

## Hyperparathyroidism

2019

{Music}

Host: Welcome to AACE's Bone Resource Center Podcast Series. This podcast series is intended for endocrinologists and other interested clinicians that treat patients with bone disorders. Each podcast will feature experts in the field discussing diagnosis and management of different bone-related disorders.

Dr. Vin Tangpricha: Welcome to this podcast on hyperparathyroidism. Today we have a guest speaker, Dr. Elizabeth Holt, FACE, and also member of the AACE/ACE Board of Directors. She practices with the Raleigh Endocrine Associates in Raleigh-Durham and she's also Assistant Consulting Professor of Medicine at Duke University. Welcome, Elizabeth.

Dr. Elizabeth Holt: Thank you.

Dr. Vin Tangpricha: Dr. Holt, can you tell us a little bit about yourself and your practice in Raleigh?

Dr. Elizabeth Holt: Sure. So, I practice at Raleigh Endocrine Associates. We're a private practice general endocrinology practice where we see adults with all sorts of endocrine disorders.

Dr. Vin Tangpricha: You must see a lot of patients with hyperparathyroidism.

Dr. Elizabeth Holt: Yes, I see quite a few.

Dr. Vin Tangpricha: Tell us about hyperparathyroidism. Is this something that people should be worried about? Is it a common disorder?

Dr. Elizabeth Holt: So, it's becoming more common over the years. That actually may be a phenomenon of more broad spread biochemical screening; most people are getting general chemistry panels that include calcium levels and we detect hypercalcemia before it becomes symptomatic. And in the evaluation often we find primary hyperparathyroidism which is the most common cause of hypercalcemia.

We also find it sometimes in people who have osteoporosis when we're trying to look for underlying causes of osteoporosis and we find that the person has hyperparathyroidism.

Dr. Vin Tangpricha: That's interesting. It sounds like hyperparathyroidism might be mostly a silent condition. Would you say that?

Dr. Elizabeth Holt: It seems to be that way now. Historically we didn't discover hyperparathyroidism until patients became symptomatic. And that's how we were taught in medical school, that patients presented with the classic symptoms described by Fuller Albright of stones, bones, moans and groans, meaning they had kidney stones.

They had skeletal fractures or findings on x-rays of cysts in the bones or bone resorption and they would have musculoskeletal pains and oftentimes some neuropsychiatric symptoms of fatigue. And so, they had that type of presentation; usually the hypercalcemia was fairly marked at that time in order to cause those symptoms.

But again, nowadays that we're doing biochemical screening and finding people with more mild forms of hypercalcemia, we're not seeing those classic symptoms and we have to actually do a little bit of digging to find out if people are truly symptomatic or not.

Sometimes the symptoms can be a little more subtle with some increased urination or some constipation, there might be kidney stones that haven't necessarily become symptomatic yet, there might be calcium deposits in the tissues of the kidneys called nephrocalcinosis, there might be osteoporosis which you know is very common but may not be recognized as being a consequence of hyperparathyroidism.

Dr. Vin Tangpricha: It sounds like most people come in without any symptoms. How do you think they get screened in the first place or how do they present to you?

Dr. Elizabeth Holt: Oftentimes they're referred to me because their primary care physician just on routine annual testing did a chemistry panel and they were found to have a mildly elevated calcium. And then also patients are referred to me for another reason or they're one of my own patients and I notice the hypercalcemia as I'm doing evaluations for other things. Or again, just on a general routine annual chemistry panel and then we go pursuing it and find out that they have hyperparathyroidism.

Dr. Vin Tangpricha: So, let's take an example. You have a patient who's referred to you with an elevated calcium. Does that patient have hyperparathyroidism?

Dr. Elizabeth Holt: That's a good question. So, the odds are that that person does; it's the most common cause of hypercalcemia. But certainly there's a very long list of other causes of hypercalcemia.

So, when we have somebody who presents with hypercalcemia, one of the first tests we do is, of course, to repeat the calcium level, but also to check a parathyroid hormone level.

Now, sometimes somebody appears to have hypercalcemia and they actually don't. Calcium is a highly protein-bound substance and changes in serum albumin levels can actually elevate or decrease the total calcium level in the bloodstream.

So, when I see somebody who is referred to me with an abnormal calcium level, I look at the albumin level on that chemistry panel. And there are online calculators where you can do an easy mathematical correction for the serum albumin level if it's higher or lower than 4.0 and do a calculation we call an albumin-corrected total calcium.

Now, if that albumin-corrected total calcium is still elevated, then we want to then confirm that that person has hypercalcemia and proceed with the workup. We could also do a serum ionized calcium level which will then just look at the unbound fraction of calcium to see if the person is hypercalcemic or not.

