Treating Adult Patients with Growth Hormone Deficiency: Diagnostic Tools and New Treatment Options for Optimal Health

CMEO Podcast Transcript

Kevin Yuen:

Hello, everyone, and welcome to our session today entitled, "Treating Adult Patients With Growth Hormone Deficiency." My name is Dr. Kevin Yuen, and on behalf of the CME Outfitters, I would like to take this opportunity in thanking you for joining us today on our session, which I hope you'll find educational.

This activity is also supported by an educational grant from Novo Nordisk. Again, my name is Kevin Yuen. I am actually from the Barrow Neurological Institute in Phoenix, Arizona, and I will be moderating this session. And sitting beside me, I'm delighted to be joined by my two distinguished colleagues whom I will ask to introduce themselves, starting on my left with Dr. Julie Silverstein.

Julie Silverstein:

Good evening. I'm Julie Silverstein. I'm medical director of the Pituitary Center at Washington University in St. Louis.

Mark Molitch:

And I'm Mark Molitch. I'm professor emeritus at Northwestern in Chicago, and I'm certainly happy to be here with you, and hopefully we can have an educational program this evening.

Kevin Yuen:

Thank you, both of you. And I look forward to an educational discussion, and so let's just get started, without further ado. So our first learning objective today is to outline the clinical challenges associated with the management of growth hormone deficiency. But first, let's get your responses to a question that is being put up here. So the question is, after pituitary tumor, which of the following is the most common etiology of growth hormone deficiency in adults presenting with hypopituitarism? You could go ahead and place your votes now.

So most of you voted for irradiation, and then some of you voted for hypophysitis, and I don't know. So, yes, the correct answer, most of you voted, is irradiation. Okay.

So I'd like to start with some background information on this topic. So, as you know, growth hormone deficiency is a condition that is thought to be present in approximately 6,000 adults. So roughly about 6,000 adults are diagnosed a year, which is approximately 50,000 diagnosed adults. I suspect that this figure perhaps could be higher, but really it depends on those who are diagnosed.

Kevin Yuen:

The prevalence is roughly about two to three per 10,000 population. And if you can see below here, there's a breakdown of the types of patients who present with growth hormone deficiency, those that present as a child, and those that present as an adult, with boys slightly a bit more presenting in childhood onset compared to girls, and in adult onset about 1.9 men compared to 1.42 in women. Because of the differences in the timing of the presentation of these patients, their phenotypical features may defer between these types of patients. Also, really depends on the etiology of the presenting features, presenting causes of the childhood onset versus adult onset.

So the next slide, what I'm going to do is to present to you a case of a 50-year-old electrician. His name is Chad, and he is a patient who actually presented with nonfunctioning pituitary macroadenoma with mass effects. And as normally what happens is that he underwent transsphenoidal surgery, roughly about three years ago. And because he had quite a substantial area that was still noticeable on MRI, underwent stereotactic radiosurgery a year later. As a result, he now has pituitary hormone deficiencies and is on thyroid and steroid hormone replacement. He has an IGF-1 standard deviation score of minus 1.5, and he presents to you with roughly about a five-pound weight gain over the past six months, and is persistently fatigued. That is affecting his work. He also has a family history of osteoporosis, hyperlipidemia, and cancer.

So the discussion points of this patient, when he is seeing you, would be the following: Why would you consider treating adult growth hormone deficiency? And if you are deciding whether to treat or not, who would you consider testing? What test to use for adult growth hormone deficiency? And if you decide on the test, what kinds of tests and what types of cut points would you consider using? As you know that in the recent months there has been publications about long-term growth hormone, and the issue is that whether there's any safety concerns or not, and what is the status of use of growth hormone for non-growth hormone deficient conditions?

