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Urate Homeostasis and Risk of Hyperuricemia in Kidney Disease

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The weak organic acid uric acid (pKa 5.8) exists as urate at physiological pH. Uric acid, the last product of exogenous and endogenous purine metabolism, is generated mostly in the liver. In humans, it is eliminated mostly by the kidneys and, to a lesser extent, the gastrointestinal tract. The kidney is essential for uric acid balance and elimination. The four-component model of renal urate physiology consists of four steps: glomerular filtration, reabsorption from the glomerular ultrafiltrate, subsequent secretion, and then post-secretory reabsorption.
In the kidneys, glomerular-filtered urate is efficiently reabsorbed back into the bloodstream through the concerted activity of URAT1 and GLUT9, located on the apical and basolateral sides, respectively. Some medicines, such as probenecid and losartan, could lower serum urate concentrations by inhibiting URAT1. Emerging data indicate that GLUT9 is involved in urate transport that is voltage-dependent. GLUT9 was initially characterized as a fructose or GLUT transporter.
According to biochemical and physiological research, NPT1, NPT4, ABCG2, OAT1 and OAT3 are involved in uric acid secretion, and genetic variants that impair the activity of these transporters are related with elevated sUA levels and gout. OAT1 and OAT3 are localized to the basolateral membrane of the proximal tubules of the kidney. In experimental mouse models, the loss of OAT1 and OAT3 results in impaired renal urate excretion. ABCG2 is a protein produced on the epithelial cells of multiple organs, particularly the placenta, liver, and gut, and it mediates the transport of numerous chemical substances, including anticancer medicines. It is expressed on the apical side of proximal tubules in the kidney. It was recently shown to excrete urate, although given its increased expression in the liver and intestine, it presumably regulates intestinal urate excretion rather than renal urate excretion. Many factors may impact the renal clearance of uric acid, including electrolyte changes, extracellular fluid volume, acid-base balance, and insulin resistance.
Hyperuricemia is associated with gout, hypertension, diabetes, kidney disease, and cardiovascular disease. Several pathways are responsible for the pro-inflammatory effects of UA: 1) The activation of the mitogen-activated protein kinase (MAPK) pathway; 2) The suppression of the adenosine monophosphate-activated protein kinase (AMPK) route; 3) The activation of the phosphatidylinositol-3 kinase (PI3K)-Akt pathway; and 5) Other pro-inflammatory features.
Soluble, intracellular uric acid may also cause CKD via a crystal-dependent and independent process. Both soluble and crystalline uric acid can induce considerable kidney injury, characterized by ischemia, tubulointerstitial fibrosis, and inflammation in hyperuricemic animals. Once transported into the cell, UA becomes a prooxidant and induces oxidative stress by increasing reactive oxygen species. Also clinical studies have also shown that hyperuricemia is associated with RAS activation and vascular dysfunction.
In conclusion, kidney damage caused by hyperuricemia was brought on by crystalline effects, RAAS, and oxidative stress. Understanding the homeostasis that controls uric acid excretion has a big impact on clinical practice because it helps us better understand pathophysiological changes and makes it easier to create new, effective treatments.