Screening, Diagnosis and Treatment of CKD

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DR. BAKRIS: Hello, I'm Dr. George Bakris, Professor of Medicine and Director of the American Heart Association, Comprehensive Hypertension Center at the University of Chicago Medicine. I'm going to speak with you today about the pathophysiology and epidemiology of chronic kidney disease. Kidney function as you can see, there's a Homer Smith version 1952 of a nephron. And I'm not going to insult you by going through this, the detail of a medical student. But clearly you can see that it's basically a filtering head of capillaries, artery, capillary artery and then the tubule which does a lot of the work for reabsorbing and maintaining sodium as well as excreting things.

And moving on, this is the basics of the plumbing system. And this is what it looks like under the microscope. There's the glomerulus and the tubules are here, the distal tubule versus the proximal tubule. If we overlook the pathophysiology, we can't really make any general discussions about pathophysiology because if I discuss diabetes, that's one thing. If I discuss glomerulonephritis, that's another thing. There are multiple different diseases that can affect the kidney and the pathophysiology would be unique to that disease.

There are certain commonalities however that you need to be aware of. And one of them is inflammation. Inflammation does resolve in nephron loss regardless of what's causing it. Inflammation does result in a loss on interstation which is the supporting structure of the nephrons. And then ischemia results in limited blood flow to parts of the nephron and that can cause all kinds of changes in blood pressure and other things as well as ultimately if it's not fixed kill nephrons, so this is very important.

If we look at stages of progression, you basically have increased risk for CKD and there are a number of reasons that you could have increased risk for CKD. Primarily, lifestyle issues, blood pressure, diabetes, etc. And then if those are not fixed or dealt with appropriately in an early time fashion, you'll have damage to the kidney and then you'll lose nephrons. If you lose nephrons, GFR start falling, ultimately resulting in kidney failure and ultimately cardiovascular death. There is a strong relationship between losing kidney function and cardiovascular death.

Now if we look at the causes of kidney failure. This is a very important slide. And the bad news is, this is 2007. If I were to show you 2021, it would look exactly the same. Diabetes is by far number one. Hypertension is a more distant number two. And the other disease is pale by comparison, so important to understand.

Again just to remind you, these are the glomeruli and those are the tubules, proximal and distal. Now this looks at morphologic changes. This is diabetes. And there are mild ischemic changes here and there's changes of Bowman's capsule. I mean if you're looking at this, you can see some changes here. There's clear changes here consistent with diabetes. There we go. More changes here. You can see that morphology changes.

Now glomerular scarring and glomerulosclerosis is leading impaired kidney function. That's an end stage event. And ischemic kidney disease which by the way is relatively uncommon today because smoking has stopped, which is a major cause. Atherosclerosis which is a major cause is now being treated. This is really not that common anymore. But

nevertheless, this gives you an idea what it looks like. The term benign atherosclerosis is no longer used. By the way this is 1986. But I don't know if you think this is benign, I think we need to have a reevaluation of your vocabulary.

This clearly is a problem. And this is what it looks like in people that are chronic smokers who have poor atherosclerotic or have poorly controlled atherosclerotic disease. CKD is very common and it occurs more than 1 in 7 adults, 15% of the US or 37 million people have CKD. This is a big deal. And a lot of people don't know it because in fact as many as 9 in 10 adults with CKD don't know they have CKD. And 2 in 5 adults with severe CKD don't know it. So, it's a silent killer. Everybody says hypertension is a silent killer. Presence of kidney disease is a silent killer.

Now this looks at the percentage of US adults over 18 with CKD. And of course, yes, if you're over 65, that's going to be the largest percentage. Notice there's not a huge difference between male and female. And the African Americans, the blacks, not Hispanic blacks, definitely have the line share of kidney disease, again very representative data here.

Again if you look at ESRD, you can see here by age that there's a reduction in older people going on to dialysis and there's a little bit of a reduction in people, the next slide down, 65-74. But bottom line is there's not a significant reduction. It's still pretty high.