The second case that I'd like to present is Max, who is an 18-year-old college student. He underwent surgery and radiation for a suprasellar germinoma and subsequently developed panhypopituitarism. He appropriately was treated with desmopressin, hydrocortisone, testosterone, and levothyroxine, and presents to you with an IGF-1 SDS that is quite low at minus 1.8. He has been off growth hormone treatment for the past six months. You consider testing this patient for growth hormone deficiency, and he subsequently underwent a growth hormone stimulation test, macimorelin, and the results as follows: The serum growth hormone levels, and you can see on your slide here, on the screen, that the peak growth hormone level was 2.27 micrograms per liter. He was amenable to resume growth hormone therapy after he was discontinued as a child, and his childhood growth hormone dose was two milligrams a day.

So the next points that we want to talk about in this young patient who is transitioning from childhood to adulthood is the fact that when do you consider retesting these patients, and if so, what types of tests would you consider using? Then you would think about whether or not this patient needs to be treated, and if so, what dose do you resume growth hormone therapy on? What about safety concerns regarding long-term growth hormone replacement? And these patients may actually ask you that question, given the fact that if they were to be on growth hormone, it would be over a period of many years. And so there is the possibility that they may be concerned about the safety aspects of long-term growth hormone. And finally, the treatment of growth hormone requires daily administration of self-injections, and the issue of long-term adherence should also be discussed. So for the next few slides, maybe I will turn to Dr. Molitch, and he could talk to you about how he would evaluate these patients.

Mark Molitch:

Thank you very much, Kevin. So I think the first issue is why are we even thinking about treating adults with growth hormone deficiency? And so you've all seen slides like this of growth charts the pediatricians have kept on their patients, and here we see what happens if you have a child who's falling off the growth chart, as you see on the left-hand slide, looking at height in the upper portion of this and weight at the bottom. So he's starting to fall off the growth curve where the arrow is, and then growth hormone deficiency was diagnosed. Growth hormone therapy was initiated, and then he started growing again, coming back up to where he was initially, and started growing in a normal fashion. So the idea of growth hormone deficiency in children is pretty straightforward, but what happens when they stop growing? Do we really need growth hormone therapy for adults?

So there is a growth hormone deficiency syndrome in adults. So we know that if you are deficient in growth hormone, there's a general increase in fat mass with respect to its relationship to muscle mass. So an increase in fat and less muscle. Overall, there's a decrease in energy with an increase in fatigue. Bone marrow density is decreased and the more severe the growth hormone deficiency, the greater the decrease in bone marrow density. Overall quality of life is impaired, and when treatment is initiated, growth hormone will reduce many, but not all of these in any individual person. But it's true that growth hormone therapy is really only effective if the person has true growth hormone deficiency. If an adult is not growth hormone deficient, then giving them growth hormone is really not going to do any good except to decrease their pocketbook.

Okay. So I like this slide because it illustrates ... Oh, before that, we'll look at the listing of the benefits of therapy. So one is on cardiovascular mortality. And this really goes back to almost twenty- plus years ago, where we're shown that patients who had panhypopituitarism had an increase in cardiovascular mortality compared to those who did not have panhypopituitarism, and it was thought that this was due to the lack of growth hormone therapy. Whether that's true is still under debate. This is not proven that growth hormone will decrease cardiovascular mortality. Although there's some suggestion that may be true, it's certainly not been definitively proven. But body composition will improve with growth hormone therapy. There's an improvement in exercise performance. Some modest cardiovascular dysfunction risk factors can improve as well. And then finally, quality of life. And we'll just touch on a few of these.

Here we see a really pretty gross example of what can be seen. I don't know how many of you still get the *Hot Farm Management* magazine along with the *New England Journal*, but when you look at the picture here, it really illustrates what happens was on the right-hand side, this little piggy received growth hormone, and on the left, that little piggy received none. So you can see the relative difference between fat and muscle, and the same kind of thing occurs in humans, perhaps not quite to that extent. But we look at quality of life. This looks at the baseline and then one year in this study, and showing the change in quality of life, and so as the numbers go down here, the blue as baseline, so low levels, and then that improves that one year shown in pink. And you see the great difference that occurs even after one year.

