Transcript Details
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What Drives the Progression of Chronic Kidney Disease in Type 2 Diabetes?

Announcer:
Welcome to *Spotlight on Chronic Kidney Disease in Type 2 Diabetes* on ReachMD. This medical industry feature, titled "What Drives the Progression of Chronic Kidney Disease in Type 2 Diabetes?" is sponsored by Bayer and is intended for physicians.

Here's your host, Dr. Edgar Lerma.

Dr. Lerma:
Hello, and welcome to this 3-part series focused on the unmet needs of patients with chronic kidney disease, or CKD, and type 2 diabetes. I'm Dr. Lerma, and today I will be talking with Dr. Argyropoulos, Chief of Nephrology in the Department of Internal Medicine at the University of New Mexico School of Medicine. We will be discussing the drivers of chronic kidney disease progression and type 2 diabetes.

Dr. Argyropoulos, thank you for joining us here today.

Dr. Argyropoulos:
Thank you for having me.

Dr. Lerma:
So, to start us off, could you explain to us just how prevalent chronic kidney disease is in patients with type 2 diabetes?

Dr. Argyropoulos:
Sure. Around 34 million Americans have diabetes, with type 2 diabetes accounting for 90% of all diabetes cases. Type 2 diabetes is the most frequent cause of kidney disease, and about 40% of patients with type 2 diabetes have CKD stages 1 through 4. But the significance of CKD is not only the number of people it affects but also the morbidity and mortality associated with it. CKD in type 2 diabetes is associated with high mortality, especially compared with patients with either CKD or type 2 diabetes alone. CKD can shorten life expectancy of patients with type 2 diabetes by up to 16 years. In fact, patients with high albuminuria and reduced estimated glomerular filtration rate have a cumulative incidence of 10-year all-cause mortality of 47% compared with 4.1% in patients with type 2 diabetes alone. That's a nearly 12-fold increase in mortality.

Dr. Lerma:
Indeed. And just to add to those important points, although the natural history of chronic kidney disease and type 2 diabetes varies, the most recognizable consequence of CKD is end-stage kidney disease. Some of our audience may also be surprised to hear that diabetes is the leading cause of end-stage kidney disease in many developed countries, and the prevalence of end-stage kidney disease is 10 times higher in patients with diabetes as compared to those without.

Dr. Argyropoulos:
Exactly. And the standard treatments for end-stage kidney disease, transplant or dialysis, are far from optimal. Dialysis has significant patient burden and a mortality rate of up to 20% per year, while transplantation is limited by organ shortages. Once patients reach end-stage kidney disease, 60% will die within the next 5 years. Even the finest dialysis care or transplant can't reverse the disease course, so clearly it's extremely important to protect the kidney from CKD progression.

Dr. Lerma:
And I'm glad that you brought that up, because protecting the kidney from CKD progression is very much a patient concern. With

increasing severity of CKD, various clinical assessments have shown that health-related quality of life decreases significantly. These include both the burden of kidney disease on life, family and time as well as how kidney disease affects daily life, including diet, ability to work or travel, and stress or worry.

Dr. Argyropoulos:
I'd also add that there is a high economic burden and substantial healthcare expenditure costs associated with CKD in type 2 diabetes. In 2017, CKD and type 2 diabetes-related expenditures approached $21.5 billion in the Medicare population age 65 and older. Per person, the cost was 51% higher in patients with CKD and type 2 diabetes versus those with type 2 diabetes alone.

Dr. Lerma:
Thanks for that, Dr. Argyropoulos. So, let's turn to therapeutic considerations then. Current guidelines recommend managing CKD in type 2 diabetes through a combination of lifestyle modifications and pharmaceutical interventions. Lifestyle modifications include things like smoking cessation, a healthy diet, and exercise and weight loss among those who are overweight or obese as part of a multifactorial risk reduction strategy. Meanwhile, pharmacological targets include metabolic factors, like elevated blood sugar, and hemodynamic effects, like elevated blood pressure. So, with these approaches in mind, do you find that the recommended lifestyle modifications and pharmaceutical interventions have limitations for your patients?

