—the standard American dietary sweetener—which upon cellular metabolism induces adenine release and subsequent uric acid production. This effect is mediated by the urate transporter SLC2A9 that encodes GLUT9 and is inhibited by fructose.[7] A spike in serum urate concentrations follows ingestion of high-fructose corn syrup–containing soft drinks.[8] Without a reduction in the use of this sweetener, the incidence of gout will likely increase, even with adoption of the oft-prescribed, classic "low uric acid" diet and the recently described "urate-lowering drinks," coffee and milk, the latter of which contains the uricosuric orotic acid.[9] Conversely, uric acid stones are more the result of an "unduly acidic urine pH" associated with obesity, metabolic syndrome, and insulin resistance.

Hopefully, a "low uric acid diet," which also reduces net acid production, and consumption of more fruits and vegetables will be accompanied by a reduction in

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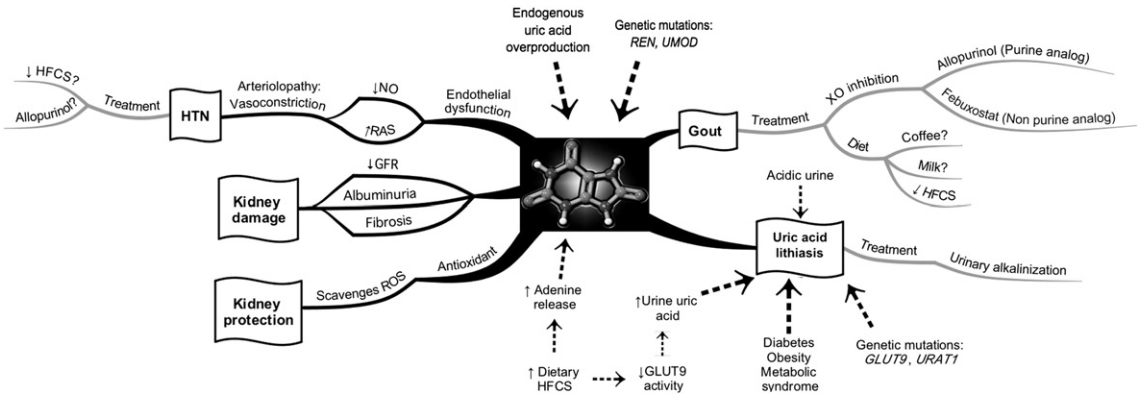

Figure 1. Proposed model of uric acid/urate pathophysiology in humans. Abbreviations: GFR, glomerular filtration rate; GLUT9, glucose-like transporter 9; HFCS, high fructose corn syrup; HTN, hypertension; NO, nitric oxide; RAS, renin-angiotensin system; REN, renin gene; ROS, reactive oxygen species; UMOD, uromodulin gene; URAT1, uric acid transporter-1. Diagram by Pablo Buitrón de la Vega, with iMindmap v. 6.0, ThinkBuzan, Cardiff.

the frequency of uric acid stone formation. In addition, with advancing knowledge of renal urate handling, opportunities for the specific augmentation of uric acid excretion by the kidneys may arise in the pharmacologic literature, although urinary alkalinization will be necessary to ensure uric acid's continued solubility. Until then, we depend on a mainstay of xanthine oxidase inhibition by the purine analogue, allopurinol (K_i 0.5 μM),[10] or the more potent, nonpurine inhibitor, febuxostat (K_i 0.6 nM), which is metabolized in the liver.[11] The former's association with hypersensitivity reactions has often given pause to its prescription; however, these reactions may result from genetic predisposition rather than dose accumulation.

Uric acid's role in producing a reversible form of high blood pressure stems from increasing levels of uric acid that may induce the renin-angiotensin system, which, if prolonged, becomes resistant to the uric acid–lowering effect of xanthine oxidase inhibitors.[12,13] Structural damage from persistent, sodium-dependent hypertension transcends an initial uric acid–mediated vasoconstriction, induced by restriction of vasodilatory nitric oxide, coincident with afferent arteriolopathy, a pathologic condition not unsurprisingly magnified by concurrent cyclosporine administration.

This mechanism of hypertension has been demonstrated by pharmacologically induced hyperuricemic hypertension in a rodent model, and correlative studies that have repeatedly illustrated an epidemiologic association between uric acid and elevated systolic and diastolic blood pressures.[14] This association is strongest in adolescents in whom treatment of hypertension with allopurinol restored blood pressure to normal.[15] Moreover, a non-uric acid-mediated reduction of the blood pressure by allopurinol has been detected in an experimental rat model of hypertension, and this effect may involve CD-5 cells as well as the renin-angiotensin system.

Would lowering the uric acid in patients with CKD provide an improved outcome? The data regarding this hypothesis are sparse but compelling. First, however, one must acknowledge that although hyperuricemia is worsened by progressive CKD, its serum concentration should have been higher than measured at any given level of CKD. Whether there is enhanced gut secretion of uric acid and uricolysis[16] and/or downregulation of xanthine oxidase activity in urate-producing tissues is conjectural but plausible. In addition, the hyperuricemia of CKD may be protective, since uric acid/urate may act as an antioxidant in some circumstances, scavenging reactive oxygen species (Fig 1).[17-19] In short, the hyperuricemia of CKD deserves some equanimity, as it may confer some biologically and clinically positive aspects.[20,21]

Multiple cross-sectional studies have correlated elevated uric acid levels with reduced estimated glomerular filtration rate (GFR) and/or microalbuminuria. In a 54-person 1-year randomized interventional study of individuals with hyperuricemia and CKD stages 3 and 4, xanthine oxidase inhibition by allopurinol was salutary.[20] Namely, progression of CKD was attenuated in those in the treatment group whose serum uric acid levels were purposefully diminished. A 2-year study that compared allopurinol to conventional therapy in 113 patients with estimated GFR less than 60 mL/min/1.73 m^2 demonstrated a positive effect of allopurinol, whereby the treatment group had a lesser slope of decline of GFR.[21] In fact, the slope of the treatment group was unchanged. Notably, because there is an increment of the serum uric acid concentration concomitant with a reduction in GFR, the relationship may be self-fulfilling. Obviously, larger interventional rather than observational trials of uric acid lowering are required.

Forerunner reflector telescopes suffered from chromatic aberration as did our previous understanding of uric acid. Certainly, the authors of this issue of *Advances in Chronic Kidney Disease* have eliminated many of the distortions regarding this diprotic acid (Fig 2). Its refocusing into a much clearer image mandates its belated return to the metabolic panel and warrants its further investigation.

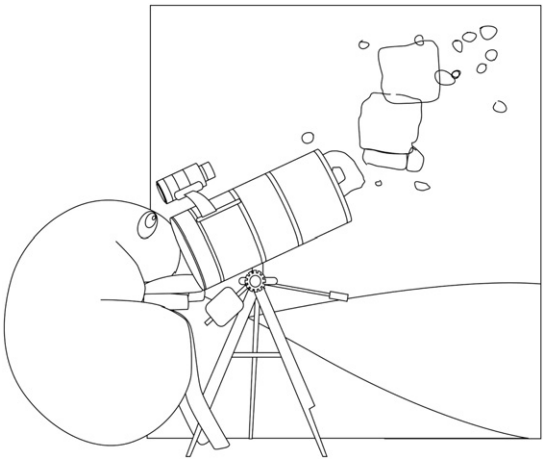

Figure 2. The nephrologist focuses sharply on the constellations of uric acid/urate, in order to resolve this entity's physiology and pathophysiology. Illustration by Tom Mattix, Mattix Illustration.

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Editor

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