

Strategies for Ongoing Testing and Follow-Up of Patients with Diabetes

Andrew South: Hello, everyone. Welcome to the third podcast in the five-part series on the relationship between chronic kidney disease and cardiovascular disease and the importance of albuminuria and estimated GFR (glomerular filtration rate) testing for chronic kidney disease. The relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other. We will discuss strategies for ongoing testing and follow-up of patients with diabetes in particular. As we get started, I want to mention this series is sponsored by Bayer and the recommendations and opinions presented may not represent the official position of the American Heart Association (AHA). This podcast is for educational purposes only and do not constitute an endorsement or instruction by AHA. The AHA does not endorse any product or device.

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I'm Dr. Andrew South, your moderator for today's podcast. I'm a pediatric nephrologist at Wake Forest University School of Medicine and Brenner Children's Hospital, and I'm thrilled to be joined today by two terrific guest speakers on our podcast. First off, I would like to introduce Dr. Leslie Gewin.

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Leslie Gewin: Thank you, Dr. South. I am an associate professor at Washington University in St. Louis in a staff physician at the St. Louis VA. I'm a practicing nephrologist and also have a basic science lab investigating the mechanisms of tubular injury and repair, and I'm excited to be here today.

Andrew South: Joining us as well is Dr. Niloofar Nobakht.

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Niloofar Nobakht: Thanks much for including me to this podcast. I'm an associate professor at UCLA David Geffen School of Medicine. I'm a nephrologist and involved with clinical trials as well. My research interest focuses on management of hypertension in patients with kidney disease as well as addressing lifestyle-related metabolic conditions such as diabetes and obesity along with their associated injury and damages. I'm thrilled to be here as well today.

Andrew South: Terrific. All right, well let's get started. Dr. Gewin, I'm fascinated, especially with your preclinical background. With the current recommendations that patients with type 2 diabetes be screened annually for albuminuria with a urine albumin-creatinine ratio (uACR) and estimated GFR, I'm curious both for your clinical practice, what have you seen that's been working well, as well as what are some of the opportunities you see that we can improve globally? And then I think a big part of it, at least in my practice, is how can we educate in a practical way the inherent limitations to such testing in terms of accuracy and validity?

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Leslie Gewin: Thank you very much, Dr. South, for that question. One of the things that I've been really encouraged to see in my practice as staff physician at the St. Louis VA, is the increase in testing of albuminuria in patients with type two diabetes. I don't recall seeing this that much five to 10 years ago, but the prevalence of testing has really increased, and what I'm hoping is then that will lead to earlier implementation of some of the guideline-directed medical therapy and treatment options that we'll be

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- [00:03:40] talking about later on in the podcast. So, I'm very excited that there's more of an awareness about the importance of albuminuria and eGFR in patients with type 2 diabetes even early on.
- Andrew South: [00:04:00] Dr. Nobakht, what have you observed in your practice, and have you seen a corresponding increase in such testing, especially annually per the guidelines? Or have you seen a delay in an opportunity for improvement in testing annually as the recommendations currently state?
- Niloofar Nobakht: [00:04:37] We're standing in a much better position than we have been, at least compared to a decade or 15 years ago when my mentor was pointing out the urinary protein expression that is, for one, an indicator of microvascular disease, impacting endogenous damages such as brain, eyes, heart, and kidneys. Given all the new advancements and significant outcomes related to this metabolic condition with UPCR (urine protein-to-creatinine ratio), we are seeing an improvement compared to that 5, 10 years ago and I think, not just in academic programs, but community practices are getting encouragement to check UPCR more often. There are practices that I see every six months as soon as they hear someone has diabetes or CKM (cardiovascular-kidney-metabolic syndrome). [00:04:55]
- Andrew South: [00:05:25] Dr. Gewin let's switch gears to patients with type 1 diabetes. The current recommendation is for those patients who have had type 1 diabetes for five years or longer, they should be screened annually with urine albumin and creatinine ratio in eGFR, do you see a similar increase in uptake in those guideline recommendations or what have you observed?
- Leslie Gewin: [00:05:55] It's a little tricky to compare because we have such a bigger patient population with type 2 diabetes in the VA as compared with type 1 diabetes. So, I'm not a hundred percent confident that this awareness is applied to type 1 diabetes. But I think that people are more cognizant of the importance of albuminuria and I'm hoping that this will apply to patients with type 1 diabetes as well.
- [00:06:15] I think one potential for improvement would be after patients are noticed to have increase in albuminuria or a decline in eGFR, to start implementing some of the exciting new therapies that we have available. Frequently, patients that have abnormal albuminuria or a decline in eGFR are referred to nephrology, but [00:06:38] unfortunately there are not enough nephrologists to meet this growing demand of patients with diabetes and CKD (chronic kidney disease). So, I'm optimistic that in the future primary care doctors and others will feel comfortable starting therapies such as RAS (renin-angiotensin system) blockade or SGLT2 (sodium-glucose transport protein 2) inhibitors when abnormalities are detected in albuminuria.
- Andrew South: [00:07:07] Yes, we certainly see similar recommendations and patterns in pediatrics. I run our hypertension clinic, and we certainly screen at least annually in patients with either type one or type two diabetes who also have hypertension. eGFR is usually once a year and urine albumin testing is sometimes more frequent than that, just depending.

