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The Podocyte Problem: Understanding FSGS

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, "The Podocyte Problem: Understanding FSGS ," is provided by KDIGO and supported by Travere. Here's your host, Dr. Kirk Campbell.

Dr. Kirk 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 today for a discussion on FSGS is distinguished guest, Dr. Alessia Fornoni. Dr. Fornoni is the director and chair of the Peggy and Harold Katz Family Drug Discovery Center and assistant dean for Research Training and Development at the University of Miami Miller School of Medicine. As a physician scientist, her work has provided novel and seminal contributions to our understanding of the pathogenesis of kidney disease. Dr. Fornoni, welcome to the podcast.

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

Dr. Kirk Campbell:
Great. Let's begin our discussion with an overview question. How is FSGS defined and classified?

Dr. Alessia Fornoni:
Well, the first thing I want to say when we talk about FSGS, focal and segmental glomerulosclerosis, it becomes very clear that the definition of FSGS has been largely based on histological pattern of injury. In fact, we have always relied on the Columbia classification for this disorder, identifying different variants—tip, collapsing, cellular, perihilar, not otherwise specified variants—that respond differently to treatments.

But it is exciting that with the new knowledge that we have generated about the disease, we are now ready to look at the classification of FSGS with a more clinical lens. In fact, if we look at the KDIGO classification, we now can better define FSGS as primary, which we know is largely immunologically driven; genetic, with more than 60 genes being identified responsible for this; secondary; or undetermined, because we still have room for certain diseases that don't fit any of these criteria.

Whatever the classification is, whether we classify based on the histological pattern or on the clinical presentation, the key aspect of FSGS is that this is a podocytopathy. This is a disease caused by podocyte injury, which really is responsible for both the clinical manifestations of the disease—proteinuria and loss of GFR.

Dr. Kirk Campbell:
Yeah, podocyte injury does seem to be the key unifying feature of FSGS. So how does podocyte injury cause FSGS? And what are some of the signaling mechanisms that are responsible for disease pathogenesis?

Dr. Alessia Fornoni:
So we have got to learn a lot about this with the excellent science done by many investigators in this space. Number one, there's nothing as important as human genetics to confer a cause-effect relationship between a given gene and a disease. And if we look in the past

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few years, there have been more than 60 genes that have been associated with mechanisms of podocyte injury in FSGS, and many of them confluence on actin cytoskeleton regulation.

However, more recently, there's many other pathways targeting calcium, lipids, mitochondria, complement, apolipoproteins that really come into the picture. And among them, really angiotensin II, endothelin-1, that can really act in a systemic autocrine, paracrine way and really contribute to the injury. And although those pathways were thought to be primarily responsible to just change the hemodynamic, they've actually been demonstrated through precision medicine approach to actually alter also some other pathway that I've considered to be extremely relevant to podocyte injury in the context of FSGS.

Now, another very important discovery in what causes podocyte injury in FSGS is this concept that has been around since the early '90s about the existence of the permeability factors that would actually cause podocyte injury in a subset of patients with primary FSGS. And we've been chasing this factor for many years. Didn't know whether this could be a protein, a lipid, or anything else.

And it's exciting to see that there starts to be some knowledge about a potential autoimmune cause of focal segmental glomerulosclerosis, with a subset of patients presenting with anti–slit diaphragm antibodies that, in some cases, have been shown to have a cause-effect relationship with the injury pattern that we see in FSGS.

Dr. Kirk Campbell:
So with recent drug approval news in this space, a lot of attention is being placed on angiotensin II and endothelin-1. How do angiotensin II and endothelin-1 signaling cause podocyte injury in FSGS?

Dr. Alessia Fornoni:
Oh, these are 2 amazing culprits of podocyte injury and mechanisms that have been extensively studied experimentally and finally coming to fruition.

And one of them, endothelin-1, is a stress response peptide that is made by glomerular cells, including the podocyte. This can act actually in both an autocrine and paracrine manner, and very elegant studies demonstrated this crosstalk between podocyte-derived endothelin-1 and the activation of endothelin receptor A on adjacent endothelial cells, resulting in oxidative stress, endothelial dysfunction, which ultimately lead to the degradation of the glycocalyx, that is really the sensor from endothelial cells of what passes in the bloodstream.

And what is interesting is that these modulation of the glycocalyx in this crosstalk by endothelin-1 and endothelin receptor A really further goes back to the podocyte, initiating this vicious self-perpetuating loop of podocyte-endothelial–back-to-podocyte crosstalk that ultimately leads to irreversible injury.

Angiotensin II had been studied for a longer period of time. Angiotensin II acts primarily on the AT1 receptor on podocytes. And once AT1 is actually activated, there's a variety of signaling pathway that are being activated, and this signaling pathway goes from a cytoskeletal remodeling to apoptosis, loss of slit diaphragm protein, and resulting eventually in proteinuria.

And that's actually why this combo makes a lot of sense, because working in tandem with endothelin-1, angiotensin II can even induce endothelin-1 and amplify the effect of endothelin-1, which is one of the reason why targeting both pathway is biologically current, and it's plausible.

