Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Expert Opinions on Renal Compensation and Renal Functional Reserve

Announcer:
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What is the fundamental idea behind the intact nephron hypothesis?

Dr. Radhakrishnan:
So there was a very interesting and a seminal observation and a hypothesis that was forwarded by Dr. Neal Bricker back in the 60s. People with the so-called Bright disease eventually went on to need dialysis you know because of progressive kidney damage. So Dr. Bricker came out with this theory that if you've got damaged nephrons, the remaining nephrons will pick up the slack and try to sort of adapt to this loss of the damaged nephrons by essentially working harder and working overtime. And this led to this concept that a kidney that's damaged leads to adaptation. And this adaptation initially is very useful in preventing the glomerular filtration rate from dropping. But over time, if as long as the kidney is you know continuing to see stress and injury and this progressive loss in more and more nephrons, there comes a threshold moment when this adaptive process becomes maladaptive.

Announcer:
At what threshold does the compensatory mechanism of nephron loss become maladaptive?

Dr. Herlitz:
We know it's sort of north of 50% where that threshold becomes too intense a stressor to really continue to compensate for extended periods of time. So that initial response is adaptive in a short-term response, but as you get to longer-term or more intense stressors, that adaptive response becomes maladaptive, because those nephrons burn out and they scar. And then they leave behind the residual nephrons, which now have to take on more and more. And it's this sort of self-fulfilling prophecy, where the more nephrons you lose, the more stress you put on the remaining nephrons, and the more likely and the more quickly those nephrons are to scar and eventually become sclerotic. And that's how you end up progressing to end-stage kidney disease.

Announcer:
How does the intact nephron hypothesis influence our understanding of nephron function today?

Dr. Radhakrishnan:
There are processes even before the creatinine goes up, which, by the way, we call this a lagging biomarker, because it takes much more damage to cause the creatinine to go up. So that's a point that we hadn't understood previously, but it's very valid. For example, with progressive glomerular disease, is not to wait for the creatinine to go up and institute your preventive measures for progressive nephron loss way ahead of that event, because by and large, when the creatinine does go up, there's irreversible damage.

Dr. Herlitz:
One of the things I encounter on a daily basis in my clinical practice, especially when I'm looking at biopsies from patients with rare glomerular diseases, is just how much nephron loss there can be in a biopsy when their clinical parameters are completely normal, especially their creatinine level and their eGFR. So you can have a relatively young, healthy patient who maybe gets biopsied for proteinuria and hematuria and has a completely normal GFR. And I'll see under the microscope 50% glomerular scarring, maybe 20 to

30% interstitial fibrosis and tubular atrophy. And so really, GFR is a lagging indicator, so that patient who's young, who needs that renal function for decades to come, is already down 30 to 50% of their renal mass, and we haven't even seen it yet reflected in their creatinine level and their GFR.

Announcer:
What is the renal functional reserve and how does this concept impact our understanding of kidney function and response to injury?

Dr. Radhakrishnan:
It simply means that if you have ongoing nephron loss from injury, the remaining nephrons pick up slack by hyperfiltering at the level of each nephron. Important point to note is that because of the nephron reserve concept, you are actually masking ongoing damage, which you said very well, you're seeing a lot of damage on the microscope, but the kidney function is totally normal because of this concept of nephron reserve.

Dr. Herlitz:
So most patients, when they're young, have a lot of renal reserve. But in young patients who develop these rare glomerular diseases like IgG nephropathy or lupus nephritis, they'll have this sort of waxing and waning episodic disease course, where sometimes the disease is very active, and that might result in an acute period of nephron injury. But when that goes away or calms down, they'll compensation, that renal reserve will kick in, and they'll get back to a completely normal creatinine. And you'll have episode after episode of this happening, and yet, we don't appreciate a loss in GFR until multiple episodes and multiple hits have resulted in significant scarring, which I can appreciate on biopsy. So even in that first episode, you know I'll see activity, but not a lot of chronicity. But if you biopsy somebody after a couple of years of having multiple episodes, you may still see a normal GFR, an intact creatinine, maybe some proteinuria and some hematuria, but what I'll see under the microscope is a significant amount of glomerular scarring and even evolving tubular interstitial fibrosis. And when I see that, even if a patient has a normal creatinine, what that's telling me is that there's going to be progressive renal injury that accumulates over a lifetime.

Dr. Radhakrishnan:
What is this person's renal reserve? So we have to use markers of injury and assume that if the patient has ongoing proteinuria and/or hematuria, there is ongoing injury, and there is going to be a loss of renal reserve in this patient.

The renal reserve, which is the amount of adaptability, is one way of looking at it, progressively goes down as we keep losing these nephrons. So by the time the kidney function worsens to you know to when your GFR is down, your creatinine's up, there has been a significant loss of nephrons up to you know 50% of your kidney is essentially gone. And it's not reversible.

Dr. Herlitz:
It sounds like the downside of renal reserve is that it basically masks that loss of nephrons, which I can appreciate under the microscope, but you can't appreciate with eGFR until we've already lost more kidney than we'd like to lose.

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