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Burden and pathophysiology of APOL1 kidney disease

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Burden and pathophysiology of APOL1 kidney disease,” provided by KDIGO and supported by Vertex. Here’s your host, Dr. Kirk Campbell.

Dr. Campbell:
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Kirk Campbell, chief of the renal division at the University of Pennsylvania. Joining me to discuss the burden and pathophysiology of APOL1 kidney disease is Dr. Bessie Young. Dr. Young is vice dean and medical director for the Office of Healthcare Equity at the University of Washington, where she also serves as professor of medicine in the division of Nephrology. Her clinical and research interests include genetic testing and APOL1, health outcomes in home dialysis, and health inequities in kidney disease.

Dr. Young, welcome to the podcast.

Dr. Young:
Thank you, Dr. Campbell. It's a pleasure to be here.

Dr. Campbell:
Thank you so much. So let's begin our discussion around APOL1. Since it's a relatively new genetic finding, can you discuss the history of the discovery of APOL1? Provide some background on how quickly the findings have been translated into clinical knowledge?

Dr. Young:
Thank you for that question. So the APOL1 gene story is really one of discovery. For years researchers have been searching for a gene associated with kidney disease and African American individuals or Black individuals. Or specifically people with recent African ancestry. And we know that the rates of end-stage kidney disease are significantly higher in those who are Black compared to those who are white. And Black individuals usually developed kidney failure 10 years earlier than white individuals. So there was a real search for something that was related to a genetic finding that was related to kidney disease.

So there was a potential hit that was found with MHY9 in 2008. And people started to look at that. But then in 2010, Dr. Genovese and Martin Pollak discovered an association of trypanolitic APOL1 variants with kidney disease and African American individuals, which was published in 2010 in Science. And the same year, Dr. Tzur discovered the same APOL1 genetic variants were associated with greater rates of kidney disease and those with recent African ancestry.

So these variants are named G1 and G2, and that has to do with their amino acid substitutions and deletions. G1 has two amino acid substitutions and G2 has two amino acid base pair deletions. And these variants are protective from African sleeping sickness from Trypanosoma brucei. I would say that this information has been relatively rapidly translated into clinical medicine. APOL1 genetic testing is currently available and there are recent clinical trials that have been initiated with biologics that interfere with APOL1 and definitely long-term studies that are still recruiting for applicants with APOL1.

Dr. Campbell:
Thank you so much for that very detailed yet concise history regarding APOL1. Can you tell us a little bit more about APOL1 kidney disease? What exactly is it, and what's the prevalence, epidemiology, manifestations, and different phenotypes that one could see?

Dr. Young:
Sure. So we know from epidemiologic data that there are approximately 30% of African American individuals who have G1 or G2 or both G1 and G2. And we also know that about 13% of those with recent African ancestry in the US have both G1 and G2, which are termed high-risk APOL1 variants. So this is roughly about 5 million people in the US who have the high-risk APOL1 variants. It is thought that these APOL1 variants are passed down as autosomal recessive as a genetic trait. And we also know from recent data that the prevalence of APOL1 high-risk variance is probably greatest in West Africa. There was a recent paper in The New England Journal of Medicine that showed that the individuals from West Africa have really high rates of G1 and G2, and it varies by tribe and country. We also know that those with high-risk variants have the greatest risk of developing end-stage kidney disease and going on to dialysis while those who have either one of the variants, G1 or G2, have an increased risk of developing chronic kidney disease or albuminuria.

And we also know that there's been a lot of progress in regards to APOL1 kidney disease. So now APOL1 kidney disease is termed APOL1-mediated kidney disease, or AMKD. You'll see that in some of the literature. There's also an ICD-10 approval in the 2025 ICD-10 update so that there are now diagnosis codes for APOL1. But as you know, in a conference in Ghana with patients, researchers, and others, the term APOL1 kidney disease was also chosen to represent kidney disease in those with APOL1. So there are a lot of names out there for APOL1-mediated kidney disease, and I think it just depends on where you're coming from in terms of what name you use, but AMKD is showing up in the literature more and more.

APOL1 kidney disease was initially associated with FSGS, or focal segmental glomerulosclerosis. It was also shown to be increased in those with HIV nephropathy and hypertensive kidney disease. So originally there were case control studies that showed that there was a 7- to 10-fold greater risk of FSGS end-stage kidney disease in those with APOL1 positivity. It was also shown in those early case studies that HIV nephropathy had an odds ratio of 28% to 29% increased risk of HIV nephropathy and end-stage kidney disease. So with larger population-based cohort studies, that risk decreased to about twofold. But there's still an increased risk of APOL1 kidney disease with end-stage kidney disease and kidney disease progression. And then pathologically, I'd say the spectrum of kidney disease associated with APOL1 is probably that of the collapsing variant of FSGS, and it's known to affect podocytes. It can cause tubular injury and interstitial fibrosis and global sclerosis if it's diagnosed later on.

Dr. Campbell:
If you're just tuning in, you're listening to the KDIGO podcast on the burden and pathophysiology of APOL1 kidney disease. I'm Dr. Kirk Campbell, and I'm speaking with Dr. Bessie Young.