Dr. Kirk Campbell:
Thanks so much. If you're just tuning in, you're listening to the KDIGO podcast on The Podocyte Problem: Understanding FSGS. I'm Dr. Kirk Campbell, and I'm speaking with Dr. Alessia Fornoni.

So, Dr. Fornoni, let's discuss the translational impact of these important perspectives. What clinical features should medical practitioners focus on to determine the extent and potential reversibility of podocyte injury?

Dr. Alessia Fornoni:
There's a couple of very important concept here that we need to understand. I think proteinuria goes hand in hand with foot process effacement, and proteinuria, in certain case, can be reversible. And we know that with certain intervention, either all the traditional

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intervention or the new drugs, including disease-modifying agent, we see reduction of proteinuria, and this is usually accompanied by restoration of foot process effacement.

The problem comes when this results in podocyte injury. And as we all know, podocytes are terminally differentiated cells, and once we reduce the podocyte number, the ability to restore this, it's really not too feasible, which brings us 2 points now.

Number one, the loss of podocyte has a certain threshold, after which the lesion results in glomerulosclerosis and tubulointerstitial fibrosis, resulting in loss of glomerular filtration rate. So that podocyte number is really what I think would drive the GFR loss and the progression to end-stage kidney disease. While the foot process effacement and the proteinuria are more reflecting of early stage. And those are the stage where we want to intervene, because we want to intervene early in the disease process in a way that the reduction of proteinuria will also results in preservation of podocyte number and prevent that irreversible transformations of podocyte loss to glomerulosclerosis into interstitial fibrosis. No?

So really early recognition matters, because once we lose the podocyte, once we lose the threshold, the sclerosis is irreversible, and the damage continues to accelerate no matter what we do. And this gives us a sense of therapeutic urgency, the need to identify patients early, the need to have the patient on a lifelong treatment strategies to reduce the progression of the kidney disease.

One of the problems we have that's intrinsic to this disorder, proteinuria or GFR loss are not painful and are often not properly recognized by the patients. And I'm sure it's in the practice of many providers to have patients coming when podocyte injury is already there, when GFR loss is already there. So really, actually engaging also other providers in the primary care sector to help us identify those disease at early stage, I think it's key.

Dr. Kirk Campbell:
Yeah, we definitely want to identify, make the diagnosis, and start to treat before that point of no return.

So do our currently available treatment options effectively address podocyte injury?

Dr. Alessia Fornoni:
So we know there's a lot of limitations in the way we approach the treatment of FSGS these days, and this has largely been opinion-based and not necessarily evidence-based. No? We have been treating FSGS with steroids, with other immunosuppressants. But I have to say, we have been screaming a little bit in the dark here. No?

Number one, we have been using a lot of immunosuppressive agents not knowing whether the disease was truly immune mediated or not, not knowing whether some of these drugs would work for direct podocyte repair versus a systemic effect, and really aware that a lot of these drugs cause very significant side effects, mostly in our pediatric population, but overall in the large population and large affected by FSGS.

But what is also clear that this medication will be utilizing historically, they don't really address the underlying podocyte injury effectively, so we don't have a tool to stratify which patients will be responsive to a drug versus another, and therefore, really, natural history studies with precision medicine approach will help us to better understand how to match the right patient to the right drug at the right time. And it's just very exciting to see how many new medications are now becoming available that are more really targeting a given pattern of injury.

Think about what we just discussed now, the endothelin-1 and the angiotensin II pathway being so nicely demonstrated to be upregulated, with great experimental study supporting a cause-effect relationship between this pathway and the development on proteinuria loss in GFR. And now the recent approval of medication such as sparsentan, so emerging therapies that are dual endothelin-1/angiotensin II antagonist that really tie back to the concept that we can preserve podocyte directly and early in the disease process.

So I'm very happy as a prescriber. I think it's great these days to be out there and to have options for our patients other than medication that have been maybe effective in a subset of patients but also with major safety flags.

Dr. Kirk Campbell:
Certainly a lot of progress, but a long way to go. So before we close, are there any final messages you'd like to leave with our listeners?

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Dr. Alessia Fornoni:
Well, I don't know about all you guys, but I'm extremely excited about being a nephrologist in this era. I've been shaking the hand of my patients for many years saying, sorry, there's not much more I can do. And really, the tools and medication I had available 20 years ago when I started were very limited.

And right now, mostly for those who are working in the glomerular disease space, and today we're talking specifically about focal segmental glomerulosclerosis, it's really an exciting time. We have options. We have options that are biologically plausible and options that make us believe that we may be able to cure the disease or at least prevent a rapid progression to the need for renal replacement therapy.

So I hope the audience is excited with me about this time in nephrology, and I really want to thank you for asking me this question.

Dr. Kirk Campbell:
So I want to thank my guest, Dr. Alessia Fornoni, for joining me. It was great having you on the podcast.

Dr. Alessia Fornoni:
Thank you. It was great to be here.

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

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