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Secondary Hyperparathyroidism: A Hidden Danger in Chronic Kidney Disease

Announcer:
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[CHAPTER 1]

Dr. Cozzolino:
We know that patients with chronic kidney disease have a high risk for developing secondary hyperparathyroidism, or SHPT. If left untreated, SHPT can lead to bone fractures, cardiovascular problems, and increased mortality. So what are the underlying mechanisms of secondary hyperparathyroidism in chronic kidney disease? And what insights can clinical trial data provide that can help us better manage our patients with secondary hyperparathyroidism in non-dialysis CKD?

This is CME on ReachMD, and I am Dr. Mario Cozzolino.

Dr. Kielstein:
And I'm Dr. Jan Kielstein.

Dr. Cozzolino:
We have a lot to discuss today, so let's begin.

In the first chapter, we will look at the relationship between vitamin D status and secondary hyperparathyroidism in chronic kidney disease patients. Jan, to get us started, can you give us an overview of the pathophysiology of secondary hyperparathyroidism in CKD and how this disease can impact our patients' quality of life?

Dr. Kielstein:
Thank you for this question, Mario. This is a very important one. Our kidneys do exciting things. They eliminate toxins and metabolites, they eliminate water from the body, but they're also producing things. And one of the exciting products of the kidney is active vitamin D. And as kidney function declines, the production of active vitamin D also declines, and this represents a silent threat. Why is that so? Well, they're countermeasures. When you have a decrease in active vitamin D levels in the body, your parathyroid glands will produce more PTH [parathyroid hormone]. This, at first, makes sense because it makes sure that you will not suffer hypocalcemia. But if it persists, it destroys your bone structure, and it will eventually lead to calcification of your blood vessels. So controlling hyperparathyroidism is important to prevent CKD-MBD [chronic kidney disease-mineral and bone disorder]. That means the vascular calcifications, heart disease, and the bone disease that comes with chronic kidney disease.

The important thing to remember is that this process takes a very long period of time, years, sometimes decades, and this process is silent. There's no pain; there's nothing patients will report to you, or only a little bit of symptoms that occur very late in the course of the disease. So for that reason, we have to actively look for SHPT, and we have to think about treating it early before the negative consequences like bone fractures and stroke and heart attack occur.

And doing that, it is very important to not only measure vitamin D levels, but also to talk about the level we are aiming for and the tools

and the medication we should use for to reach an adequate vitamin D level, and at the same time prevent negative side effects like hypercalcemia and hypophosphatemia.

We have an animation about how a calcium-phosphorus imbalance can result in elevated PTH in CKD. Let's take a look.

[ANIMATION]

Announcer:
In CKD there is reduced renal capacity to convert 25-hydroxyvitamin D, or 25D, to 1,25 hydroxyvitamin D, or 1,25D, also known as calcitriol. Decreased 1,25D reduces absorption of calcium and phosphate, causing reduced serum calcium levels or hypocalcemia.Hyperphosphatemia, decreased 1,25D, and hypocalcemia stimulate the secretion of parathyroid hormone, or PTH. This causes secondary hyperparathyroidism or SHPT. A reduced glomerular filtration rate increases serum phosphorus and stimulates PTH and FGF-23. Hormone and mineral imbalances cause mineral and bone disorder which affects the skeletal and cardiovascular systems. While nutritional vitamin D is commonly used to treat SHPT because it increases 25D, it only inconsistently reduces PTH. Active vitamin D increases 1,25D and reduces PTH, but also increases FGF-23, phosphorus, and calcium. This increases the risk of hyperphosphatemia and hypercalcemia. Extended-release calcifediol, a novel prohormone of vitamin D, gradually increases 25D and 1,25D, which reduces PTH with minimal effects on calcium, phosphorus, and FGF-23.

Dr. Kielstein:
I hope that this animation made it clear just how important vitamin D is in maintaining the homeostasis of calcium, phosphorus, and PTH. But of course, before we can treat SHPT, we have to diagnose it. Mario, can you explain both the importance and the challenges of making an early diagnosis of SHPT?

Dr. Cozzolino:
Well, it is very important to have lab values early to make the diagnosis and manage secondary hyperparathyroidism. Looking at the guidelines, we should take care of any serum calcium, serum phosphate, PTH levels, and vitamin D levels early. And early means CKD stage 3 – 3A and 3B. So this is important to make the diagnosis of secondary hyperparathyroidism, because we know very well that the PTH starts to go up in this stage of chronic kidney disease.

