Intestinal Hyperuricemia as a Driving Mechanism for CKD

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The observation that hyperuricemia can predict the development of CKD has led to the hypothesis that lowering serum uric acid in hyperuricemic individuals might reduce both the development and progression of chronic kidney disease (CKD). Nevertheless, the CKD-FIX trial reported that allopurinol treatment, when prescribed irrespective of serum uric acid levels, did not slow progression of CKD.[1] Although the trial can be criticized for not including individuals with a history of gout (who might be expected to have the most benefit) and including normouricemic individuals (who would be expected to show the least benefit), its results suggest that indiscriminate treatment of CKD with allopurinol is likely not beneficial. However, it does not answer the question of whether certain subgroups might benefit from urate-lowering therapy.

Related Article, p. ***

In this issue of *AJKD*, Ohashi et al[2] present evidence about one subgroup that may benefit from urate-lowering therapy. These are individuals with hyperuricemia who have genetically reduced function of a specific urate transporter known as ABCG2 (adenosine trisphosphate [ATP]-binding cassette subfamily G member 2, also referred to as breast cancer resistance protein [BCRP]). ABCG2 is an ATP-dependent transporter that is heavily expressed in the brush border of the proximal tubule, where it pumps sodium urate into the urine, and it is also expressed in the villi of the small intestine, where it pumps uric acid into the intestine.[3] ABCG2 is the main transporter driving urate excretion in the gut and intestine. The other 2 major urate transporters are involved in the reabsorption of uric acid from the urine; they are URAT1 (encoded by *SLC22A12*), which is expressed on the brush border, and GLUT9 (encoded by *SLC2A9*), which is expressed primarily on the basolateral aspect of the proximal tubule (Fig 1). GLUT9 is also expressed in the intestinal epithelium, where it mediates urate excretion as opposed to reabsorption, as it does in the kidney.[4]

Ohashi et al studied 1,885 Japanese adults who at baseline did not have gout and had no evidence for CKD (defined as estimated glomerular filtration rate ≥60 mL/min/1.73 m^2) and who were followed for a mean of 9-10 years. Individuals were genetically tested for the presence of 2 polymorphisms of ABCG2 associated with reduced function—the Q126X variant (which has near-absent function) and Q141K (which has half-function). Since each individual receives 2 alleles, the individuals were categorized as having full function, 75% function, or ≤50% function based on the number of alleles they had for the 2 variants; these groups corresponded with baseline rates of hyperuricemia (defined as serum uric acid of >7 mg/dL) of 12.6%, 17.8%, and 28.4%, respectively. The primary finding was that among individuals with hyperuricemia and early CKD stage 2, the group with markedly reduced (≤50%) ABCG2 function showed a more rapid worsening of kidney function compared to groups with >50% ABCG2 function.

The study is significant, as it suggests that there may be subsets of individuals with hyperuricemia who may specifically benefit from urate-lowering therapy. However, limitations of the study include the small number of patients, the lack of a validation cohort, and its restriction to an Asian population. Nevertheless, the study represents a conceptual breakthrough that may provide key insights into how uric acid may cause CKD, as discussed in the following paragraphs.

Most mammals regulate uric acid levels by degrading uric acid via the hepatic enzyme uricase, but that enzyme was lost during human evolution, with the consequence that humans must excrete uric acid. As uric acid can crystallize at high concentrations and especially in the presence of acidic urine, intestinal excretion provides a key buffering system to reduce the risk for urate crystallization in the urinary tract. In this regard, studies have shown that knocking out ABCG2 in mice dramatically reduces intestinal excretion of uric acid, forcing the kidney to excrete the majority of uric acid.[3,5] Since ABCG2 is also expressed in the kidney, one might expect reduced renal excretion as well, but studies in both mice and humans show that urinary excretion tends to be high,[3,6] which almost certainly reflects a compensatory decrease in URAT1 and GLUT9 function[7] (Fig 1). Indeed, the high urinary uric acid levels are consistent with the old phrase "urate overproduction," but in this case are due to reduced intestinal excretion rather than increased production (as can occur in conditions such as tumor lysis syndrome).