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- [00:07:35] Okay, so once our patients with diabetes are actually diagnosed with chronic kidney disease, the guidelines recommend urine albuminuria and eGFR testing more often, at least every three to six months, along with conventional cardiovascular disease risk factors, as to your point, Dr. Gewin, earlier, to accelerate that implementation of guideline-directed medical therapy, which we will refer to GDMT during the podcast. So, I'm curious if you've seen a similar shift once they're diagnosed or if we still have some opportunities for improvement.
- Leslie Gewin: [00:08:07] Yes, I think that there's still some opportunities for improvement. Once patients do have abnormalities in albuminuria and/or eGFR, I think that the patterns of testing don't always increase and instead sometimes that's the point where primary care doctors will refer patients to nephrology. However, I think an awareness of these guidelines, and particularly the relationship between increased albuminuria and cardiovascular events as well as decreased eGFR and cardiovascular events, may help primary care doctors have this increased testing on their radar and prompt them to start some of these therapies such as SGLT2 inhibitors and RAS blockade.
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- [00:09:00] Andrew South: Dr. Nobakht, have you seen a lot of empowerment of patients with these screening guidelines, both the annual screening, and then once diagnosed, more frequent? Do you get the sense that, on average, patients understand why we're doing this testing? Or do we as providers need to do a better job of educating them about that and bringing them in to be able to do this type of management?
- [00:09:30] Niloofar Nobakht: To be honest, as most of these patients get referred to nephrology office when they are facing another GFR at CKD 4 or 5, it is much more pivotal to educate our clinicians, primary care doctors for optimizing these patient outcomes by addressing the CKM care collectively and checking UPCR or addressing the referral earlier if possible. But we, the nephrologists, see these patients much later than primary care doctors.
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- Andrew South: [00:10:28] Dr. Gewin, I'm eager to hear and learn from you. I came of age, so to speak, in my medical training when the first wave of really impressive data came out for both kidney health and cardiovascular health with advent of ACE inhibitors and angiotensin receptor blockers 20-ish years ago. So, can you kind of tell us where we stand right now in RAS blockers, the renin-angiotensin-aldosterone system blockers, in patients with diabetes and proteinuria?
- Leslie Gewin: [00:10:48] Absolutely. The use of RAS blockade, specifically angiotensin receptor blockers and ACE inhibitors, have really improved the outcomes in patients with diabetes and proteinuria. So, all patients who have diabetes and albuminuria, as defined as urine albumin-creatinine ratio greater than 30 milligrams per gram of creatinine, should be initiated on RAS blockade.
- [00:11:15] I feel like this message has really been well received in the community and there is widespread use of ACE inhibitors and ARBs in this patient population. The one

[00:11:47] barrier sometimes to using full-dose RAS blockade has been hyperkalemia and I think the advent of K-binders and the partnership with pharmacists and utilizing these K-binders has led to full utilization of RAS blockade in patients with diabetes and proteinuria. I think this is really an important advance, not only the use of RAS blockade, but also with these K-binders to be able to optimally use them in order to suppress proteinuria, which we know has been associated with improvements in renal outcomes.