Dr. Vin Tangpricha: So, I see. There could be issues with calcium. Maybe a person might have, like, nephrotic syndrome and their calcium might be even normal and with an albumin that's low, you're saying that they could, in fact, have hypercalcemia.

Dr. Elizabeth Holt: Exactly. Sure, the mathematical formula would correct for that. What I am more likely to see is somebody whose total calcium is elevated but their albumin is also elevated; not necessarily above the top of the normal range, but above 4, within the upper half of the normal range.

And when we do the mathematical correction, a calcium that might have looked like it was 10.5 or 10.7 with the math correction might actually come down to 10.1 or 9.9 and actually be normal and then that person actually does not have hypercalcemia and the evaluation stops there.

Dr. Vin Tangpricha: So, that appears to be a very important point to confirm that they have hypercalcemia. I understand that there's also issues with the parathyroid hormone testing. Can you tell us about that?

Dr. Elizabeth Holt: Sure. So, intact parathyroid hormone is the test that should be ordered and it's turned out that biotin supplements that the patient might be taking can interfere with measurement of parathyroid hormone in the test tube and it might actually make the parathyroid hormone level look lower than it is.

So, somebody might come in with true hypercalcemia, I draw a parathyroid hormone level and it's not elevated and I might say, "You don't have hyperparathyroidism." But if they discontinued the biotin supplement for several days and we redraw the blood, it was just laboratory interference in the test tube—nothing in the bloodstream, just in the test tube—and we find that they do have hyperparathyroidism.

So, that's always a question to ask your patients. And oftentimes they don't realize that a supplement they may be taking that's labeled for hair or skin actually contains biotin. Now, the amount of biotin that's in a multivitamin generally is not enough to cause that assay interference.

Dr. Vin Tangpricha: Yes, I've heard a lot about this biotin impacting endocrine testing. So, I've myself in my practice started to ask questions about that. So, that's a very important point you bring up.

Let's say the person comes in, they have elevated calcium, you do the formula you suggested and correct it for albumin, it's still high and you've ruled out any biotin intake and they have elevated parathyroid hormone. Is that now enough to say that they have parathyroidism?

Dr. Elizabeth Holt: It is. Now, it could also be that they have vitamin D deficiency which would physiologically elevate the parathyroid hormone level. Now, they would have then both, because a vitamin D deficiency should not cause hypercalcemia. But the parathyroid hormone level may be higher than it otherwise would be because they're vitamin D deficient.

So, we would pause on finalizing that diagnosis until we correct the vitamin D deficiency and get that vitamin D level over 30 nanograms per milliliter. Some suggest even in this situation to try to get it over 40 just in order to see how far down the parathyroid hormone level comes before you finalize that diagnosis of primary hyperparathyroidism.

Dr. Vin Tangpricha: So, I know a lot of endocrinologists will do additional testing ruling out genetic conditions causing elevated parathyroid and elevated calcium. Is that something you do in your practice as well?

Dr. Elizabeth Holt: Well, there can be genetic mutations that cause primary hyperparathyroidism. We can certainly screen with a family history and see if anybody else in the family has that. Hyperparathyroidism can be the sole manifestation of a mutation or it can be part of a multiple endocrine neoplasia syndrome.

And so, genetic testing I don't necessary do it on all my patients because most of the time it's sporadic and not part of a mutation and we have to see the cost to the patient of genetic testing which is changing and evolving all the time.

But certainly if there is any hint of a family history of hyperparathyroidism, it's worth exploring that.

Dr. Vin Tangpricha: I know many endocrinologists also worry about FHH, familial hypercalcemia hypercalciuria, where there's a mutation in the calcium-sensing receptor where the set point is set higher. Is that something that we should look at as well?

Dr. Elizabeth Holt: Well, it's certainly something I consider especially if somebody's hypercalcemia dates back decades. But FHH is, as you said, a genetic disorder; people are born with it, it's not acquired. And usually it has a fairly high penetrance and now that we're doing, again, chemistry panels fairly routinely, if you have somebody who has a history of normal calcemia and especially if it's a postmenopausal woman, it's almost always hyperparathyroidism rather than FHH.

FHH is actually fairly rare, so we do consider it; and we can screen for it by looking at the fractional excretion of calcium by measuring calcium and creatinine in 24-hour urine and serum calcium in creatinine and comparing the fractional excretion rate. But there's overlap with primary hyperparathyroidism and FHH, so even that's not 100% conclusive.

Dr. Vin Tangpricha: So, you might be more reassured if the patient had normal calcium maybe five years ago and now has high calcium that this person indeed has potentially hyperparathyroidism versus FHH then?

Dr. Elizabeth Holt: Yes, that would be correct.

Dr. Vin Tangpricha: So, let's say you have someone you've – has high calcium, high parathyroid hormone, it seems to be something that's new in the past five to ten years, are we now just sending them to surgery to remove that gland? Or what is your decision-making process for that?