Given these findings, reduced ABCG2 function would be expected to increase the risk for severe uricosuria and urinary crystal formation. Although high levels of uricosuria can activate proximal tubular cells and stimulate inflammasome activation independently of crystals,[8] crystalluria is increasingly recognized as a risk factor for CKD,[9] and also likely results from activating inflammasomes after attaching to the distal tubules and collecting ducts. Furthermore, tubular injury from urate crystals is thought to lead to breaks that allow the crystals to migrate into the interstitium of the outer medulla, where they may continue to cause local inflammation and injury.

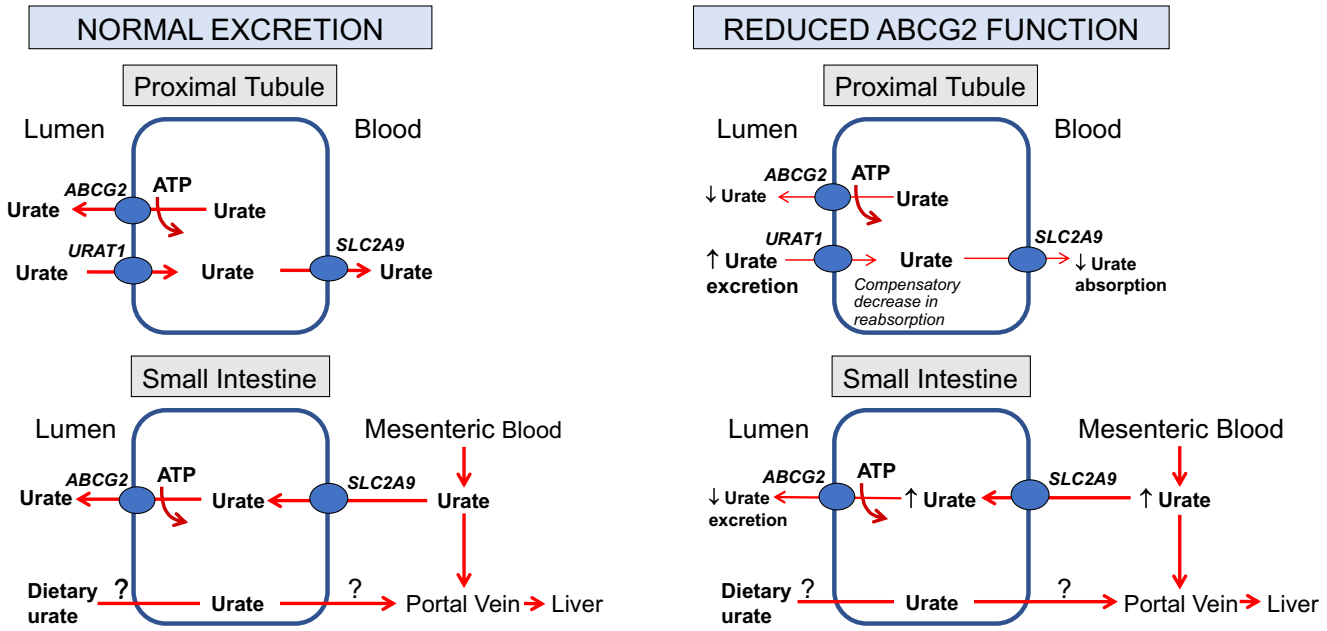

Figure 1. Urate transport in the proximal tubule and small bowel. In humans uric acid is excreted primarily by the kidney (two-thirds) and the gut (one-third). In the normal setting (left side), uric acid is pumped into the urinary space via the ATP-dependent ABCG2 urate transporter, while reabsorption from the urine requires the coordinated effects of URAT1 (expressed on the apical side) and SLC2A9 (ie, GLUT9; primarily expressed on the basolateral aspect of the tubule). Intestinal excretion also involves pumping uric acid into the intestine via the ABCG2 transporter. However, in the intestine SLC2A9 (which is primarily expressed on the basolateral side) also stimulates excretion into the gut, while the mechanisms driving intestinal absorption are still being determined. In contrast, when ABCG2 function is impaired (right side), the reduction in intestinal excretion is marked, and the consequence is a rise in serum uric acid that includes increased delivery to the liver, which may contribute to the metabolic syndrome. In the kidney the inhibition of ABCG2 also reduces its ability to excrete uric acid, but because of the marked rise in serum uric acid there is a compensatory decrease in reabsorption of uric acid in the kidney, resulting in an overall increase in urinary uric acid excretion (uricosuria).

