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The Pathophysiology of sHPT: Understanding the Calcium-Sensing Receptor Pathway

Announcer:
You're listening to ReachMD. This medical industry feature, titled "The Pathophysiology of sHPT: Understanding the Calcium-Sensing Receptor Pathway"is sponsored by Amgen.

Dr. Russell:
Welcome to today's program on ReachMD. I'm Dr John Russell. Today on the program I have the opportunity to talk with experts in the field of nephrology to explore the pathophysiology of secondary hyperparathyroidism, which is also known as sHPT, in patients with chronic kidney disease.

I have two guests joining me today for this discussion. First up is Dr Kevin Griffiths, a nephrologist from Washington, DC. Dr Griffiths, great having you with us today!

Dr. Griffiths:
Glad to be here.

Dr. Russell:
Also joining us today is Anna Chambers, a renal dietitian from Chattanooga, Tennessee. Thanks for being with us, Anna.

Ms. Chambers:
It's my pleasure, thank you.

Dr. Russell:
Today's topic is really important. You're here today to share some insights into secondary hyperparathyroidism. What interests you about sHPT, Dr Griffiths?

Dr. Griffiths:
Well, I have great interest in sHPT. Our kidneys play a critical role in regulating calcium and phosphorus homeostasis. When the kidney function decreases calcium metabolism is disrupted, which leads to increases in PTH secretion and the development of sHPT. When these multiple electrolyte disturbances occur, sHPT becomes a very complex disorder not only to understand but also treat in patients who suffer from CKD who are on hemodialysis.[1]

Dr. Russell:
From our previous conversation, I understand these systemic issues translate to real dangers for patients.

Dr. Griffiths:
Yes, sHPT represents an adaptive response to maintain serum calcium levels and control calcium metabolism systemically in patients with impaired renal function.[1] It's characterized by persistent elevations in PTH as a consequence of inadequate calcium signaling through the calcium-sensing receptor, or CaSR.[2]

Additionally, these elevated PTH levels affect bone turnover.

In recent years sHPT is now considered a component of CKD-MBD, which is a systemic disorder that can include abnormalities in bone turnover, calcium, phosphorus, PTH, or vitamin D metabolism.[3]

Dr. Russell:
So, Dr Griffiths, are those the aspects of sHPT management that make it particularly challenging?

Dr. Griffiths:
They definitely are. PTH is primarily a calcium-regulating hormone, but also affects phosphorus and vitamin D metabolism.[4]

PTH is contributing to the elevations in serum phosphorus due to the release of phosphorus from bone.[5]

Abnormalities in phosphorus and calcium metabolism are reasons to effectively manage the disorder. If the labs are not controlled, it complicates the patients' clinical course.[6] So, you cannot consider these things independently because they frequently change together.[7] And this needs to be considered in clinical decision making.[6]

Dr. Russell:
You're listening to ReachMD. I'm your host Dr John Russell and I'm talking with nephrologist Dr Kevin Griffiths, and Anna Chambers, a renal dietitian, who specialize in managing adult patients with chronic kidney disease and secondary hyperparathyroidism.

Dr. Russell:
Well, it's obviously important to help patients understand what's happening so they believe in their treatment plan. How do you do that, Anna?

Ms. Chambers:
When we discuss sHPT we are using biochemical markers to assess the severity. We track them over time to determine if the management is working or if the disease is progressing.

However, when talking to asymptomatic patients, we tell them how these trends are going andby being transparent with these lab values and by constantly reinforcing that if the patients do not keep their lab values within the normal range, they could be in danger. Patients appreciate the transparency and honesty, which helps to develop a good bond of trust.

And patient's trust of their nephrologist and care team in monitoring their lab values makes it easier to convince the patient to take the appropriate medications, which ultimately leads to better management of this disorder. The challenge of course is to keep patients in sync with taking their medications, that they maintain proper levels and help avoid large, out-of-control movements in the lab values that may prove detrimental to their health.

Dr. Griffiths:
Well, that's a great way to frame it, Anna. When we choose a treatment option, we need to think of the pathophysiology in terms of the lab value, specifically how PTH affects the calcium-sensing receptor, or CaSR, which is the key regulator of PTH release.[1]

Dr. Russell:
How has the understanding of sHPT pathogenesis evolved?

