Transcript Details

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Exploring Drivers of DKD: Metabolic Rewiring and Mitochondrial Dysfunction

Announcer:
Welcome to *Clinician's Roundtable* on ReachMD. On this episode, Dr. Kumar Sharma will discuss how metabolic rewiring and mitochondrial dysfunction contribute to inflammation and fibrosis 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:
There's been a lot of work on understanding what metabolic rewiring actually means and what mitochondrial dysfunction means. We know that both things are happening in a diabetic kidney, and the question is, what is compensatory in keeping the kidney functioning, and what is detrimental and will lead to kidney failure in the long run?

Now, we know that diabetes is the number one cause of kidney failure in the United States, and it's increasing on a yearly basis, and more and more patients are getting diabetes. Understanding this metabolic rewiring is quite complicated, specifically in the proximal tubular cell, because if you take the cell out of the body, it's outside of the normal architecture.

So is it really true that when it's inside the kidney, it would work in the same way? And what's happening in terms of other cells in the neighborhood? And how are those cells being affected by the proximal tubular metabolic rewiring? And what does the mitochondria have to do with all of that?

So what's been really groundbreaking in the field in the last five years or so is having access to these biopsies. So when we can access the kidney biopsies at different stages of diabetes, especially in the early stages, we can start understanding this heterogeneity. And another key tool is something called spatial biology, spatial omics, and spatial metabolomics, and that's what we do; we try to understand localized regions within the kidney at a metabolic level by measuring metabolites and then putting all the pieces together in the clinical context.

And so what we found is that the proximal tubular cell is responding to diabetes in certain ways. It's producing excess lactate. It's doing more glycolysis. Some of the glycolysis metabolites, which are being overproduced now, are actually toxic to the mitochondria. And so the mitochondria are now being recognized as, instead of a highly efficient organelle, actually a source of dysfunction. Because when the mitochondria aren't working, it's causing havoc.

So what happens with mitochondria is when it loses its very intricate structure, it starts leaking molecules out of the mitochondria. And one of those molecules is mitochondrial DNA, which actually leads to inflammation if it leaks out of the mitochondria into the cytosol. So the cell thinks it's being invaded by different organisms and has this very heightened inflammatory response, which ultimately affects its neighbors and affects scarring ultimately, and the whole thing starts collapsing.

The other thing that happens is when you're shifting from fatty acid oxidation to more glycolysis, you start engaging other pathways that aren't that involved in normal biology and normal proximal tubular function. One of those pathways is called the pentose phosphate shunt. And so molecules from carbohydrates go through the pentose phosphate shunt and generate purines. And purines, when in excess inside the cell, are also very toxic. And so what we had found was that one particular purine called adenine is produced in excess in the tubular cell in conditions of high glucose and in diabetes, and the adenine is also a driver of inflammation and fibrosis.

Announcer:
You just heard Dr. Kumar Sharma discussing how metabolic rewiring and mitochondrial dysfunction play a role in diabetic kidney disease. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the

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