Mark Molitch:

One of the interesting things about this, of course, is that it seems to vary a lot, depending upon the age of the individual. So the younger the individual, the greater the improvement in quality of life, between 25 and 35 compared to over 65, there's a pretty significant difference. I think one of the things that we'll talk about is also that's really not talked about in literature very much is the time from when the person became growth hormone deficient to the actual onset of treatment for their growth hormone deficiency. And I think that's something we can discuss as we go along here.

Looking at some of the potential adverse consequences of growth hormone therapy, these are data from the HypoCCS study, which was a long-term follow-up of patients who were treated with growth hormone with the Lilly preparation, but they also collected data on people who decided not to be treated with growth hormone. So the mean time of follow-up here was 2.3 years. They were in the middle age at that entry in here. One set of growth hormone deficiency was adult, about 80-plus percent. And when you looked at differences in mortality, in the subsequent development of cancer, any regrowth of a pituitary tumor or craniopharyngioma, there really was no increase in those who were treated with growth hormone compared to those individuals who were not treated with growth hormone. And then other things that were looked at were diabetes and cardiac abnormalities, and these were not different between these two groups as well. So from an adverse consequence point of view, the growth hormone therapy really appears to be pretty safe.

Now there are differences between the childhood-onset growth hormone deficiency and the adult-onset growth hormone deficiency, and I'll point these out here. First of all, looking here, you see the idiopathic was the major cause of growth hormone deficiency in childhood in this study from 1990, but this really persists into the present as well with organic causes being less than a quarter of these individuals. One of the issues, then, as children who are diagnosed with growth hormone deficiency, present to us as clinicians as adults is what's the difference between the idiopathic versus the organic causes of the growth hormone deficiency?

And so if you retest individuals out there off growth hormone, as they are young adults, to see whether they are truly growth hormone deficient, you can look here that those who are shown here in blue versus with organic disease versus those who had idiopathic growth hormone deficiency shown in pink, and then they're tested with insulin-induced hypoglycemia, you see that 90% of those with organic growth hormone deficiency had peak levels less than five, whereas those who had idiopathic, it was down only about 10%. And then you can see that the growth hormone peaks are much higher than those who had idiopathic growth hormone deficiency, versus those who had organic causes.

So it's clearly well worthwhile retesting individuals in young adulthood or the end of puberty to see if they are indeed truly growth hormone deficient before considering going on with growth hormone therapy. And so one question that arises are, why do some growth hormone deficient children have normal growth hormone testing as adults? And we don't have a good answer for this. We know that there's imprecision in the testing that we do for diagnosing growth hormone efficiency, really, both in childhood and in adulthood. And in addition, looking at the dosing that we use for growth hormone therapy, we use a much higher dose for kids than we do for adults. And it may well be that there's a greater amount of growth hormone that's needed to stimulate growth in childhood, then, to maintain body composition on quality of life and adulthood. So there are a number of potential reasons.

Mark Molitch:

So we have this thing called transition, and the transition really refers, as shown here, to a broad set of physical and psychological changes that are arbitrarily defined as starting late in puberty and ending in full adult maturation. And so this applies a period between mid to late teens until six to seven years later, after achievement of final height. And this often coincides with the patient going from pediatric to adult care. They're also going away from home, going off to college or jobs, and they have loss of parental supervision of care.

So for the child who had diagnosed growth hormone deficiency, you really need to think about retesting these individuals to consider continuing growth hormone therapy. I'm not going to show you the data, but clearly, in those individuals who were growth hormone truly deficient as children, and if they restart growth hormone as an adults, that they see continued bone mineral accumulation and changes in fat and muscle that are really a benefit compared to those kids who do not continue with growth hormone.

So in practice, then, if a child has achieved about 98, 99% of predicted final height and they have a growth velocity of less than three centimeters per year with adequate growth hormone replacement, then it's time to reevaluate them for this transitional growth hormone therapy. And so we really required a change in the paradigm by pediatricians several years ago now that they were told at the beginning that they would be able to stop the growth hormone after they achieve final height. But I think that this needs to be changed, and we may need to consider whether lifelong therapy with growth hormone may be important. I think we still don't really know the answer as to how long people should be treated, but in fact, growth hormone should be continued during this transition if they are truly growth hormone deficient and not stopped when reaching final height in appropriate patients.