Dr. Young, thank you for that description of APOL1 kidney disease. Can you describe what we know about the disease mechanisms based on the current pathophysiology? Are there any protected variants, for example, we should be aware of?

Dr. Young:
Yeah, thanks, Kirk, for that question. So the disease mechanism of the APOL1 genes are complex. And I think people are still trying to figure out the exact mechanism. But what the research data has shown and points towards is there is injury of the podocyte. So APOL1 can basically form a pore or an ion channel in the podocyte, which leads to an increase in chloride or other ion flux and causes osmolysis of the podocyte. And this is a similar mechanism to that found in the trypanosomes, which basically leads to their death in those who have APOL1 variants. So this osmolysis leads to podocyte effacement and detachment, which can then result in increased inflammation and probably leads to what we see when people actually have biopsies and we see inflammation or we see FSGS.

APOL1 has also been shown to cause misfolding of the endoplasmic reticulums and it could compromise mitochondrial functions. So it has a wide variety of functions and I don't think we know all the mechanisms of disease, of APOL1. APOL1's also found in the lung. It's found I think in the liver. It's found in vessels, so there may be some additional function that we're not aware of. It's also thought that environmental stressors, such as inflammation or high interferon states, may really exacerbate APOL1 disease and lead to progression. And some of the drivers that have been found include things like viral infections. So the research really points towards HIV sort of being a driver of APOL1 kidney disease. We know from the COVID pandemic that COVID and those who had COVID and developed kidney disease, they had faster progression and they had acute kidney injury that was associated with APOL1. There's ischemia reperfusion as a driver, and there's an increased risk of progression in individuals who have sickle cell disease. We know that there's kidney allograft

rejection that might be a driver associated with APOL1 disease. And then in lupus we know that autoimmune diseases can lead to worse disease with APOL1.

And then you asked about a protectant variant in APOL1. So there is a study from Dr. Adriana Hung at Vanderbilt, who used data from the Million Veteran Program, the Vanderbilt biobank, and the NIH All of Us study to look to see if there were any protective variants, and they found one called p.N264K. And I assume that they'll probably change the name of that. But this variant was shown to basically block the pore-forming function of APOL1 and the ion channel conduction and reduce the toxicity of APOL1. It kind of plugs the hole of the pore, if you will, and decreases the pathology associated with the podocyte. So there are people who have this variant. But the one study that I think led to the discovery of this variant showed that if a person has this variant, they actually are susceptible to African sleeping sickness.

Dr. Campbell:
Story certainly is getting more complex and interesting. Can you describe what studies are out there that might provide additional information to our listeners regarding APOL1 kidney disease?

Dr. Young:
Sure. There are additional studies that will provide information about APOL1 gene and the development of adverse kidney outcomes, and one of this is called APOLLO, or the APOL1 Long-term Kidney Transplantation Outcomes Network Study. And this is a study that will look at the long-term effects of APOL1 on kidney donors prospectively to determine who progresses and if there's an increased risk of donation of kidney failure in people who donate a kidney. There are also many studies that are looking at new medications that are coming out, and I think we'll have another podcast on these. There are studies that are looking at APOL1 small molecule inhibitors, antisense oligonucleotide inhibitors, and the JAK-STAT inhibitors that are currently in clinical trials. And I also just wanted to point towards there is one recent paper that is more of an epidemiologic paper that really shows the high risk of a APOL1 in Africa that was recently published that just showed very high rates in in Western Africa. So I think there are more trials out there, more research out there that's being done. And so the story is not completely known in terms of treatment, in terms of the mechanisms, and probably there's more that needs to be known in terms of the epidemiology as well.

Dr. Campbell:
Thanks for sharing those resources. So before we close, Dr. Young, are there any final messages you'd like to leave with our listeners?

Dr. Young:
Sure. I would just like to say that the APOL1 gene and knowledge regarding pathophysiology and treatment are a major step forward for modern medicine and research. End-stage kidney disease is a deep disease that, as you know, affects African Americans and other individuals who have recent African ancestry. And we've been waiting for something that really shows that it's not just lifestyle but there's really something intrinsic about either a gene or something that is associated with end-stage kidney disease. And this, I think, has really changed the way that we look at kidney disease. This is a disease where you can truly say that research changes lives. I would say that the speed at which treatment was developed is relatively swift, 15 years, but it still lags behind many other diseases, such as COVID, where a vaccine was developed in 6 to 12 months. And so I'm hoping that the treatment for APOL1 kidney disease will advance very quickly and that there will be more clinical trials to prevent thousands of people from having to go on dialysis in the future.

Dr. Campbell:
Yeah, certainly a lot of progress with more work to be done to lead to direct patient benefit. But thank you so much again, Dr. Young. I'd like to thank you for joining me. It was great having you on the podcast.

Dr. Young:
Dr. Campbell, thank you again for inviting me. This series will help our listeners understand APOL1 kidney disease a bit better, and I really look forward to the other sessions.

Dr. Campbell:
I am Dr. Kirk Campbell. To access this and other episodes in our series, visit kdigo.org/podcast. Thanks for listening.