Transcript Details
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Metabolic Rewiring in DKD: The Role of Tubular Cells

Announcer:
This is *Clinician's Roundtable* on ReachMD. On this episode, Dr. Kumar Sharma will explain our current understanding of the metabolic rewiring of tubular cells in diabetic kidney disease. He's the Chief of the Division of Nephrology and Vice Chair for Research in the Department of Medicine at UT Health San Antonio. Here's Dr. Sharma now.

Dr. Sharma:
The proximal tubule was always thought as not doing glycolysis and only relying on fatty acid oxidation and using mitochondria to generate ATP, because that's the most efficient way of taking a fatty acid molecule and getting the most ATP out of it—by using all of the carbons from the fatty acid.

The understanding of why the kidney starts switching its metabolism to do more glycolysis and less fatty acid oxidation was only recognized in the last 10 years. Dr. Susztak did a lot of this groundbreaking work in animal models, and recently, in patient samples through the Kidney Precision Medicine project, we actually got kidney biopsies from patients with diabetes at early stages. And we found that both within the kidney and in the blood and urine, we can identify the switch—that the proximal tubule starts switching from using fatty acid oxidation to doing glycolysis for their energy requirements.

So what happens is the proximal tubular cells are used to a tight range of glucose in the blood and in the urine. And if you think about it evolutionarily, humans are always glucose deficient because there isn't a lot of glucose sugar in the environment. Only recently with civilization and increased carbohydrate intake are we now in an era of carbohydrate excess, and so the kidney and the body really aren't used to high levels of glucose. It's not evolutionarily built for that kind of state. And so its recourse is to get rid of the extra glucose in different ways. So part of it is it just doesn't take up the glucose from the urine once it reaches a certain threshold, which is around 180 milligram per deciliter, and it dumps it into the urine. So a patient with diabetes has polyuria because they're putting all the sugar into the urine and getting rid of it, but the cells are also taking up that extra glucose because it doesn't know exactly what is the right amount it should take up, and so it's faced with a lot more intracellular glucose than it's normally used to. So then it starts having to use up these carbon molecules, and it diverts it into different metabolic pathways.

And one of those pathways is glycolysis, because it has to consume that glucose, and it makes lactate. It makes a lot of lactate, which is thought to be a harmful state, because when the body produces excess lactate, that suggests it's not using its mitochondria. And it's not using its mitochondria because there's lack of oxygen. But that's not the case in diabetes; you have plenty of oxygen available, but you're not using it. So the proximal tubular cell makes a decision: "I'm not going to use my mitochondria, but I need to get rid of the glucose." So this is a way of doing that. And so it generates a lot more lactate, and that lactate can be used until it gets to too high a level.

So what we found is that excess lactate production is actually detrimental to the body and the kidney, and it's a marker of excess glycolysis. And when you have very high levels of lactate, you actually have a negative feedback system to prevent your mitochondria from working properly.

So that's one consequence of excess glycolysis and less fatty acid oxidation.

Announcer:
That was Dr. Kumar Sharma talking about the metabolic rewiring of tubular cells in diabetic kidney disease. To access this and other episodes in this series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

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