

SPEAKER:

So what are the indications for treating this? So now you found the high calcium level and the high PTH level. Maybe the patient has some symptoms. May they don't. It doesn't really matter. All patients with primary hyperparathyroidism should be seriously considered for treatment.

Why is this? It's very simple. There's a lot of pretty robust, large-scale population studies that have been done in various populations from Europe to the US to Asia. And they found that primary hyperpara, if left untreated, is associated with significantly worse outcomes on multiple variables. We'll go over that a little bit in a few slides.

But generally, it makes you physiologically older than you should be. And in the long run, it probably contributes to you dying earlier than you also should. So we'll go through that a little bit.

Oh, I'm sorry. So the specific ways in which people have found that primary hyperpara can worsen outcomes is it decreases bone mineral density and increases the fracture risk in individuals, increases the risk of kidney stones up to five times out of the general population-- that's male and female.

It leads to progression in the severity of hypercalcemia. So people who may have had mild hypercalcemia, in about 15% to 20% of the time, will go and develop the type of calcium levels that you should be really worried about on an acute basis. It drastically worsens quality of life overall-- muscle strength, things like that. And then lastly, we'll go into some of the risk factors for cardiovascular disease.

I'm sorry for the busy, small-print slide. Now, most of these, again, are being caught at earlier, milder stages. So the endocrine and the endocrine surgical communities have had ongoing discussions about whether or not there are subsets of patients that can be safely observed. And so since 1990, it started at the NIH. Then it became international.

There have been multiple workshops of experts trying to determine, are there a few criteria where a few patients can fall into where it's actually OK not to immediately offer surgical treatment? And they found that in folks that are on the older side, if they didn't have frank osteoporosis yet on bone density scans, that they didn't have kidney stones, et cetera, then it may be OK to safely observe them.

The problem with these guidelines is that people will take that table, which is actually usually available on Google or something. And then there's this mental effect that happens. When you see guidelines, you say, well, you've got to check a box. Otherwise, you shouldn't be doing surgery.

And that's really not what the founding authors intended. The default treatment for primary hyperparathyroidism is treatment. It's not necessarily to say, default is, just follow this. It's not going to bother you for the rest of your life.

So why is this, even in patients who, quote, "don't have symptoms" at the time that they're presenting with disease? Even mild disease can cause significant problems. There's no correlation, actually, between one's absolute calcium level and the development of any of those symptoms or the sequelae that I talked about.

So why is this? It's because normal reference ranges for calcium are 8.8 to 10.2. That's based on entire populations that have nothing to do with your specific calcium level that's right for you. So if my normal calcium should be at 8.9 and I get a calcium level that's 10, even though that's in the normal reference range, that's actually quite hypercalcemic for me. And that can cause all of those other sequelae that we talked about even though someone may say, on a primary care screening lab, that everything is fine. So it's really easy to not have those antennae up for milder-disease patients.

Another way that people are talking about, quote, "mild or asymptomatic" disease is trying to return this as an early or insidious onset disease, because it's a chronic disease that has to start somewhere. But it's eventually potentially going to go into places where you don't want it to go with respect to long-term outcomes.

So again, I talked about a lot of these large population-based observational studies. Unfortunately, we can't do too many randomized controlled trials on something like this. It takes too much money for way too much of a follow-up time. There's no drug company or any funding agency that's going to fund an RTC of that scale.

But we have good surrogate data with these larger population-based studies. One of these was in Scotland. There was a group that studied 2,500 patients in a population in the region of Scotland, and they followed them over 20 years.

And in those 2,500 primary hyperpara patients, they found that basically, every long-term, bad outcome was higher in that group compared to the rest of the population. And that's after controlling for confounding variables, including age, other comorbidities, et cetera. And these include everything from overall mortality; fatal and nonfatal cardiovascular events; stroke, in reference to the previous speaker; kidney stones; fractures; psychiatric disease; hypertension. There's even maybe a slight increase in the risk of various types of solid tumors, although that's the weakest association on that graph.