So this leads us to managing this time of transition as to what do we do with these children. So in those who were diagnosed with growth hormone deficiency in childhood, then we stopped the growth hormone for at least a month, and those who've got high likelihood of severe growth hormone deficiency that is organic growth hormone deficiency, measure in IGF-1, if it's less than two standard deviations, your diagnosis is confirmed. If it's greater than two SD, then we do a growth hormone stimulation test. If they have normal growth hormone, then we have to reconsider the diagnosis. If it's a low-growth hormone, then we can consider the diagnosis reestablished and restart the growth hormone.

On the other hand, if we have children with a low likelihood of severe growth hormone deficiency, especially those with idiopathic growth hormone deficiency, then they need both a growth hormone stimulation test as well as an IGF-1. Of course, if both of those are low, then the diagnosis is confirmed. If they're both normal, then the diagnosis is not confirmed and they really don't have to be considered for any future growth hormone therapy. Sometimes we see discordant results. The stimulation test may be positive, but low IGF-1 may be there. On the other hand, you can see the opposite, a normal IGF-1 with a low growth hormone, and that's when we, as clinicians, actually have to look at the patient and make a clinical decision as to what to do with those individuals.

So thinking, then, about individuals who develop growth hormone deficiency as adults, that entity of idiopathic growth hormone deficiency is almost vanishingly low, and we really have organic causes of growth hormone deficiency as shown here. Excuse me. Mass lesions occurring causing hypopituitarism, brain injury with trauma, and surgery being a form of trauma, radiation being a form of trauma to the hypothalamic pituitary area. And then you see less common other indications listed below.

Mark Molitch:

So what we need to do when we think about, then, of adult-onset growth hormone deficiency is when do you evaluate that patient? As soon as you suspect it? After all of the other hormones that may be deficient, do you wait till those are corrected before testing? How about the patient who feels perfectly normal? Do you have to retest them? Do you test them at all? How about if they say they don't feel back to normal with repletion of all the other hormones? Do you wait for signs and symptoms of growth hormone deficiency to occur? And of course, are there sufficient data to support treatment in a completely asymptomatic patient? I think these are questions that I think we can ask about how we treat our patients. I'll go back to you, Kevin.

Kevin Yuen:

So if you were seeing the patient, how soon would you consider retesting these patients, going over from transition like that?

Mark Molitch:

I think in the patient who's finished their transition and are now maybe leaving for college or whatever, and they clearly have achieved their final height, then that's really the right time before they probably go off to college to do that. And again, they go off growth hormone for at least a month or two, recheck the IGF-1 and do a stimulation test to see if they're deficient. And I think, very importantly, is the education of that patient and the family by the pediatric endocrinologist or pediatrician, whoever's doing this, to let them know that this retesting is going to need to be done because that person may well need growth hormone therapy for several subsequent years.

Kevin Yuen:

There's a question here, actually, maybe either you can answer. How long do you wait after you've started growth hormone? Do you see a response?

Julie Silverstein:

Yes, that's a excellent question. So the one-line answer is it depends on what response you're evaluating. So in terms of the benefits that Mark talked about, how do we objectively measure those things? So you can measure things like waist circumference, body mass, and after a year or two, you may see a change. Some of the other factors, like the benefits in terms of lipid profile, you may see again after six months to a year.

Another thing probably we should all be doing is a quality of life questionnaire. That's probably one of the biggest things that I consider in terms of whether or not a patient's benefiting from growth hormone is you can objectively give them a questionnaire and follow their scores. I don't think that patients will tell you right away they feel better. Well, some may. But I feel like it's more gradual and it's very hard, sometimes, for them to describe in what ways they feel better.

Mark Molitch:

It's also important that we don't ... I mean, because we're going to titrate up the dose also.