And also, it is important because we can have patients with chronic kidney disease that can have resistance to current therapies, and current therapies of natural vitamin D, and all active vitamin D, such as calcitriol or vitamin D receptor agonist. So the message is that make diagnosis early and prevent and treat secondary hyperparathyroidism early. So, Jan, is there one key message from this chapter that you want to be sure our listeners heard?

Dr. Kielstein:
There are 5 points that are important to remember. SHPT has to be looked for; this is number one. And you have to measure at least 3 laboratory parameters: calcium, phosphorus, vitamin D, and the fifth one, the important one, PTH. So measuring those 5 things over time, and looking at the slope of those laboratory values, especially PTH is important. The second part of this key take-home message is another 5 – better, it's a 50 because right now we are aiming for higher vitamin D levels, and 50 ng/mL is what we previously thought 30 would be. So it's our new goal for vitamin D levels.

Dr. Cozzolino:
Thank you very much.

So in Chapter 2 we'll be reviewing the pros and cons of vitamin D therapies used in the management of secondary hyperparathyroidism in chronic kidney disease. Stay tuned.

[CHAPTER 2]

Dr. Kielstein:
Welcome back. In the first chapter, we covered the pathophysiology of SHPT and its association with CKD-MBD. Now let's dive deeper into how to treat patients with this disease. Mario, what are your thoughts?

Dr. Cozzolino:
Well, let's start from natural vitamin D. So we use this type of vitamin D to supplement patients that have a deficiency or insufficiency of 25-D levels. But there are limitations because in CKD stage 3 and 4, non-dialysis, the use of natural vitamin D can have an effect of the levels of 25-D. But several studies demonstrate that there are no effect on the control of PTH, so on the therapy of secondary hyperparathyroidism. So this is why, especially in the past, we use active vitamin D. We use calcitriol, we use paricalcitol, we use maxacalcitol. But looking at randomized clinical trials in CKD patients non-dialysis such as PRIMO and OPERA studies, we elaborate the risk, the potential risk for PTH oversuppression, hypercalcemia, and hyperphosphatemia. This is why the KDIGO CKD-MBD

guidelines emphasize that we should not use routinely active vitamin D for the treatment of secondary hyperparathyroidism in CKD patients stage 3 and 4.

So what we can do, we should start to use extended-release calcifediol. Why this is important? Well, this is important because we have a randomized clinical trial demonstrating that at the same time, patients with CKD stage 3 and 4 can have a very well control of PTH with an increase in 25-D levels without any changes in the lab value for serum calcium, serum phosphate, and importantly, for FGF-23, the fibroblast growth factor-23. So with this extended-release calcifediol, we can really follow the guideline suggestions and recommendations, because we can have a control of 25-D levels and the control of secondary hyperparathyroidism. So this is really the goal to reach for vitamin D based on clinical trials.

So, Jan, what's your goal for the level of vitamin D in your patients?

Dr. Kielstein:
This is a great question. As always, in treating patients with CKD, the goal is that the correction and the treatment of one factor goes in concert with all the other risk factors we treat. And this is important because we spend a lot of time and effort and advice to prevent phosphorus level rising by diet. But at the same time, we have used, in the past, active vitamin D to control the PTH, and this resulted in an increase of phosphorus. So I think your point that we now have the opportunity to stop the upward slope of PTH with extended-release calcifediol without paying the price of hypercalcemia and hyperphosphatemia, this is a great progress in the treatment opportunity we have. So changing the dynamics of PTH, and we only know the dynamics if we measure PTH and all the other compounds at a regular level; this is important.

So, Mario, what would be your key messages from this chapter regarding the management of SHPT in non-dialysis CKD patients?

Dr. Cozzolino:
It is important to control patients with CKD stage 3 and 4. And the first thing is to check for CKD-MBD values, calcium, phosphate, PTH, and 25-D. This is the first point. And then try to prevent and treat secondary hyperparathyroidism. So to prevent, we should start early because we know that the PTH levels can go up very early, CKD stage 3A, and then start with the right therapy. So instead, to give 2 different therapies, natural and active vitamin D, we can use extended-release calcifediol that can decrease PTH and increase 25-D level without modification of serum calcium levels and phosphate levels.