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Andrew South: Okay Dr. Nobakht, to you I'm very curious because I don't get to do this much in pediatrics yet because we're kind of behind the times. So as much amazing progress over the past 20 to 25 years we've made in patients with diabetes and proteinuria with RAS blockade, we still are missing the mark, and we still have a fairly high proportion of patients who are not adequately controlled for either hypertension or their persistent proteinuria as well as on-going high cardiovascular disease risk. So, tell us about your experience and hopeful excitement about SGLT2 inhibitors and GLP-1 (glucagon-like peptide-1) receptor agonist and the role they play in patients with CKD and diabetes?

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Niloofar Nobakht: The sodium-glucose cotransporter inhibitors such as empagliflozin or dapagliflozin, they came up with significant CKD benefits by targeting glucose uptake in the kidneys and renal cardiovascular benefit is beyond their glycemic control. They've shown this consistent benefit in reducing hospitalization for heart failure regardless of baseline risk and they can offer protective effects against atherosclerotic cardiovascular event in high-risk patient populations with CKD and dying. When it comes to renal benefit, it's slowing CKD progression by reducing the hyperfiltration of proteinuria and intraglomerular pressure showed the protective effects of kidney function independent of glucose-lowering mechanisms. We also need to keep that in mind. They have these metabolic benefits with promoting modest weight loss and reducing blood pressure. They also enhance natriuresis and can reduce albuminuria.

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Andrew South: Dr. Gewin, I'm curious, with your preclinical translational science lens, with the intersectionality among these therapies, RAS blockers, SGLT2 inhibitors, and GLP-1 receptor agonists, where do you see the field going for those patients in terms of optimizing the combination of those therapies?

Leslie Gewin: Thank you, Dr. South, for that great question. I think one of the most exciting parts about these new therapies is that they really could be synergistic because their mechanisms of action are so different. We know that addition of SGLT2 inhibitors to RAS inhibition can further reduce proteinuria and acts through complimentary, but different, mechanisms. As mentioned earlier, the SGLT2 is blocking that sodium-glucose cotransporter in the proximal tubule and likely have some effects that may even be independent of hemodynamic effects, such as metabolic changes, that we don't fully understand that may contribute to the renal protective effects.

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[00:15:50] The GLP-1 receptor agonists are very intriguing and there's more data, I think, in the REMODEL trial that's ongoing that will shed light on their mechanism of action, which is incompletely understood. However, it is known that these GLP-1 receptors are expressed on inflammatory cells and may have a protective anti-inflammatory effect, which may contribute to the positive cardiovascular effects as well as expressed in the vasculature of the kidney and may have other effects on the kidney that we're still exploring right now.

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[00:16:52] However, I think the take-home message is that because each of these therapies, talking about RAS blockade, SGLT2 inhibitors, and GLP-1 receptor agonists, have such different mechanisms of action, I really feel like the combination of medications can be very powerful way to reduce albuminuria, protect kidney function, and reduce cardiovascular events. I do think there are some questions about which subpopulations with kidney disease and diabetes would benefit the most from these therapies, and ongoing trials should hopefully provide some answers.

Niloofar Nobakht: As Dr. Gewin mentioned, as far as the metabolic synergies, the impact that these agents can add on to standard of care via weight loss because they have the defining impact of SGLT2 when it comes to weight loss and the combination effects along with all the improvements of metabolic package, including blood pressure, glycemic control, anti-inflammatory, reduction of albuminuria, can basically highlight the agent's potential as a critical therapy in high-risk patients. But you mentioned the treatment with this agent is still for combination with SGLT2 needs further trials to address unmet needs in the CKD population.