Now again looking at causes of kidney disease, diabetes is number one by far. High blood pressure is number two. Polycystic kidney disease is important. Polycystic kidney disease is probably number three and that's something totally different than diabetes and hypertension. But I think we have to keep that in mind as you can see here on the slides.

If we look at race, the point I want you to know in the slide is if you look at data from 2010 to the present, there is a nice reduction in people that are African American or black. It's going down. This is really good about people going on dialysis. It's also true for the American Indian and the Alaskan native. That's also going down. This is very important data and shows that we're making some progress. However, worldwide if you look at the left, there's a clear increase in people going into dialysis. In fact by 2030, we will have more than doubled the number of people in dialysis compared to 2010. And Asia is by far number one leading it. But look where we are, we're right there, North America, Latin America, highly competitive.

Important thing about CKD, if you look at people with CKD, now the CKD by the way, we have a frame of reference, CKD is a GFR below 60, anything below 60 is CKD or at least the way I'm using it. Heart failure, look at this, 43% of the people have heart failure whereas if you don't have CKD only 18.5% do, so very important distinction there in terms of heart failure and CKD relationship.

I mentioned earlier about CKD being a cardiovascular risk factor. Well, take a look at this data. This is data from the Kaiser, over a million people. If you look at all across mortality, which is what this is, if you have a GFR below 45, you have an almost five-full high risk of all-cause mortality. And if you go below 30, it really jumps. But if you just care about the cardiovascular events, while even if you're between 45 and 59, you've got

an almost four-fold increased risk for cardiovascular event. That's a whole another lecture or make no mistake, presence of kidney disease dramatically increases cardiovascular risk.

Now this is something really important if you look at cardiovascular mortality in the general population versus people on dialysis. If you look at people in the general population, if you're 85 then you come over here, you'd have to be 45 to have the same mortality. If you're on dialysis in 45, you get the same mortality risk with somebody's who's 85. That's a problem. It doesn't matter if you're black, male or female, etc., very important point. Dialysis survival is shorter than some cancers. This is very important. If you look at survival probability here, when you look at dialysis, if you have colorectal cancer or breast cancer, your probability of surviving is actually better than if you're on dialysis. Now this data is about 10 years old but still it makes the point. And for men, if you have prostate cancer or colorectal cancer, you got better odds of surviving when you do if you're on dialysis. I think it's important to keep in mind, you don't want people going to dialysis.

It is prevalent in the general population CKD, unappreciated but take a look at these numbers. Look at stage III, stage III is where the money is. You do not want to go below stage III. And look at how many people there. And what happened here? You've got 7.6 million people here and 400,000 here, what happened between here and here? It's called cardiovascular death. That's what it is, so keep that in mind.

Now this is a 17-year follow up of people in hypertension. This is hypertension alone, no diabetes, nothing else, just hypertension. If you don't control blood pressure and you don't have a stroke, what are the odds of going under dialysis? Well if you're pressure is above 180 over 17 years, you've got a very high probably of going on. But interestingly if your pressure is below - - your odds are not that high. They're high but they're not that high. Important to know that even the kidney has some buffering ability to protect itself. However, this is the problem, so keep that in mind.

Now let's take a look at stages of CKD and associated risks. Here you have normal GFRs. Here you go, 20-70 plus. And basically we lose about 0.8 ml per minute per year, roughly. That's normal circumstances. If you do the math, 70-year-old, 80-year-olds, their GFRs are going to be in the 60s. That doesn't mean they have advanced CKD. That's appropriate for age. Just keep that in mind and remember that CKD is relative to age, and so keep that as a key point.

Now again I want to make the point, when you're assessing CKD, it's not just the GFR, it is the albuminuria. You need both. For example, if you have a GFR of 75, let's just say, but you're spilling 2 grams of protein for whatever reason, you'd be in this box. I don't think I have to tell you the patient would figure out you're in trouble. Even if you weren't, let's say you're here, you're spilling 300 mg, you're still in trouble. You need albuminuria. This is not good enough. Just keep that in mind. That box is what we know about stages of kidney disease from clinical trials. And again just making the point, if you have kidney disease, your cardiovascular risk is very high. I mentioned this earlier but here it is again.

