[MUSIC PLAYING]

JAMES R. JOHNSTON: So this is going to be a kidney-centric talk about calcium and the elderly. I would also like to thank Dr. Rubin, who gave me a very nice compliment when I walked in. He said, hello to my fellow geriatrician. And I really do feel like a geriatrician, because so many of my patients are in this particular age group.

So this is "Calcium and the Elderly." I have no disclosures. And my first goal was to finish on time, which I will do, because I really tried to keep this as straightforward as possible.

You can't put a kidney doctor up in front of an audience without having a review of normal calcium metabolism. I'm going to introduce fibroblast growth factor 23, which I'm going to subsequently refer to as FGF 23. And just polling the audience, how many of you have heard of FGF 23? Oh, wow, virgin territory. All right.

This is really pretty hot right now in nephrology. So I hope to introduce this. And then I'm going to do specific calcium issues in the elderly, and then a really basic approach to how we can treat our patients.

So that's elemental calcium shown there. You can't expose it to oxygen, because it's very reactive. It is the fifth most abundant element in the human body. And this is what it does.

All of us are aware within our population about how important it is for bone formation. It's also important for your muscles to work. It's important for neurotransmitter action and signal transduction within the cell.

And yes, here we go. It wouldn't be a kidney doctor without a diagram. So all of us have had a very nice lunch. We probably did not get 1,000 milligrams of calcium in our lunch, not by a long shot-- the pita chips, definitely not.

You get 1,000 milligrams a day that come in as dietary intake. And then you have intestinal absorption, which is controlled. It's a 100% controlled. It's unlike phosphate.

Where phosphate is 30% passive re-absorption, the calcium needs a hormonal modulator in order to get into the body. And yes, we do secrete calcium back into the gut. And so of the 1,000 that we take in, we lose about 800 or so that comes out in the stool.

What we absorb goes into the intracellular fluid calcium. It's a minuscule amount. It's only about 1.4 grams. And that's in balance and equilibrium with the intracellular calcium.

Then we have the bones, going back and forth. And look at the bones. They are not the pikers, by any means. In terms of, these other places are grams, the bones are kilograms.

So basically, what you have is about 1.2 kilograms of calcium inside your bone. And bone is going back and forth between the extracellular space in terms of resorption and formation.

Now why is FGF 23 important? Because, after all these years, we finally have a hormone from the bone that talks to the kidney and that talks to the intestine indirectly. Up until this time, it's been the parathyroids, it's been the kidney, back and forth with their cross-talk. But FGF 23 now is the way that the bone talks to the kidneys and tells it what to do. And we'll go into that a little bit later.

Now, the kidney is not to be outdone. Here is the intestine-- a mere 1,000 milligrams a day. The kidney filters 8.8 grams a day. And of that, the kidney being the kidney, it really absorbs 8.6 grams of that a day. And the urinary loss is roughly 200 milligrams.

So you can see that, basically, we stay in balance under homeostatic conditions-- what goes in, what comes out. But these things are regulated. And the way that they're regulated is fourfold-- parathyroid hormone, which go over, regulated by the four parathyroid glands, 1,25-dihydroxyvitamin D--

Anybody know why 25-dihydroxyvitamin D gets all the attention? Because 1,25 is the one that does all the work. Any ideas? It's because 25-dihydroxyvitamin D represents the storage form of the precursor, and it corresponds directly to the amount of 1,25 that you have, so that, if you measure 25, you get a good idea of what 1,25 is, unless the patient has chronic kidney disease. Because then you have the organ that manufactures this that's important.

Fibroblast growth factor 23-- and it's story wouldn't be complete unless I mentioned Klotho. Anybody hear of Klotho? K-L-O-T-H-O. Klotho, the goddess of life, one of the three fates. It was the fate that spun the yarn of your life. And then the next fate basically put it together into the fabric. And then the last fate cut the thread of your life.

It's called the goddess of life because, if you overexpress Klotho in mice, the mice live longer. And so I want you to keep that in the back of your head. That's why it's called the goddess of life.

And one of the other things I'll just drop right now is, guess what stimulates Klotho. Vitamin D. Guess what inhibits vitamin D. FGF 23. So you've got a little balance back and forth. And that's going to be important as we come along.

Then we come to the last one, calcitonin. When was the last time you gave somebody calcitonin for hypercalcemia? I did it last week, because it was just something to do, and because it never works.