Specific interactions of genetically reduced intestinal urate excretion with environmental factors can also be predicted. Crystal formation would be more likely to occur in the setting of low urinary pH, such as can occur in the setting of dehydration or heat stress.[10,11] Not surprisingly, low urine pH is also an independent risk factor for CKD,[12] and heat stress has also been linked with urate crystalluria and CKD.[11] Uricosuria is also common in poorly controlled diabetes, and we found that bicarbonate therapy can reduce urate crystalluria in association with a reduction in tubular biomarkers for kidney damage in these patients.[13] One wonders if the benefit of bicarbonate therapy on CKD is not by treating metabolic acidosis but rather by reducing urate crystallization by alkalinizing the urine. Urate crystals can also predispose to both urate and calcium nephrolithiasis, and it is of interest that as many as one-third of individuals with gout have kidney stones, and this subset may have elevated risk of CKD.[14]

The ABCG2 polymorphisms associated with reduced function might also have an interaction with diet. For example, ingestion of fructose or purines can result in a transient and sometimes dramatic rise in postprandial urinary uric acid that appears to be worse in individuals with gout.[15,16] ABCG2 function is dependent on ATP, and fructose ingestion reduces ATP levels in the intestine[17] and kidney.[18] This could contribute to impaired ABCG2 function, which coupled with fructose-induced reduction of ABCG2 expression in the ileum of rats, could explain why fructose decreases the intestinal excretion of uric acid.[19] Interestingly, individuals with the Q141K variant of ABCG2 do not show much of a rise in serum uric acid with fructose owing to a greater excretion in urinary uric acid.[20] Ingestion of fructose also lowers urinary pH[10] and stimulates urinary concentration.[21] Thus, if increased urinary uric acid is important in how hyperuricemia causes CKD, then this insight carries important implications for future studies investigating the relationship of such genetic polymorphisms with diet.

Reduction in intestinal uric acid excretion is also expected to result in higher uric acid levels in the portal vein and liver (Fig 1). Most of the metabolic effects of fructose are dependent on effects of intracellular uric acid in the liver.[22] Indeed, it is of interest that mice that have had intestinal excretion of uric acid reduced by specific targeting of the gene encoding GLUT9 in the intestine develop metabolic syndrome.[4] Similarly, hyperuricemic male mice with knock-in of the lower-functioning Q141K polymorphism of ABCG2 also develop features of metabolic syndrome, including insulin resistance and fatty liver.[23] Hence, one might predict that reduced ABCG2 function from diet or genetics could also be a mechanism for driving features of metabolic syndrome.

Although this was not observed in the Ohashi et al study, these individuals were young and relatively lean. In contrast, one study in individuals with type 2 diabetes reported that those carrying the Q141K variant had significantly higher fasting blood glucose and HbA1c levels,[24] while another linked this polymorphism with higher cholesterol levels in individuals from Mexico.[25]

In summary, reduced activity of ABCG2 may be a risk factor for the progression of CKD, either by increasing urinary uric acid excretion (increasing the risk for crystalluria) or by driving more metabolic effects by increasing urate delivery to the liver. It is also possible that the association is not driven by uric acid itself, as the transporter can also mediate transport of other molecules, including indoxyl sulfate.[2] In the meantime, it seems important to include testing for ABCG2 polymorphisms such as Q141K in future studies. This polymorphism is especially common in the Asian population (30%), as opposed to non-Hispanic White (15%), Hispanic and Native American (20%), and African American (3%-10%) populations.[26,27] Indeed, in one study of Japanese individuals with hyperuricemia, 75% carried either the Q141K or Q126X allele.[6] The Q141K variant may also explain as many as 10% of cases of gout in White individuals.[28] Perhaps this might explain why studies performed in Asia tend to show more benefit with lowering uric acid than studies run in Australia or the United States. Clearly, the power of the Ohashi et al study is that it is hypothesis-generating, and this should be welcomed by all of us who are trying to better understand the biology of this complicated subject.

Article Information

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