Dr. Kielstein:
Well, thank you, Mario, you summarized it very nicely. I still want to add one more thing, because we should not forget patients after renal transplantation. And I think extended-release calcifediol gives us the opportunity to also treat those non-dialysis CKD patients that sometimes need treatment with PTH-suppressing medication. So I think even this population might benefit quite a bit from extended-release calcifediol.

In Chapter 3 we will take a look at the current practice guidelines and the application of clinical trial data in the medical setting. Stay tuned.

[CHAPTER 3]

Dr. Cozzolino:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Mario Cozzolino, and here with me today is Dr. Jan Kielstein. We are discussing the vascular calcification effects of mineral bone disorders associated with chronic kidney disease and secondary hyperparathyroidism.

Welcome back. In the second chapter, we discussed the treatment options and vitamin D goal for patients with secondary hyperparathyroidism, especially in stage 3 and 4 non-dialysis chronic kidney disease. Jan, let's get a little bit more specific now. What should physicians keep in mind when developing a treatment plan for their patients?

Dr. Kielstein:
Extended-release calcifediol is not an acutely working drug. So it's not a catecholamine for the bone. It is a drug that needs time, and the pathophysiology and the pharmacokinetics and dynamics are aimed to have a sustainable effect on the PTH level in a way so that counteractive metabolism is not happening. Because this is true for vitamin D that is immediately released. You elevate vitamin D levels very abruptly, but at the same time you trigger enzymatic processes that will again metabolize vitamin D, so you induce counteraction. And extended-release calcifediol sneaks in very slowly but surely, and then has its effect on PTH.

So the current clinical practice guidelines' targets for vitamin D levels are maybe a little bit on the low side, as we have discussed previously. And we need to review those practice guidelines that were written at a time where extended-release calcifediol was not

available. So in my daily practice, this is the way I look at this problem. If I see, under the current treatment, the steady increase of PTH, this is the point in time where I think about using extended-release calcifediol. I also think about this if other treatments lead to hypercalcemia or hyperphosphatemia. So we always look at several lab data, and this helps us to guide therapy.

Dr. Cozzolino:
Thank you very much. Very important information, and I think that we should think about our patient profile and give suggestions in real practice how to manage secondary hyperparathyroidism.

So my mind, there are 3 different types of patients. We can have CKD patients stage 3 and 4, non-dialysis, in which I mean serum PTH is in the normal values and also calcium and phosphate are okay, and 25-D levels are normal, so we don't need to use any treatment. But unfortunately, we do not have many patients that are with normal values as CKD stage 3 and 4. So the second patient that I have in my mind is a patient in which 25-D levels are low, but PTH is still normal, and calcium and phosphate are normal. So in those patients, independently by renal function, we can start to use natural vitamin D such as cholecalciferol, for example. But then, in our patients with CKD stage 3 and 4, the majority of them, they have high PTH levels and low 25-D. And still in CKD stage 3 and 4, serum calcium and serum phosphate is in the normal range. But we don't want to create the increase in calcium and phosphate. So this is why we can start with extended-release calcifediol and to look at patients to control PTH, to control 25-D levels without increasing calcium and phosphate. And also, and only in the late stages of CKD 5, we can eventually when PTH is extremely high, start with active vitamin D.

So before we wrap up, Jan, do you have any final take-home messages for our listeners?

Dr. Kielstein:
Well, I think, Mario, you wrapped it up very nicely. I have an additional thought. And the additional thought is that it really makes sense to early on invest into controlling risk factors, risk factors that turn out to be silent killers in the end. Because what does it mean to prevent or positively influence CKD-MBD? This translates into an elderly patient not having a femoral fracture, losing independence, being forced to go into a nursing home. Early intervention translates into less cardiovascular events and this is also important for the growing population of renal transplant recipients, because non-dialysis CKD also means post-kidney transplant patients that even have a higher risk of bone-related problems due to the steroid treatment that comes with the renal transplantation.

Dr. Cozzolino:
Thank you, Jan, for these final take-home messages.

So unfortunately, that's all the time we have today. So I really want to thank our audience for listening in and thank you, Jan, for joining me and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Kielstein:
Well, thanks for having me. It was a pleasure, and I hope all the listeners now feel encouraged to treat SHPT.

Announcer:
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