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Andrew South: Thank you, both, for that nice view of the horizon where we can hopefully move. Now, with that being said, we still have a lot of patients relatively speaking, who, despite optimization with RAS inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists, still do not see adequate control of their hypertension and/or still have persistent proteinuria. So, in those patients with chronic kidney disease and diabetes, Dr. Nobakht, can you tell us about the role of non-steroidal mineralocorticoid receptor antagonists, or nsMRAs? Again, I would love to learn from you, because as a pediatrician, we don't really get to use those drugs very often and so I'm very intrigued of where the field is going for apparently resistant hypertension or proteinuria and the roles that those drugs can really play.

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Niloofar Nobakht: The non-steroidal mineralocorticoid receptor antagonists, or nsMRAs, such as finerenone, act on mineralocorticoid receptor blocking its overactivation, which is indicated in inflammation, fibrosis, and vascular dysfunction. Unlike traditional MRAs, they have higher selectivity for the mineralocorticoid receptor and minimizing off-target effects such as gynecomastia or hyperkalemia. They show anti-inflammatory and anti-fibrotic properties beyond the impact on sodium and water retention. So, when it comes to nsMRAs, it's a good agent for resistant hypertension among patient populations with diabetes and proteinuria. They can lower the blood pressure by reducing vascular stiffness and inflammation and

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counteract aldosterone's effect on sodium reabsorption in the kidneys.

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Andrew South: All right, so tying it all together, both screening patients at risk for chronic kidney disease, following up disease progression and treatment response in those once they're diagnosed, and optimizing medical therapy with these really interesting options now, I would love to hear from both of you, how can we empower patients and their families to understand why we're using guideline-directed medical

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therapy and how we can best partner with them to ensure that the follow-up of patients with diabetes and CKD is appropriate so that we can best determine if patients are responding to our therapies and how we can optimize the dosing of such. I think we have a lot to learn there, and I'm really interested to know how we can, in an equitable way, best empower our patients so that we can partner in their management.

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Leslie Gewin: Dr. South, thank you for that question. I think it's really important to educate our patients more about this dynamic relationship between chronic kidney disease and cardiovascular risk so that they can understand that when they have increased albuminuria and decreased eGFR that that has really important implications for their risk for cardiovascular events.

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[00:22:20] My hope is that by educating patients about this close relationship between CKD and cardiovascular risk, they may be more interested in following albuminuria, and in the future, albuminuria may become like hemoglobin A1C. Most of my patients are very aware of what their hemoglobin A1C is for their diabetes and track that number over time. I'm hoping they can understand that reducing albuminuria and trying to reach that normal level of less than 30 milligrams per gram would really be optimal for their cardiovascular risk profile.

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Niloofer Nobakht: I agree, and I think we can add to the education and instruction that CKM health is basically a combination of the tabulate abnormality that our lifestyle plays a significant pivotal role in management outcome and end organ damages that

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include heart, kidneys, and our microvasculature. So close monitoring on urinary albumin excretion, which is a very easy, non-invasive, non-pricey test, and it can predict the lifespan of these precious organs, will be a great add-on, and patients, along with primary care physicians, educational podcasts that you are making here

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with us, will be very, very pivotal and I'm sure that we can do more and improve our patient outcomes in collective collaboration alongside primary care doctors, endocrine, nephrology, and cardiology.

Andrew South: Any final thoughts from either of you?

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Leslie Gewin: One thing I think will be very interesting in the future to look forward to is the role of some of these exciting therapies in patients who do not have increased albuminuria but do have diabetes and chronic kidney disease as diagnosed by reduced eGFR. I think it's still an open question, it's the FLOW trial in the New

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England Journal of Medicine that looked at GLP-1 receptor agonists, mainly enrolled patients with a high degree of albuminuria. So, I'm excited to see what the field reveals about the use of these medications in our non-albuminuric CKD patients with diabetes.

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Andrew South:

Well, thank you both so much, Dr. Gewin and Dr. Nobakht, I really appreciate this wonderful and enlightening conversation. I want to thank our audience, we really appreciate y'all, thank you for joining us. Thank y'all for your time. Please make sure to check out the rest of our podcasts in this series as well as our corresponding toolkit on the AHA website and stay tuned for our next podcast. Thank you all very much.