Dr. Elizabeth Holt: So, that's a good question because we don't necessarily need to operate on everybody. As we follow people and look at the natural history of primary hyperparathyroidism, some people don't progress; they have very stable calcium levels and remain asymptomatic over a number of years.

So, there have been consensus panels that have met to come up with guidelines for when we can follow somebody medically and when we might want to consider surgery. So, we need to do an evaluation.

One evaluation is to assess for symptoms and so I talked a little earlier about the various symptoms that people can have, but we also want to look for what we call symptoms but are silent symptoms, like a decreased bone density or hypercalciuria; that may not be something where people actually present with symptoms, but it still counts as "symptomatic hyperparathyroidism."

So, when we have somebody who presents with confirmed primary hyperparathyroidism, on the initial screening we'd like to look at not only calcium and parathyroid hormone levels, but phosphate levels, maybe alkaline phosphatase, vitamin D level, 25-hydroxy vitamin D level, we'll get a 24-hour urine to evaluate for total calcium; if it's markedly elevated over, say, 400, then we'd want to also send the urine to look for markers of kidney stone formation.

We want to do a bone density test. Now, in people with hyperparathyroidism, interestingly, the cortical bone in the distal one-third radius often is the first



bone to be affected by primary hyperparathyroidism. So, when I order a DXA scan in my patients who have hyperparathyroidism, I specifically request not only spine and hip, but also the one-third radius and I make sure that I look at that one-third radius result when I decide whether that person has a normal bone density or not.

We also can do a lateral vertebral assessment with the DXA machine. It's a – which most DXA machines can do to look for any unsuspected spinal fractures. And then some people can do trabecular bone scores if they have that software on their DXA machine.

And then we also want to look a little bit more in-depth for nephrocalcinosis or nephrolithiasis by imaging the kidneys either with an ultrasound or plain radiograph or a CT scan.

Dr. Vin Tangpricha: So, it sounds like you decide if someone needs surgery based on whether or not they have end organ damage, either bones or existing kidney stones or issues with kidney function. If they don't have those, what do you do with those patients?

Dr. Elizabeth Holt: So, if they don't have those – and there's additional criteria, so if somebody's younger than age 50, even though we know there can be prolonged stability without progression, there's a lot of decades to go, hopefully, if somebody's under age 50 at presentation. So, often we will send those people for parathyroid exploration, parathyroid surgery, even if they don't have any of those findings.

Another reason to send somebody to surgery is that the serum calcium is persistently over 1 milligram per deciliter or higher above the top of the

normal range. So, if the top of the normal range, let's say, is 10.2, if they're persistently 11.2 or higher, we would want to send that person to surgery.

And then if the person chooses to have surgery, that would be a reason to send that person to surgery because otherwise they need to have ongoing medical monitoring to make sure that these complications don't develop.

Dr. Vin Tangpricha: I see. That sounds like a reasonable approach. If someone's very, very young, there's a higher chance that they're going to develop end organ damage and so that person would be benefitting from surgery early, I see. Is that correct?

Dr. Elizabeth Holt: Correct, yes.

Dr. Vin Tangpricha: What about the patient who absolutely does not want surgery, that they're either not ready to make that decision or just are opposed to surgery? What do you do about those patients?

Dr. Elizabeth Holt: So, if they meet the criteria but don't want to have surgery—of course we're not going to force anybody to have surgery—so, we would continue to follow them medically, just like the people who don't meet the criteria and don't care to have surgery, so we say, “Okay, well, that's fine. We can follow you medically,” we follow them the same way.

And so that would mean that we monitor the serum calcium level, albumin-corrected serum calcium level, at least once a year if not twice a year, that we assess with a DXA scan; remember, all three sites: the one-third radius as well as the spine and hip at least every two years, if not annually.

And we also question them about maybe vertebral fractures: Have you had back pain? Have you had a loss of height? And if they have, then we need to assess either with a lateral vertebral assessment or with a spine x-ray for vertebral fractures.

And then we also want to monitor their serum creatinine. If the EGFR starts to decline, if it goes under 60, that would then meet your threshold for wanting to send somebody for surgery. Or if they develop kidney stones or, again, develop marked hypercalciuria over about 400 for 24 hours.

Dr. Vin Tangpricha: Is there a medication that someone could use to treat their hyperparathyroidism?

Dr. Elizabeth Holt: It depends on what the manifestation is. So, if you're trying to treat a low-bone density, alendronate, the oral bisphosphonate, actually has good data at preserving or improving bone density in patients who have primary hyperparathyroidism, but it doesn't affect the serum calcium levels.

If you have somebody who has hypercalcemia and is symptomatic from that but can't have surgery. let's say they have medical contraindications for surgery or they've had prior neck surgery and it would be very difficult to find their parathyroid glands or they just don't want to have surgery but they have this hypercalcemia, there's a medication called cinacalcet that can be given that will help lower the serum calcium level and people can stay on that long term, but it doesn't affect bone density.