Julie Silverstein:

Yes.

Mark Molitch:

And it may take us four or six months to get to an IGF-1 that's in the upper part of the middle of the normal range. And so they may not start to feel substantial benefit till that's present for several months.

Julie Silverstein:

Right.

Mark Molitch:

So we're really talking about close to a year before somebody might say, "Oh yes, I really do feel differently." I've had a bunch of people say, "I don't really feel different at all, after a year, year and a half of therapy. I don't want to continue this." They stop the drug, and then two or three months later, they call and say, "Yes, I really felt better when I was taking it, and I don't feel anywhere near as good now." And so then they restart therapy. So I think around a year, plus or minus a few months is when they feel substantially better, if they're going to feel better.

Kevin Yuen:

And sometimes I think, also. if you are looking at the bone aspects as well, you probably want to wait longer because bone changes take longer than a year, maybe even 18 months or 24 months. So at least a year, but if not longer, I would say, depending on which parameter you're looking at. Actually, the next question actually falls nicely into what Julie is going to talk about, which is which stimulation test you would prefer to do, which leads me to your talk, Julie, or your section.

Julie Silverstein:

Okay.

Kevin Yuen:

Okay.

Julie Silverstein:

Okay. So I'll be talking about diagnostic testing, and our learning objective is to incorporate evidence-based diagnostic testing to achieve an accurate diagnosis of growth hormone deficiency in adults. So we'll start with an audience response question. So which of the following is an oral growth hormone stimulation test available in the United States: Insulin tolerance test, glucagon stimulation test, growth hormone releasing hormone arginine, macimorelin, or I don't know?

Good. So I'm not sure I need to keep talking. Right. So 72% of you got it right. So macimorelin is the only oral, I think, available anywhere, right? Agent for growth, hormone stimulation testing. So the first question is, who should we be testing for adult growth hormone deficiency? And we want to test patients in whom we have a clinical suspicion. So this would be patients who have organic hypoglycemic pituitary disease from one of the causes that Dr. Molitch mentioned, like a pituitary tumor, radiation or surgery.

So you have such a patient, and if they have three or more non-growth hormone--so starting on the left here--deficiencies and a low IGF-1, over 95% of those patients would fail a growth hormone stimulation test. You don't need to do further testing. You can treat them. By contrast, if you have a patient who has a reason to have growth hormone deficiency, just had surgery for pituitary tumor, and they have fewer than three hormone deficiencies in addition to the growth hormone and a low IGF-1, we really need to do further testing with a growth hormone stimulation test.

And one part that's not on here is if you have someone who has organic pituitary disease, but you really have no clinical suspicion of growth hormone deficiency, and they have a normal IGF-1, you probably don't need to test them. So we'll talk more about these tests. So our option in the United States is insulin tolerance test, which is really performed less and less. So I don't have too much detail about that, but abnormal is considered a peak growth hormone less than five. The macimorelin, we'll talk more about this. The FDA-approved abnormal peak is less than 2.8, and then the glucagon stimulation test can also be done, and the peak cutoff for that test depends on a patient's weight, and we'll talk more about why. So we use a peak growth hormone of less than three in a normal weight individual, or an overweight patient with a high pretest probability, and a peak growth hormone less than one, less than or equal to one in someone who's overweight with a low probability or obese.

This just goes over a comparison of those. So starting with the insulin tolerance test, that, of course, is IV insulin. The cutoff is there again, and this is something, since it causes hypoglycemia, is contraindicated in patients with epilepsy, ischemic heart disease, older patients. It can be cumbersome. It requires close medical supervision, usually with a physician. It's not speedy. It takes a couple hours, but it is inexpensive.

Compare that to the glucagon stimulation test, which is given intramuscularly, we talked about the cutoffs, this is considered safe. Really, the main side effects are nausea, vomiting. It can cause delayed hypoglycemia. It is pretty simple to do, not speedy. It takes four hours, but it's relatively inexpensive. You compare that to the oral macimorelin test, we'll talk about those diagnostic cutoffs again in a second, this has been shown to be safe. It's simple. It takes an hour and a half. The downside are cost, and you have to be careful, make sure patients are not on medications that are known to prolong the QT interval. And also it's unclear whether or not it can be used in patients with hypothalamic disease.

