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Applying CKD Interventions

Announcer:
Welcome to this episode of KDIGO Conversations in Nephrology. This episode titled, Applying CKD Interventions, is provided by KDIGO and supported by an independent educational grant from AstraZeneca.

Here's your host, Dr. Peter Lin.

Dr. Lin:
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Peter Lin, Director of Primary Care Initiatives at the Canadian Heart Research Center and a Family Physician in Toronto, Canada. And joining me today to discuss the importance of applying CKD interventions is Dr. Joel Topf, who is an Assistant Clinical Professor of Medicine at Oakland University, William Beaumont School of Medicine. But Joel is really famous for his Twitter account, Kidney Boy, where he discusses all things kidney. He is also the co-founder of NephMadness and NephJC, a journal club, and he's also the host of the Freely Filtered podcast. So Joel, welcome to this program.

Dr. Topf:
Peter, I'm really glad to be here. I'm a huge KDIGO stan.

Dr. Lin:
Awesome, awesome. Let's get started. Let's go back to basics, Joel. Let's talk about salt. What's the latest in the sodium story and what's the latest thinking, and how do you explain sodium intake and diets to your patients?

Dr. Topf:
Ya, Peter, it's like everything in medicine. What we thought was simple, the more we looked into it, became more complex. So sodium has been like the common villain in nephrology for 50, 60, 70 years and the advice has always been reduce your sodium intake, reduce your sodium intake, and as we've looked into it more and more, it's more complex than that and it does seem that the ratio of sodium to potassium intake is what's really important and that, in addition to trying to lower your sodium, you want to increase your potassium in take for optimal vascular health. And we're seeing that vascular health paid dividends in terms of reduced cardiovascular disease and reduced chronic kidney disease. So getting that ratio, and it's not just reducing the sodium, but making sure patients get a rich source of potassium in their diet and it kind of rings true when you kind of think about in your mind what's a healthy diet. You think of fruits and vegetables, and those are all going to be rich in potassium and that's just a real important part of that. This was best demonstrated in the recently published SSASS trial. This came out of rural China where they replaced the usual high quality sodium chloride that patients use in their salt-shakers with a mixture of sodium chloride and potassium chloride and so villages that were randomized to the potassium chloride intervention, those villagers, had modestly reduced sodium intake but a pretty significant increase in their daily potassium intake. And then they followed them for a few years, and they saw reductions in stroke and cardiovascular disease.

And so pretty nice demonstration that it's not just the sodium, that it's the sodium plus the decrease in sodium and increase in potassium intake. And this is something I find when I talk to my patients, they're all hungry for nutritional information. A lot of my patients really want to know, hey what kind of lifestyle modifications, what can I do besides just taking this pill, can I do to minimize my risk of being on dialysis and I think this is good advice and something people can really operationalize.

Dr. Lin:
And that makes a lot of sense. It's a balancing act that's important as opposed to one component or the other. So the ratio is important and that's something that we didn't know about so thanks for bringing that up

Dr. Topf:
The other thing is that when patients reach out for just kind of dietary guidelines just using general internet, what they often see is

reduce the potassium intake, which is you know, good advice if your in very late-stage CKD getting close to dialysis where potassium becomes a real issue, but for the vast majority of our CKD patients, you know, potassium balance is just not an issue for them and that having the restricted potassium there is probably pushing them towards a diet that's not so good for them.

Dr. Lin:
That makes sense because we always thought about reducing potassium, reducing sodium, reducing all of these things, but what you're saying is that in the early stages, that balancing acts between sodium and potassium is really important and not just in terms of kidneys but in terms of cardiovascular risk as well.

Dr. Topf:
Absolutely.

Dr. Lin:
Joel, there's been a lot of excitement in the last 5 years about SGLT-2 inhibitor trials and things like that. I have never seen nephrologists so happy in my life. And are we using enough of this SGLT-2 and specifically, which patients are you putting on SGLT-2 inhibitors?