Dr. Vin Tangpricha: So, at least that's some – that's your other options for someone who doesn't want to have surgery, then.

Dr. Elizabeth Holt: Right. We also need to talk to people about their calcium and vitamin D intake. It turns out that if somebody restricts their dietary calcium thinking that that will help treat the hypercalcemia, they can actually then stimulate the parathyroid glands to increase parathyroid hormone secretion because those parathyroid glands somehow seem to sense that the dietary calcium intake is low.

So, we want to counsel our patients that they should actually meet the Institute of Medicine's recommended daily dietary calcium intake, of course depending on gender and age, in order to avoid that extra stimulation to the parathyroid gland.

They also should be sure that they get their vitamin D levels monitored and treat any vitamin D deficiency that might be present because, again, that will stimulate the parathyroid glands to increase parathyroid hormone secretion which can have adverse skeletal consequences.

So, a pretty safe vitamin D intake would be 1,000 International Units of vitamin D3 once daily.

Dr. Vin Tangpricha: So, that might sound somewhat counterintuitive for a patient to hear that they have high serum calcium in their blood to continue to take calcium. And so, how do you explain that to a patient?

Dr. Elizabeth Holt: Well, I tell my patients I don't necessarily want them on calcium supplements but that I don't want them to restrict dietary calcium intake. And I will explain to them that the parathyroid glands respond to calcium intake and, if it's deficient, that will actually stimulate their parathyroid glands to secrete parathyroid hormone in higher quantities, again, which can then have adverse effects on their bones.

Dr. Vin Tangpricha: Now, there's a lot of new imaging techniques to image the parathyroid gland. When do you image the parathyroid gland and what is the rule for imaging?

Dr. Elizabeth Holt: So, the diagnosis of hyperparathyroidism is a biochemical diagnosis based on blood tests. So, I don't image to help make the diagnosis. Once I've made the diagnosis, if we've decided to observe medically and not proceed with surgery, there's no real reason to image.

So, imaging plays a role as preop localization for the surgeon. Most people have four parathyroid glands in the neck; they're called parathyroid glands because they're located near the thyroid: there's usually two on the left and two on the right. But the location can be a little bit variable and sometimes there can be three glands, sometimes there can be five glands.

And the surgeon would prefer to have an idea ahead of time as to the laterality of the abnormality: Are they going to go in and focus on the left side of the neck or the right side of the neck? Or does this person have multiple glandular disease? And it might alter the surgical approach and, of course, the time that they schedule in the operating room.

So we will often then want to do preoperative localization. So, that can include a high-definition ultrasound and that's often available in the endocrinologist's office or in your parathyroid surgeon's office. The surgeon I work with locally prefers to do his own ultrasounds. So, while I could do an ultrasound as well, I will let him do it since he's going to do it anyway and he's the one operating so he would like to see it personally.

But there's also other imaging. Sestamibi scans can be done or even CT scans or four-dimensional CT scans can be done.

So, the test that's picked actually depends on what's available. There can be idiosyncratic techniques to finding that parathyroid gland. They're not always markedly enlarged and so you want to use your local expertise; if somebody has a lot of experience with ultrasound and not much with 4D CT, then, in that community you would want to order an ultrasound and vice versa.

And of course the most important prelocalization technique is to localize that expert parathyroid surgeon.

Dr. Vin Tangpricha: Yes, I agree. That's really important to find that surgeon or the parathyroid gland that's hyperfunctioning because it's – they're very small.

So, this has been a great conversation today, Dr. Holt. I was wondering if you had any last-minute take-home points or key messages from your talk today?

Dr. Elizabeth Holt: Sure. So, I think if we go back to the beginning, one of the most important things to be aware of is to actually recognize when hypercalcemia exists. I see a fair number of patients in my practice for reasons totally unrelated to hypercalcemia who when I look at their labs I see that they have hypercalcemia, I request labs going back in time and see they've actually had it for several years and nobody ever addressed it.

And because of the potential renal and skeletal consequences of hyperparathyroidism, we do want to make sure that we recognize it and diagnose it appropriately.

Dr. Vin Tangpricha: Thank you. Well, it's been a very good conversation. I hope that the audience enjoys this podcast and hope that you tune in for our future podcasts all focused on different disorders of bones.

So, thank you, again, Dr. Holt for participating and I hope to see you on a future podcast.

Dr. Elizabeth Holt: Thank you.

{Music}

Host: Thank you for listening to AACE's Bone Resource Center Podcast Series. You may find more information and resources about the diagnosis and treatment of bone-related disorders on AACE's Bone Resource Center along with a transcript of this podcast.

THE END