Julie Silverstein:

So first, I just wanted to review this data from this study, a landmark study that compared five different stimulation tests. So this was actually before the glucagon and the macimorelin were available. But what they did is they recruited patients from five US pituitary centers, and they looked at patients with hypothalamic pituitary disease and multiple hormone deficiencies and compared them to controls. And they also looked at the usefulness of an IGF-1 level to diagnose growth hormone deficiency.

So this summarizes the results. So you can see at the top is what we consider, really, our gold standard, the insulin tolerance test with a very good sensitivity and specificity, and right about the same sensitivity and specificity, right underneath it, is the arginine growth hormone releasing hormone test, which we can't do in the United States because we don't have growth hormone releasing hormone anymore, but it is, I think, used in Europe. And then you can see some of the other agents, arginine alone, L-DOPA alone are not as good. But I think what's interesting here is you can see that just using an IGF-1 level had not a great specificity. And in fact, in this study, about 40% of patients with growth hormone deficiency had normal IGF-1s. So normal level does not completely rule it out.

So now we'll talk about the test in a little bit more detail. How many people do the glucagon stimulation test in their practice clinics? Okay. So you have the patient come in, in the morning. They have to fast overnight. We weigh the patient. We place an IV to measure the blood draws, and then glucagon is given IM. We give one milligram if a patient weighs less or equal to 90 kilograms, and 1.5 if they weigh more than that. And then both growth hormone and glucose levels are drawn every 30 minutes for four hours. So we don't want to do this test in someone who's malnourished or hasn't eaten for over 48 hours. We don't see a great response if someone has fasting hypoglycemia. I mentioned side effects are nausea. So it's probably a good idea to have an IV antiemetic there available, and late hypoglycemia can occur. So we advise patients to eat small and frequent meals after the test.

So this shows results from a study where they took about 40 patients with suspected growth hormone deficiency in the controls. So first, on the left, you see when they took the patients with growth hormone deficiency and they had them all undergo a glucagon stimulation test and our insulin tolerance test, the gold standard, that they were very similar results. So the peak growth hormones were all less than three. And on the right, you can see they calculated the ... They show that with that cutoff of three, you have a good sensitivity and specificity for the glucagon stimulation test. Keep in mind, this is from Europe where the patients tend to be leaner than they are in the United States.

And this is another study that compared the insulin tolerance test and the glucagon stimulation test in patients after pituitary surgery, and you can just see the Y axis is showing you insulin tolerance test correlates well with the ... I'm sorry, the X axis correlates well with the Y axis, which is showing you the growth hormone peak during the glucagon stimulation test.

Julie Silverstein:

Now I mentioned, then, that body weight can affect the results, and that was shown in this study. So they took patients with suspected pituitary disease, and they divided them between those who were obese, BMI over 30, and that left graph, the obese patients are those in the circle, and compared them to non-obese patients. And what they're showing you here is the growth hormone levels during the four-hour test, and you can see as compared to the non-obese patients, the squares, the obese patients had lower growth hormone levels. And then on the right, they're showing you how weight inversely correlated with the peak growth hormone level. So the more a patient weighed, the lower their peak growth hormone during the test.

We also know that blood glucose dynamics can influence the growth hormone response. And this may explain partially why obese subjects don't have as a robust of a response. So this is showing, again, comparing on the left there, obese patients in the circles compared to non-obese patients in the squares, their glucose levels during the glucagon stimulation test. And you can see that overall, the glucose levels do not go as low in the obese patients, and the nadir glucose, at the lowest, was delayed. And on the right they show were showing how the nadir glucose inversely correlated with the peak growth hormone level.

