

Kidney Stones & Diabetes

Nephrology



Kidney Function, Diabetes, and Citrate

Patients with Type II diabetes often have problems regulating pH, leading to a buildup of acid in their blood. This condition, acidosis, has adverse effects on human health. Normally, pH balance is regulated by the kidney in a complex process that relies on citrate. The concentration of this molecule in the blood and urine is regulated by the proximal tubule of the functional unit of the kidney -the nephron. More acidotic conditions mean that more citrate is taken up by the proximal tubule in an effort to balance the body's pH. This can lead to the formation of calcium-based kidney stones, as the other important job of citrate is to chelate calcium out of the urine.

The laboratory of **Katie Hering-Smith** is focused on understanding the complex mechanisms that govern citrate transport. The lab employs a comprehensive approach to studying this question, utilizing tissue culture and mouse models coupled to patient data and clinical trials. Additionally, they are one of the few labs focused on this particular aspect of kidney and diabetes biology, as the vast majority of similar work focuses instead on the NADC1 transporter, not the citrate transporter.

Calcium, Acidosis, and Citrate

Normally, calcium exists at a concentration of 1.2 mM in the tubular fluid, and any decrease leads to an increase in citrate uptake by the kidney. Acidosis also leads to an increase in citrate uptake, meaning there is less citrate available to chelate calcium out of the tubular fluid. In diabetic patients this is especially problematic, as they are chronically acidotic and thus at an increased risk for kidney stone formation.

The Lab is currently trying to understand the complex interactions between the transporters in the proximal tubule of the kidney that participate in this process. To do this, they are analyzing RNAseq data from acidotic mice, in the hopes that differences in gene expression will serve to illuminate additional key players.

Diabetes Treatments and Acidosis

Diabetic patients are often treated with Sodium-Glucose Transporter 2 (SGIT2) inhibitors to lower their blood sugar. These drugs block the reabsorption of glucose from the urine, leading to lower blood sugar. In some patients, this treatment can lead to ketoacidosis, which results from the body switching from glycolysis (which uses sugar as a substrate) to processes that use proteins as their substrates, producing excess ketones.

While this process is readily observed in patients, not all mouse models used to study diabetes can recapitulate ketoacidosis. To study this aspect of kidney biology and diabetes, the lab uses the NADC1 KO mouse, which does become ketoacidotic. Ultimately, this will allow for a better understanding of the interplay between diabetes, treatment with SGIT2 inhibitors, and the resulting ketoacidosis and possible kidney stone susceptibility using a clinically-relevant model.

Additionally, the lab is also interested in why some patients develop ketoacidosis when taking prescribed SGIT2 inhibitors while others don't. They are currently investigating possible genetic differences between these two groups in order to try and better predict who will get the maximum benefit with minimal side effects from these drugs.

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