Dr. Topf:
Well, Peter, I love the flozins And so, we need to get away from this SGLT-2 inhibitor. They're our friends, let's call them by their name, they are our flozins. So I'm a flozinator, right? Everyday I get up and I look in the mirror and I say who am I going to flozin-ate today? And I've been very aggressive about getting my patients on flozins and I'm finding it harder and harder to find new patients because the majority of my CKD patients now are on flozins. Last November we had the announcement and simultaneous publication of EMPA-KIDNEY, which was an important piece of evidence in the chain of evidence that we have for flozins in CKD. What EMPA-KIDNEY brought to the table was it lowered the GFR from the previous record of 25 mL/minute down to 20 mL/minute. And so that was kind of a new record for how low the GFR can go but we see benefit in these patients. The other thing that it did, is that it randomized patients both without diabetes and without proteinuria. A lot of the earlier CKD data had only enrolled patients with proteinuria with one of the enrollment criteria, but EMPA-KIDNEY did have a tranche of patients that had no proteinuria and though, if you just look in that group in an isolation, they didn't reach the primary endpoint. If you look at the slope of GFR, which is going to be less sensitive to events, right? Because the primary endpoint was a doubling of serum creatinine and initiation of dialysis, and those patients have a very slow progression, right? They don't have proteinuria, they don't have one of the major risk factors for progression of CKD, but if you look at the slope of GFR, they did have a beneficial effect on slope and that really reassured me that this is really a drug for all my patients. And honestly, Peter, if you're skeptical about that slope because it wasn't the primary outcome, you could just take a look at the cardiovascular data. The cardiovascular data enrolled lots of patients with high proteinuria and they also had lots of cardiovascular benefits. And I think that's a kind of a belt and suspenders approach to this drug is that, you know, it clearly is good for the kidneys but, the vast majority of patients even with advanced CKD will die of cardiovascular disease before they get to dialysis. And in no way is that a win, but having a drug that prevents heart failure and prevents admissions from heart failure, and prevents a cardiovascular death, that's also indicated in CKD is perfect. And that's what we have with the flozins. either way you look, or any way you justify it to the patients, whether if they have particular fears about dialysis, you're like this is great for dialysis. Or if they have a sketchy heart history, you're like well, this is one of the most powerful heart medications we've ever had. Really, and the only medicine we've ever had that's been able to help patients with heart failure with preserved ejection fraction. So these are, you know, breakthrough medications and I am using them every which way but left. You know, in addition to the lack of proteinuria and the lack of GFR, they have a role in patients that have borderline hyperkalemia. They reduce episodes of hyperkalemia. Their data came out meta-analysis of flozins showed that they reduced episodes of acute kidney injury. They really are breakthrough medications and I'm trying to get as many patients on them as possible.

Dr. Lin:
That makes a lot of sense. And all the studies are pointing in that direction and initially, we didn't think that these were great drugs, right, but now they're showing up everywhere. So as you said in cardiovascular patients, they were also good for kidney disease, in heart failure patients, good for heart failure and good for kidney disease and we are now branching out from diabetes to non-diabetes patients and having those same benefits. So you're absolutely right. It seems like the population that would benefit from this is actually quite large now.

Dr. Topf:
Yeah. And we didn't even touch on the glomerulonephritis population. This is a nether group, you know, clearly shown in IGA to have a real powerful renal protective effect in the IGA population and I think we're going to see additional data coming down the pipe; lupus, membranous, FSGS. You know, data is not there yet, those are harder groups to gather but, my sense is that we are going to just see this kind of knock out one population after another.

Dr. Lin:
That's great. So therefore more and more patients will come into the funnel where they're going to be using this as opposed to: these drugs are for these specific patients. That net is actually getting very, very large now.

Dr. Topf:
That's just a generic kidney health medicine. It might be a reasonable way to think about it. And a drug that is incredibly well tolerated. You know, part of me thinks; oh, a drug that's that good probably has a lot of nasty side effects. And part of the reason that people are such fans of the drug is that it really does, it's a pretty clean profile. The drug is well tolerated. You know, probably the most ringing endorsement is that in the placebo-controlled trials there was no difference in patients discontinuing the drug from the placebo, which is kind of unheard of. Always, you know, patients on the active group have more discontinuation and more side effects. We're just not seeing that. It's amazing.

Dr. Lin:
For those tuning in, you're listening to KDIGO Podcasts on CKD interventions. I'm Dr. Peter Lin and I'm speaking with Dr. Joel Topf. So okay, Joel, besides SGLT-2 inhibitors, and I think RAS inhibitors, what are other new treatments or interventions that you're using on your patients now?