And it's made by the thyroid gland. And how many of you have difficulty managing calcium in your hypothyroid patients? I know I don't. The only time I have it is when the thyroid is surgically absent, and the surgeon basically goes, oops, and removes all the parathyroid glands. Then I have a problem managing the calcium.

The calcitonin is sort of like the appendix of the calcium-relating hormones. It's there. You can take it out, and it really doesn't make too much difference. So the first three are the most important ones.

So calcium-sensing receptors exist in many places in the body. They exist in bone. They exist in the kidney.

The most important place is in the parathyroid glands. And in the parathyroid glands, if your calcium is low, you have transcription enzymes that are induced, and, basically, you increase parathyroid hormone release. This is something that we're all pretty familiar with.

And the increased parathyroid goes down and knocks at the kidney's door and basically increases a 1-hydroxylase activity in the proximal tubule. And that causes increased formation of 1,25 vitamin D.

The parathyroid also has a direct effect on stimulating calcium absorption in the distal tubule-- basically, that it works. And secondly, for the old, gray-haired people in the room, some of whom were my teachers, we remember how we used to measure PTH activity by looking for cyclic AMP or phosphate in the urine. And that was an example of a way to do it. We do fractional excretion of phosphate. Now we can actually measure PTH levels.

But this is a hormone that causes you to retain calcium and causes you to excrete phosphate. That's its basic function in all these feedback loops that exist. It stimulates removal of calcium and from the bone by increasing osteoclast activity. And that causes release of calcium from the bone and phosphate.

Now, let me do a little footnote here. If you've got renal failure, and the parathyroid hormone comes down and tries to induce calcium reabsorption in the kidney, it's like there's nobody home, or maybe they're upstairs and they can't hear the doorbell. So what would your normal reaction be? It's to pound on the door more heavily. And whenever you do that, the physiologic response of PTH is, it increases in size.

And then it turns into a roving gang of very unhappy PTH. And if it can't get the calcium reabsorbed through the kidney, it goes to the bone and causes-- really, the renal disease is called osteitis fibrosa cystica, which basically is a demineralization of the bone. And that's because that's now the only source where PTH has to do that.

And I'm going to keep bringing up chronic kidney disease. Because, as an honorary geriatrician, duly appointed by Dr. Rubin, I have to mention the fact that we're going to talk a little bit about loss of renal function with aging.

1,25-dihydroxyvitamin D, we really don't measure that very often unless it's an at-risk population. It has a direct effect on calcium reabsorption in the kidney. And as I mentioned, calcium reabsorption in the kidney is entirely dependent on vitamin D activity. It's a regulated phenomenon. You don't have vitamin D, you're not going to reabsorb dietary calcium.

It also regulates phosphate reabsorption. But only 70% of that is a regulated phenomenon. The other 30% is passive, which also gets to be a problem if you're trying to restrict phosphate in a kidney population. Even if they're restricted in their diet or they don't have enough vitamin D around, they're going to continue to reabsorb the phosphate.

The vitamin D also is very responsible for bone remodeling. And it is the feedback loop that goes and combines with the vitamin D receptor in the parathyroid gland and shuts off PTH regulation. So if you have a deficiency in vitamin D, you're not going to have that feedback loop shutting off parathyroid hormone.

Fibroblast growth factor 23, also called phosphatonin-- and yes, folks, there are 22 other fibroblast growth factors. It's directly expressed in osteoblast and osteocytes. And it's stimulated by hyperphosphatemia.

So it's not an immediate regulator, but if your phosphate goes up, perhaps lag time might be several days. This enzyme, this hormone will be released. And it will basically go up. 1,25 will also stimulate it.

And what it does is, it goes to the kidney, and it shuts off sodium phosphate exchanged in the proximal tubule. So you don't absorb sodium. You don't absorb phosphate. With it, you shut that down, and you become phosphaturic.

So this should be a good thing, right? It's regulating all this good stuff. It also decreases the formation of 1,25 vitamin D and increases 1,25 vitamin D breakdown, converting it to 24,25 vitamin D. That's the basic mechanism of this.

The levels of this go up very, very quickly in people with chronic kidney disease. So you've already got elevated levels if you're sitting around at a GFR of roughly 70%. And the thing that has been now brought out about this is that FGF 23 is a good hormone when it doesn't go up and stay up.