Now let's talk about the relationship between heart failure and estimated GFR. You can

see here if you look at the overall heart failure admissions, these are hospital admissions. Look if your GFR is below 45, if your albuminuria is above 30 or if you got the combination. These are magic number not just for cardiovascular events, they're for heart failure hospitalizations as well.

What do you need to manage? Everybody wants to know. If you have diabetes, the three major things you need to do is control blood pressure to less than 130, control hemoglobin A1c to less than 7, and get LDL at least down to 70 or lower. And lastly, make sure the bicarbonate is at least a 23 because if it's below 23, then especially the farther it gets away from 23, you're going to have major issues in terms of kidney health. And then if you have more advanced disease, obviously there's anemia management and then there's PTH and bone management. I'm not going to get into that but you need to keep in mind,, the kidney does many, many things that are underappreciated.

I already talked about this, but this gives you a hint about when to refer. If you're seeing a patient that is in one of these red boxes, you need to refer. And in some cases, you need to treat. And I told you the magic of treating them. We don't have anything more magical than what you have. We just make sure that you get the goal and you use certain tricks. So this is what this is about.

Now if you at nephrology referrals, this is important, if you look at mortality, early referral versus late referral. Early referral you're going to dramatically reduce mortality by 50% compared to late referral. If you look at hospitalizations, you're going to reduce it by 50% or something. No matter how you slice this, early referral is better than late referral.

Alright, screening and diagnosis and prediction of CKD progression. What can you do to markedly slow down CKD progression at stage II CKD? Well blood pressure control, glucose control, lipid control. Now this is a large study, it's a study about 154 people, but it went out ultimately I'm showing you 8 years here, it went out for 20 plus years. And these are all clinic patients. They just randomized to intensive treatment versus conventional treatment. And when you look at this, these lines are where the goals are. That's the guidelines today. These studies were done. By the way these studies were started back in the early 90s. You can see that the intensive group was not even quite to the goal range and yet look at the absolute risk reduction in the intensive group, substantial benefit with blood pressure, glucose and lipids control. And in fact, retinopathy was affected, nephropathy was infected, everything except neuropathy was benefit. Again nothing magic, you just need to make sure that you do the risk factor management but do it aggressively.

This shows you the 20-year follow up, so same study but now 20 years out. If you look at the intensive treatment for cardiovascular events or death on the right, you can see the intensive group that's far better. It doesn't really take a physicist to do this. You can do it.

What's the role of albuminuria? Albuminuria is critical. If you not have albuminuria as I shown you on the EID map, you've done a half ass job in staging the patient. You need a spot in albumin and creatinine. Because it also tells you about not just the kidney, it tells

you about overall kidney injury. Everybody with diabetes is mandated to have it annually. And if it's elevated, you can check it again in six months. Hypertension, probably every two to three years it should be checked in the absence of diabetes. And then obviously more frequent screening if you have more advanced kidney disease. But this is guideline here.

How do you check it? The first morning void, well that's ideal. Morning void is ideal, ideally fasting. Ideally you don't want to have eaten. You don't want to have taken steroidals, any of that stuff. There's a number of things that can give you false positive. Now, you're going to say, wait a minute. This isn't practical. If the patient's in the office, you can check the albuminuria there and just ask them, did they have a meal lately, did they take any NSAIDs. You don't need to be this pristine. But this is ideal if you can do this. If a patient has a fever, do not check albuminuria. It will be elevated, I'll tell you right now. Because remember it's an inflammatory marker. And even if you have a lot of albuminuria, inflammation will raise it even more, so just keep that in mind.

And I think the key issue here is if you have elevated albuminuria or markedly elevated albuminuria, that is a problem. And in fact, this is an old slide that we made many years ago as terms of contributing mechanisms that affect permeability of the protocyte and the vascular epithelium and lead to microalbuminuria. And basically keep in mind that the kidney is trying to tell you something if it's spilling out albumin. It's not supposed to be spilling albumin. If it's spilling albumin, something is going on in terms of an inflammatory process and it may be affecting the kidney but it may be somewhere else, but you just need to interpret this correctly.