Dr. Griffiths:
Our understanding of factors that contribute to sHPT continues to evolve and there are a couple of points that are worth mentioning. First, we now appreciate that parathyroid gland hyperplasia can result in downregulation of the CaSR.[2]

Thus, as the PTH gland enlarges, there are less functional CaSR receptors, leading to less calcium absorption at the gland level, leading to more PTH release. Downregulation of the calcium-sensing receptor contributes to lack of inhibition of the PTH gland and, ultimately, more secretion of PTH in sHPT.[2]

Dr. Russell:
The calcium-sensing receptor is something we don't hear much about. Can you tell us a little more about it?

Dr. Griffiths:
Yeah, in essence, the calcium-sensing receptor is the key regulator of PTH secretion and it plays a pivotal role in the development of sHPT.[1]

For a while, a lot of investigation was focused on the role of the vitamin D receptor. Vitamin D analogues, acting through vitamin D nuclear receptors, regulate PTH mRNA expression, but do not directly affect PTH secretion. High phosphate levels contribute to the development and severity of hyperparathyroidism, but the factors that mediate these effects remain to be determined.[1]

The calcium-sensing receptor differs fundamentally from the vitamin D receptor. Studies done in genetically modified mice demonstrate

that signal transduction via the CaSR is an important determinant of parathyroid cell proliferation and parathyroid gland hyperplasia.[1]

So think about it like this in terms of the interplay. When calcium levels are low, as occurs as a consequence of declining kidney function, the calcium-sensing receptor is inactivated. In sHPT, chronically inadequate activation of the calcium-sensing receptor leads to persistently elevated PTH. This in turn leads to increased bone turnover, and release of calcium and phosphorus into the bloodstream.[2,4,8]

Dr. Russell:
That's fascinating and complex. Anna, what's your take?

Ms. Chambers:
Well, I'm aware of the CaSR and understood it was involved but hadn't heard its role described like this in terms of its implications. Given these factors, it's clear why it can be so challenging to manage sHPT.

Dr. Russell:
So is it fair to say that the calcium-sensing receptor has a prime role in the development of sHPT, Dr Griffiths?

Dr. Griffiths:
I think it definitely does, but as we discussed, there is a lot of interplay involved.Another important factor being explored in sHPT is the role of fibroblast-growth factor-23, called FGF23.

We've understood for some time that FGF23 is an important phosphate-regulating hormone. The serum levels of FGF23 become elevated early in the course of CKD, which serves to maintain normal serum phosphate levels. However, when renal function becomes severely impaired, the elevated FGF23 levels adversely affects the production of calcitriol 1-25D. With decreased calcitriol levels, there is now inefficient intestinal calcium absorption that contributes to the development of sHPT.[3]

Dr. Russell:
Well, for our listeners who are managing sHPT, what are some key points to keep in mind?

Dr. Griffiths:
I'd say the key takeaways are that PTH, phosphate, and calcium are interdependent and should be considered together.[7]

Strategies aimed at a single parameter can have unintended effects.[6,7] For example, excess exogenous vitamin D can lead to hypercalcemia[2,9] so replenishing vitamin D stores while avoiding hypercalcemia is important.[6,10]

Also, as sHPT progresses, several concomitant therapies may often be used.

Dr. Russell:
Alright, excellent advice, Dr Griffiths. I greatly appreciate you taking the time to be with us today!

Dr. Griffiths:
Any time. Thank you for putting focus on an area that truly needs it.

Dr. Russell:
And, Anna Chambers, thank you so much for joining us today. Do you have any parting thoughts?

Ms. Chambers:
Thanks, it was great to be here. I think I'll take away from this the interdependent nature of the processes that contribute to sHPT. And it just seems really fitting, because patients can't overcome this alone. They really need their treatment team to be united and heading down the same treatment pathway if they are to achieve that important balance we talked about.

Dr. Russell:
Thank you for listening to what was a very enlightening discussion. I want to thank renal dietitian Anna Chambers, and Dr Kevin Griffiths, for their time and insights in helping us understand more about the role of the calcium-sensing receptor in the management of secondary hyperparathyroidism.

Announcer:
This Medical Industry Feature was sponsored by Amgen. To learn more about Amgen, please visit Amgen.com. And if you missed any part of this discussion, please visit ReachMD.com. This is ReachMD. Be Part of the Knowledge.

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