There's a direct potential role of FGF 23 in cardiovascular disease. And it's thought to be one of the major modulators of cardiovascular disease in the CKD population. So this is one of the reasons why I wanted to present this at this meeting, is to be aware of this and how we might be able to interfere with it.

So of course, I keep mentioning that I'm a kidney doctor. Is the aging kidney an impaired kidney? You notice that the cane is too short, and, obviously, this person did not go to yesterday's lecture about cane length. OK.

I've shown this slide at this forum before. This is the decline in kidney function with age. And these are data from Stevens. They were published in *The New England Journal of Medicine.* This is the gold standard of renal function tests. It's an inulin clearance. That's a lab test. I used to do these when I was a fellow.

And basically, this is inulin clearance. It's men on your left, women on your right, inulin clearance on the y-axis, and your age is shown down here along the x-axis. And what you can see is that, starting at the age of 20, there is functionally a decrease in your renal function as you grow older, so that by the time you are about 50, you've lost maybe one seventh of your renal function, and that by the time you're about 90, you probably have lost one half of your kidney function.

So before yesterday's article that I reviewed, I used to tell my colleagues that, after the age of 30, you can count on losing 1% of your renal function per year, so that, for me, being 64, I now have lost 30% of my renal function. Dr. Resnick hasn't lost any of his, because he's timeless, OK? I just want you to remember that. Yeah, and I'm going to continue to abuse you, Neil.

OK. So this is the article that I reviewed yesterday and I inserted in the talk for today. And I'm going to go over this a little bit. Because the studies that have been done on aging in the kidney have not been really well done. They've been small sample sizes and so forth.

This is a study from the Mayo Clinic. And what they did was, they took their donors. And when they took their donors, these folks had a complete work-up. These are perfectly healthy kidney donors. They are ready to rock and roll. They don't have any flies on them at all.

So they go in they had a CT scan, which is standard of care for doing a transplant, because 30% of our folks that we transplant have abnormalities in the renal vasculature. And we want to know if they have two arteries, three arteries, or four batteries. The most arteries I've seen in the kidney, by the way, is five. And we transplanted that kidney, which was heroic.

But what they did was, they did the CT scans. And then, in order to assess the kidney, they did protocol biopsies on the kidney. And then they put the kidney into the recipient.

They took the protocol biopsies, and they mapped them. And they looked for the number of glomeruli per volume in that core of kidney tissue. So now, you have an estimate of glomeruli per biopsy volume. And then, using the CT scan, they were very precisely and accurately able to determine the number or the volume of that kidney in the cortex, which is where the glomeruli are. And from that, they calculated the number of glomeruli.

And then they separated them into age groups. So your 18 to 29-year-olds, 190 of them, came up with a number of nephrons of about 970,000, which, based on other data, is really pretty good, depending on your birth weight. So the bigger you are, the more nephrons you have at birth, so that if you are an offensive lineman for the Steelers, and you weighed 10 pounds whenever you were born-- god bless your mother-- but you have more nephrons than someone, whenever they were born, that weighed five pounds.

And this is thought to be one of the correlates for why certain groups develop kidney disease more prevalently than other groups. Because on average, they have lower birth weights.

So you can see 970,000. The normal range that I tell folks is, you've got about 750,000 up to 1.2 million nephrons per kidney. And yes, I can do a kidney biopsy. And I'm only going to take about 20 glomeruli. You won't miss them.

Well, one of the things I want you to look at is, as patients grow older, look what happens to the number of nephrons. And you can see that, by the time you're in the age group of people we take care of, you're down to 480,000 nephrons. Now, in my other life, I was a chemical engineer, so I just had to do this. I just was compelled to do the math.

So if you estimate from 18 to 70, and you estimate a loss of 470,000 total nephrons over that time span, it's 17,000 nephrons per year. Or while you're sitting here during Dr. Weiner's talk and my talk, you will lose a nephron. So that's the effect of the lecture. You're losing one nephron per hour.

And it actually works out to close to my old estimate of about 1% loss per year. So as a general rule of thumb, we are taking care of a chronic kidney disease population with the geriatric population. And that has to be factored in to how we take care of these people and how we think about calcium and phosphorus.