This is an old slide that I did, but basically it tells you low levels of albuminuria, think about vascular dysfunction, think about inflammation. And then if you made it over 300, then you've got high cardiovascular risk and worst vascular dysfunction. Microalbuminuria definitely means a lot of things. And look at all the different diseases you can have that can generate microalbuminuria. These are all documented. It's not theoretical. By the way, high salt intake will cause microalbuminuria. Why, because it reduces nitric oxide, just another little tip.

This just looks at albuminuria at the different ranges. But I want to point out to you here, if you look at blood pressures of less than 140, blood pressures of less than 140 with microalbuminuria, 2.2-fold higher risk for ischemic heart disease, so important observation from epidemiology. I told you, the one with these other talks that microalbuminuria should be thought of as a CRP. But look at this, this is an analysis done looking at CRP and microalbuminuria, predictors of mortality. Look at this, microalbuminuria is better than CRP in terms of predicting it. In terms of first major cardiovascular event, microalbuminuria was better than CRP. I think you need to have some respect for microalbuminuria. If you don't check it, you won't know.

Now I want to make some points here about, this is a study that looked at 19,000 patients. It looks at albumin and creatinine ratios and the changes. But if you look at people with diabetes, bottom line is mortality risk goes down as you reduce albuminuria or I said another way goes up is albuminuria goes up so does ESRD risk. It doesn't matter. That's true if you don't have diabetes, so again important points.

Now treatment of CKD stages I through IV. If you've got albuminuria greater than 300, then you have a high CVD risk. And the question about clear evidence of CKD, well, I mean if you're going to get greater than 300, here you are. Even if your GFR is 90, there's evidence of problems with the kidney. And certainly if your GFR is lower, there's problems. You need to look at albuminuria in the context of where the GFR is. By itself, it's a problem. And if you have very high albuminuria like 3 grams, well, you don't need the GFR necessarily because you know you have kidney disease.

Now what do you if you have albuminuria and why? Well, this is data from the African American study of kidney disease. This looks at the relative risk of ESRD based on reductions in the albuminuria after five years. What you find is if you had more than 50% reduction in albuminuria based on your treatment that was the greatest risk reduction for ESRD. And if you didn't, you actually had an increased risk. This is a problem.

Now this is a major meta-analysis of multiple studies, cardiovascular and renal. Basically what the take home message is here is you need a minimum reduction of 30% in albumin and creatinine ratio, minimum reduction to get a benefit, the higher the reduction, the greater the benefit. The FDA actually acknowledges this. That's why I put this up like this.

Now again looking at treating early to prevent CKD progression. It's the old standard, blood pressure, glucose, and lipids. And again, the green lines represent the guideline goals. And those guideline goals as you can see here really had not been met over the time period in 8 years and yet substantial absolute risk reduction, 20% or less. And everything except peripheral neuropathy was in fact improved. There's no question that doing the old standbys and doing them well gives you kidney protection and reduces cardiovascular risk. This is 20-year follow up. And again cardiovascular composite on the left, death on the right, again the intensive group doing far better.

Now the pharmacologic agents that reduce albuminuria and have an FDA indication for slowing nephropathy and cardiovascular risk are maximally dosed RAS blockers, ACEs or ARBs, SGLT2s and non-steroidal MRAs, finerenone specifically.

Alright. Here's the case of diabetic nephropathy with a missed opportunity. Here's a 45-year-old Hispanic male with diabetes for 10 years, reasonably well controlled. Hypertension for seven, well controlled. BMI of 30. Dyslipidemia. Family history of diabetes. Social history: he's sedentary, non-smoker. He's a comedian. On exam,, his blood pressure was 139/85. Mild obesity. And the rest is really normal. His BUN is 28, creatinine is 1.8 and his urine protein is 2+.

On the MDR and GFR equation, he's got diabetes, hypertension, metabolic syndrome, stage IIIB CKD with a GFR of 44 and a gram of albuminuria, 1 gram. Where does that put him here? His GFR is 44 and he's got a grand, whoa, he needs to be referred. Who was it? George Lopez. Now transplanted and doing quite well, but missed opportunity. Thank you very much for your time and I hope you enjoy this.