Dr. Argyropoulos:
Well, in the last few decades, advancements in glucose and blood pressure control have led to important gains in reducing type 2 diabetes complications. This is especially true with regard to cardiovascular events. But despite these improvements, patients with CKD and type 2 diabetes still face a substantial risk of CKD progression. The incidence of end-stage kidney disease in particular has improved the least, indicating that there may be a missing link in the current standard of care.

Dr. Lerma:
So, what do you think is still unaddressed in the current standard of care of chronic kidney disease and type 2 diabetes?

Dr. Argyropoulos:
I think the answer lies within the 3 drivers of CKD progression. The development and progression of CKD are driven by the combined effects of metabolic, hemodynamic, and inflammatory and fibrotic factors. For many decades, the standard of care for CKD and type 2 diabetes focused solely on managing the metabolic effects, like elevated blood glucose, and hemodynamic effects, like elevated blood pressure. As our understanding of disease etiology evolves, new data strongly supports that CKD progression is dependent on the combined effects of all 3 factors, including inflammation and fibrosis. However, inflammatory and fibrotic factors are largely unaddressed.

Dr. Lerma:
I know from my practice that even with well-controlled blood sugar, or A1c, and blood pressure, many patients still see a high risk of cardiovascular events and referral for dialysis or kidney transplant consultation. What exactly is the cause of inflammatory and fibrotic factors that contribute to CKD progression?

Dr. Argyropoulos:
Influences on inflammation and fibrosis are complex. Overactivation of the mineralocorticoid receptor, or MR, is a driver of inflammation and fibrosis. Under normal conditions, the MR influences electrolyte and fluid balance as well as tissue repair, but under certain conditions, like type 2 diabetes, the MR can become overactivated and produce proinflammatory cytokines and profibrotic proteins. We've seen a growing number of evidence supporting MR overactivation as a contributor to inflammation and fibrosis in kidney and heart disease.

Dr. Lerma:
So, how does the MR become overactivated then?

Dr. Argyropoulos:
MR overactivation can be driven by an increase in its endogenous activators or through an increase in expression of the MR. As MR activators proliferate, the cell begins producing proinflammatory and profibrotic proteins, eventually leading to inflammation and fibrosis in the kidneys, heart and vasculature. This inflammation and fibrosis can increase the risk of a cardiovascular event and declining kidney function, ultimately resulting in end-organ damage.

Dr. Lerma:
So, before we wrap up our discussion, Dr. Argyropoulos, do you have any other thoughts or takeaways regarding CKD in type 2 diabetes?

Dr. Argyropoulos:
Yes. And just to summarize, CKD progression is dependent on the combined effects of metabolic, hemodynamic, and inflammatory and fibrotic factors. At this time, inflammatory and fibrotic factors driven by the overactivation of the MR are largely unaddressed. Inflammation and fibrosis in the kidneys can lead to declining kidney function, cardiovascular decline, and ultimately end-stage kidney disease. Once patients reach end-stage kidney disease, 60% will die within the next 5 years. Therefore, it's of primary importance to protect the kidney from CKD progression by targeting all 3 drivers of progression, including inflammation and fibrosis.

Dr. Lerma:
Well put. And that's a good opportunity to remind ourselves not to forget about importance of protecting the heart as well since the damage caused by inflammation and fibrosis in patients with CKD and type 2 diabetes can also increase the risk of a cardiovascular event. Fortunately, we will be focusing on that more exclusively in our next episode, so more to come there.

But with these thoughts in mind, I want to thank you, Dr. Argyropoulos, for your insights on the drivers of chronic kidney disease progression and type 2 diabetes. It was great talking with you today.

Dr. Argyropoulos:
It was my pleasure.

Dr. Lerma:
And for our listeners, be sure to check out the next episode in the 3-part series that discusses the cardiorenal effects of MR overactivation in patients with CKD and type 2 diabetes. Thanks for listening.

Announcer:
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