I would point out that these folks are all donors that had no flies on them. They had no hypertension. They had no diabetes. They had no co-morbid conditions. They didn't have arthritis. They weren't taking non-steroidals-- anything like that.

Unless you guys have a very odd patient population compared to mine, my population has all of those things. And so they're going to lose their nephrons at a quicker rate.

So this is the impact of nephron loss over time, based on age and based on, basically, GFR. So if we start out at a normal GFR here, shown at about 95, and this is calcitriol 1,25 vitamin D, and it's shown in the green dots, you'll notice that vitamin D production drops off very rapidly, so that you are really down to levels that are considered to be abnormally low and about 75 mLsm or 75% of normal kidney function.

You'll notice the parathyroid hormone stays relatively flat until you get down to about a 50% decrement in function. And then what you see is, it starts to go up. And then that's the CKD 3 population. And just as a reminder, that's a GFR of about 30% up to about 60%. And many, many of our geriatric patients are in that age group.

If you look at calcium and PTH, here's serum-free calcium, here's intact parathyroid levels shown on this axis, and here's creatinine clearance again, normalized to 100. And again, in this particular slide, what you see, the relationship in this study was that, again, parathyroid hormone starts to go up and calcium levels stay relatively the same for a long time. It's unusual for it to bump up here. Because generally, what we're seeing is what we call the renal double-cross, where phosphate goes up and calcium goes down because of decreased renal excretion.

And then this shows the relationship with phosphate. And you can see that GFR is going along. And then when you get down to about 30%, it starts to go up.

Now, why do you think the phosphate metabolism and the phosphate levels stay at this particular level? It's because of the increasing levels of FGF 23. And we already know that FGF 23 is demonstrably increased at GFRs of 70. And now, we know that FGF 23 is a deleterious actor in this whole thing.

So one of the points I want to make is that one of the things to do is that we have to pay attention to this as geriatricians, primarily because, if we don't pay attention to this, we're missing a cofactor that increases the risk of death.

So let's talk a little bit about calcium homeostasis with aging. And I really enjoyed reviewing this, because it demonstrates some of the things that we have to be aware of.

One of the things that I was unaware of is that elderly skin makes less vitamin D than young skin. And this was demonstrated a long time ago by McLaughlin, article in 1985. They took skin and they cultured it. And then they looked at basically how well it produced the vitamin D precursors based on this.

So we have a decreased ability to make vitamin D. And then look at our patients. I mean, my mother-in-law has been institutionalized now for three or four years, and I think maybe she's seen the sun about six times. Although I do have to admit, I did see this large, yellow thing in the sky on the way down. I was unsure, since I live in Pittsburgh, what it was, because it was snowing at the same time.

But you know, this is decreased sun exposure. Our patients are homebound, as Dr. Weiner mentioned. They don't get out very much. There have a variety of co-morbidities. They're socially isolated. They may be institutionalized.

The other thing is that their diets, because of a variety of different issues, can be low in precursors for vitamin D. And another factor is that your vitamin D stores naturally decrease with age. You store less vitamin D. So your 25-hydroxy levels tend to fall.

The consequences of a low 25-hydroxyvitamin D, or osteomalacia in adults, rickets in children-- this is Tiny Tim's disease. This is what Uncle Scrooge did for Tiny Tim, was took him out of smoggy London and exposed him to sun so that his rickets could get better. He also had a distal tubular renal acidosis. But that's a topic for another talk.

And there are really a lot of associations that have been made about low 25 vitamin D levels-- muscle weakness, falls, that sort of thing. And then there is a huge number of things, as far as hair loss, diabetes, cardiovascular and metabolic systems affected by this. And one of the things that I have to tell you is, the data for that are not strong. If you want to bet the farm on something, bet the association of 25-hydroxy with fractures, falls, muscle weakness, and that sort of thing.

Dietary calcium excretion over the age of 60-- basically, the absorption in your gut decreases. And your intestinal calcium reabsorption, if you're 70 to 90 years old, is only a third of younger adults. And the other thing is, many of our patients live in food deserts, so they don't have ready access to food. And because of that, they don't have ready calcium sources in their diet.

So these are my recommendations. And there's a little bit of controversy about this. For those of you that read the *Annals of Internal Medicine,* this came out in 2015.

The US Preventative Services Task Force recommendation statement said that there was not enough evidence to recommend routine 25-hidroxyvitamin D testing in the general population in asymptomatic adults. The endocrine society came out and said, we should screen people that are at risk. And this is what I believe.