Dr. Topf:
Yeah. The thing that I'm finding that's changing my practice is that we now have a few different choices for patient tolerable and effective potassium binders. Right. You know, much of my career when we said potassium binders, the only story there was Kayexalate, which was a medication that patients hated, couldn't tolerate, didn't taste good, caused diarrhea, caused constipation, and the idea of using it chronically so that you could maintain an ACE inhibitor, I would never entertain it because it was such a miserable drug to be on. But with patiromer and sodium zirconium cyclosilicate, these drugs are well tolerated, patients take them, they don't have any trouble with it, and I am finding myself reaching for those more and more in select situations. You know, patients that I really feel strongly that we need to keep them on an ACE inhibitor. You know, patients with advanced heart failure, patients with significant proteinuria. You know, RAS inhibition in those situations is literally life-saving and if I need to give the patient a potassium binder that they take – you know, most of the patients don't even need to take it daily. Three days a week is usually enough to keep their potassium safe. That's huge, right? And I think that's going to make a huge difference for these patients. And, you know, in addition to, you know, the new kid on the block finerenone, you know, this is a drug that has significant hyperkalemia, right? They didn't even enroll patients if potassium was more than 4.7, and so patient's, you know, solidly in the normal range of potassium weren't enrolled in the pivotal trials FIGARO and FIDELIO if their potassium was at the upper-limit of normal. Well, you know, here's a way that you might be able to get your patients to either start the drug or stay on it if their potassium drifts up. And I think that's also going to pay benefits. So I think it's a pretty important advancement having a tolerable potassium binder that's available for patients.

Dr. Lin:
Yeah, that makes a whole of sense because if you can offer a tolerable potassium binder it allows you to keep all your other drugs, you know, as you were saying the RAS blockers, etc, which is one of the things that we used to be very afraid of but now you have an option around that, so that's actually very good. Now when I was in medical school, Joel, last century I guess it was, basically CKD seemed like a very gloomy-doomy kind of space. How do you see CKD now as we're moving forward in 2023 and forward?

Dr. Topf:
Peter, you just got to remember how new this field was. If you were in medical school in the last century, we didn't even call it CKD. It was chronic renal insufficiency. You know that was the big advancement around what, 2000 or 2001 was let's establish this field of chronic kidney disease, let's understand that if we are going to help patients that are headed towards dialysis or that have chronic kidney disease, we need to have a language to talk about it, stagings to grade these patients and so, you know, you go back to 25 years we're really starting from the very first steps: hey, let's figure out the names to call this. And, but you're right, since then, you know, at that time we had ACE inhibitors, ARBs were still on patent and we were talking about them as being the expensive medication, and now you look around and we have just an embarrassment of which is an incredible number of tools that are available to us with a robust evidence-base where you can really know, hey this stuff really works and it really works across these populations. Really, really is amazing.

But, it's not only in CKD. The nephrologists are happy because we are having new tools to treat glomerulonephritis, right? We're getting new tools to modify the compliment-cascade. Probably something we didn't even understand when you were in medical school in terms of it's importance for glomerulonephritis and renal damage and now we're getting multiple – you know, we already have some tools available and additional drugs that are on the way. I think that those are going to be revolutionary. We're having new medications that are designed solely for dealing with the symptoms of uremia, I'm thinking of difelikefalin for itch. You know, these patients that have had CKD associated pruritis, you know, we give them some Benadryl and cross our fingers knowing that it really doesn't work and now we have a specific medication for this therapy that's fairly effective. It's amazing the opportunities that are out there. And then, you know, we have a new endothelin antagonist, which are, you know, the first one now approved for IGA nephropathy and I think that's going to be a drug that we'll find additional uses in other GNs. It's really important.

And then the other thing is on the side of diagnosis. You know in the past we were limited to kidney biopsies and now we have genetic tests that are becoming much more affordable and opening up much more precision in the way of diagnosis, so it really is an amazing time to be a nephrologist and I guess I'm not the only one who's really happy about it. I'm glad that you're seeing that. And all these

tools, whether they're diagnostic or therapeutics, we need to know how to use them and it's almost impossible to keep up so I'm glad that KDIGO is here lighting the way forward.

Dr. Lin:
That's great, Joel. So basically you're telling us that there's a lot of positive news in this space. I think this is a great recruitment program for nephrologists because everybody's excited about this field. So, basically you're telling us that there are a lot of things that we can do to help improve the lives of our patients with CKD ranging from RAS blockade, to SGLT-2 inhibitors, MRAs, potassium binders, etc, etc. and as you said, riches of treatment, which is fantastic. And I guess the key is that we need to make sure that our patients are getting those treatments so that they can lead better lives. So thank you, Joel, for all your Twitter efforts on keeping us up to date with new CKD developments and thank you for taking the time today to share your insights on CKD interventions.

Dr. Topf:
Glad to be here. This was excellent. Thank you.

Dr. Lin:
I'm Dr. Peter Lin signing off. If you'd like to listen to this or other episodes in our series, please visit KDIGO.org/podcasts. Thanks for listening.