So I hesitate to use the term "silent killer" because it sounds sort of hyperbolic, but this may truly be the case for primary hyperpara. Because it's a benign disease, and yet, it's causing all these problems.

So what's the treatment? Conflict of interest-- I'm a surgeon, but surgery really is the only method of cure today. There are some medications that are being developed right now to try to treat it. But at the moment, there is no evidence that those medications actually do anything other than slightly lower the calcium level. They don't reduce the fracture risk. They don't reduce kidney stone prevention, all those other real important markers.

So how is parathyroidectomy or parathyroid surgery beneficial? Let's go through some of the specific disease outcomes that are being benefited. First, it's bone density-- important.

This is a study from Columbia where they followed people for over 15 years with both untreated and treated parathyroid patients. And they found that parathyroidectomy was really the only treatment that led to sustained improvement in bone mineral density over the long run, whereas medical observation basically was associated with steady progression of bone loss.

And of course, bone density should improve the risk of fractures. And indeed, the evidence does support this as well. This was data taken from the Kaiser Southern California database. That's a lot of patients.

So they compared 3,500 patients that were not treated for their primary hyperparathyroidism to 1,500 patients that underwent surgery and 1,500 patients that underwent some bone density medication treatment, bisphosphonates. And what they found was in patients either being observed or treated with bisphosphonates, their fracture risk just continued to steadily increase over time, both in the hip and everywhere else. But hip is the most important because that tends to be the most morbid for our older folks.

In contrast, patients who had parathyroidectomy actually wound up getting decreased risk for fractures, and that's already just at one year. They followed these folks for one, two, five, and 10 years. And they found that those benefits, if anything, started to magnify as time went on. So you're potentially really causing these folks to have a much greater quality of life by not potentially having a fracture that will limit them, especially as they're aging.

Now, considering that women with primary hyperpara are presenting more commonly with osteoporosis, it's particularly relevant, and we should make sure that parathyroidectomy is beneficial in this subset of folks. This is a Danish study that used advanced CT technology to look at geometric markers of bone health and bone strength. And they basically found that in folks that were successfully treated for parathyroid disease, their bone strength markers were all improving by one year. This was in contrast to their control population of folks who actually were just normal controls, healthy controls, that showed steady, age-related decreases in their bone strength.

So that's bones. How about kidney stones? Parathyroidectomy basically immediately reverses the mechanism that kidney stones are being caused by. This is a Danish study. Basically, the vertical line in that graph is the time of parathyroidectomy, and the y-axis is the risk or the number of kidney stone events.

And you can see, basically, there's a steady decrease in the number of kidney stone events after parathyroidectomy. It doesn't go down to the baseline population until 10 years. And there's a theory that people still can carry some calcium deposits in their kidneys that may manifest themselves later on in life even though the mechanism is reversed with parathyroid surgery.

The last thing is quality of life. There is a surprisingly robust amount of evidence that's showing that parathyroidectomy can lead to all manner of quality-of-life improvements. There are actually a lot of quantitative quality-of-life surveys, pretty well-run things using surveys such as the SF-36.

There are some parathyroid symptom-specific scores that have been tested on parathyroid patients in comparison to various control groups. And they've all found that markers of quality of life, including functional status, including mood changes, including all of those things, are starting to-- not starting to, but they dramatically improve after surgery.

And before this evidence started to come out in the past 15 years or so, this supports the anecdotes that most endocrine surgeons have. One of the most rewarding situations for me is a parathyroid patient that was feeling horrible, just qualitatively. You take them to do the operation. And then they tell you, literally the next day, post-op day one, that they felt as if a cloud had lifted and something had changed in their life.

So those are some of the more dramatic things that happen. It doesn't happen to everyone, and it's important to mention that. But when it does, you know that that's actually-- you probably did a good thing for them.