And I have to tell you, my entire population is at risk, because they're all kidney patients. And more than 60% of them are older than the age of 65. They upped the level for deficiency. It used to be a little bit higher, and they made it lower. Excuse me. So they made it less than 20 nanograms per mL.

And I have to tell you that I agree with the endocrine society. And the reason that I agree with endocrine society is, I believe that the geriatric population is a population at risk. And this is a group of people that we should be following closely, simply because they have, I believe, 30% reduction at minimum of their renal output, and they have decreased production of 1,25 vitamin D.

So my recommendations are what the endocrine society recommends. It's increase dietary intake. It's interesting, their recommendations for international units, which are lower than what I recommend. But if you're less than 70 years of age, they recommend 600 international units. If you're greater than 71, they recommend 800 international units. So that's one vitamin D3 that you can get. You can get they usually come in 1,000 unit increments.

Who knows the difference between D3 and D2? D3 comes from cod liver oil. It's an animal source. D2 comes from irradiated yeast. So if you have a patient that is a vegetarian, you should be giving them D2, ergocalciferol. If you have a typical Pittsburgher-- you know, meat-- 600 to 800 units of this

I tend to use cholecalciferol unless my patients are vegans. So what are the problems with this? Well, let's go on. Should we supplement calcium?

The recommendations right now are-- and you can see them in the table-- that if you're a 51 to 70-year-old male, average daily requirements are about 800, 1,000. Upper level of intake is 2,000. And then you can read the rest of the table.

I tend to go with a gram of elemental calcium a day. And the reason for that is that there's a U-shaped curve with calcium supplementation. If you go above two grams a day, the U-shaped curve increases your mortality. And the mortality is from cardiovascular mortality. So you can overdo a good thing. If you go below that, then you start to run into other problems with calcium deficiencies, such as bone fractures, increased hospitalizations, and so on.

I always recommend to my patients that they look at the back of the bottle. Because this is elemental calcium. This isn't calcium carbonate. You have to look at the total amount of counting you're getting. But for me, I usually tend to recommend around 1,000 milligrams a day.

My dialysis patients, I have a lot more freedom in, because I can vary the calcium in their dialyzate. And they're on binders anyway, which increases their calcium intake.

The goal for the 25-hydroxy is to get greater than 30 nanograms per mil. What does 25-hydroxy do? Remember the goddess of life. Klotho extends your life. 25-hydroxyvitamin D stimulates the production of Klotho. So this is a supplement that actually may improve your lifespan. The data about this are really exciting right now. Part of Klotho attaches to the membrane, but part of it gets cleaved off and becomes soluble and has a lot of immune cardiovascular benefits.

How many of you have run into problems checking 25-hydroxy levels in your patients? The last time I tried to do this more frequently than once a year, Medicare got all bent out of shape, and they would only let me do it once a year. So have others had that specific problem as well? So what I tend to do is-- there's this thing about supplementing in the winters, do this, do that. I just basically put people on standing supplementation and I'm done with it.

This is something that I did not do until I prepared for this talk. I usually don't start checking parathyroid hormone until my patients are about stage 5. But one of the things that came out of preparing for this talk was that, if you look at your renal insufficiency patients, they can have normal calcium levels, they can have normal 25-hydroxy levels, and they can have elevated parathyroid hormone levels. And that's deleterious to bone and so forth. So you should try to keep those levels down. And then I check calcium and phosphorus if the GFR is less than 60 mils per minute.

Now, looking ahead, one of the questions that you might want to ask me is, well should I be putting people on phosphate binders whenever they have GFRs of 30 and they have normal phosphates? Because if I bind phosphate in the gut, then I'm going to decrease production of FGF 23, right?

Well, we did it. The kidney doctors did that. And those data were presented at last year's American Society of Nephrology meeting, and it made absolutely no difference. So this is a story that is yet being written. That's why the skeleton is cogitating over there. And you'll see Klotho down at the bottom. I did have to get to mention that the story's not quite yet done for that

But this is my talk. I wanted to keep it as straightforward as possible. I think the most important talk was my recommendations that I made for calcium and vitamin D. I met my first goal. I finished ahead of time. I'd be happy to answer any questions if the speaker bureau here-- the Politburo-- is OK with that. Thank you.