So this is an interesting study, I think it was retrospective, about 40 patients, and basically they had three groups. So they had controls, they had patients with partial pituitary deficiency, that's the PPD, so fewer than three hormone deficiencies, and they had patients with total pituitary deficiency, TPD, which had greater than three or more hormone deficiencies. And if they compared the growth hormone cutoff of three that's in the black bars versus using a growth hormone cutoff of one, you can see, and these are overweight obese patients. Sorry. I should have said that. You can see in the controls with a cutoff of three, over 40% of them failed the test.

On the right, to highlight that more, you see that they show here the percentage of subjects in each of those groups that would be diagnosed with growth hormone deficiency, OB subjects. If you use a standard cutoff of three, that would've then been reclassified as growth hormone sufficient using the cutoff of one. So again, look at the controls. That's over 80% of them. Again, highlights why I wish we should use the different cutoffs.

Next I'll move to the oral macimorelin. So how many people have experienced using this? Okay, so nobody in the audience. So this was FDA approved in December of 2017. Again, as mentioned, the only oral agent, and it's an active ghrelin mimetic that binds to the ghrelin receptor. And it actually has more potent growth hormone stimulatory effect than the insulin tolerance test. So this test takes about an hour and a half, we give the agent, and we check the growth hormone 30, 45, 60, and 90 minutes afterwards. I'm going to talk about the cutoffs in a second. Again, you have to be careful of any drug-drug interactions. And basically, the graph on the right is showing you that the peak growth hormone during the macimorelin test, which is on the Y axis, correlates well with our gold standard, the growth hormone peak and the insulin tolerance test.

So what about those cutoffs? So in this study Dr. Yuen was a big part of, this study was actually comparing the macimorelin, I believe, to insulin tolerance test. But here, what I'm showing you is when they calculated the sensitivity in blue and the specificity using different cutoffs. So the FDA-approved cutoff of 2.8, you can see there on the left, has an excellent specificity. If you use a cutoff of abnormal being less than 5.1, you have the same specificity and actually a higher sensitivity, so better sensitivity. So that's really a better cutoff to use.

Julie Silverstein:

So just some take-home points. So you have adult patients with hypothalamic pituitary disease. They have three or more hormone deficiencies and a low IGF-1 level. They really don't require further testing. But if they have fewer than three pituitary hormone deficiencies, other than growth hormone deficiency, and a low serum IGF-1, those patients do require stimulation testing. Further testing is not required in adult patients who have a history of hypothalamic pituitary disease, low clinical suspicion, and a normal IGF-1. The cutoff peak, as we discussed, of growth hormone level during a glucagon stimulation test is dependent on weight. And despite the approved cutoff, using a peak growth hormone level of 5.1 with a macimorelin test allows for really the best sensitivity and specificity. So now I'll hand things back over to Dr. Yuen.

Kevin Yuen:

Thank you. Thank you, Julie, for a wonderful talk. I guess there are couple of questions that touch on testing. Maybe I'll just ask you, Julie, one question. Why do some patients stimulate with hypoglycemia, but not when using glucagon and vice versa? Hmm.

Julie Silverstein:

Well, actually not sure I completely understand the question. But the glucagon stimulation test, patients who don't stimulate with that also don't stimulate with the insulin tolerance test. I don't know if you're referring to the slide where I had patients whose glucose levels didn't go down. I'm not sure we fully understand the mechanism there of why patients who have insulin resistance have a blunted response to the stimulatory agents.

Kevin Yuen:

Yes. I think partly, also, the fact that we probably don't quite know the exact mechanism of glucagon as well.

Julie Silverstein:

Yes. Right.

Kevin Yuen:

But it's a tough question, I guess.

Mark Molitch:

So with all these, sometimes they'll respond to another, and even the same test, if you repeat it a second time, they might not have the same response a second time.

Kevin Yuen:

Yes. Okay. So there's a couple of questions about long-acting and safety about long-acting growth hormones, which I will actually include in my talk. So I will go on to my talk first, and then hopefully, if there's any further questions, then we will get to it. Okay? So I'm going to talk a little bit about treatment, and that is evaluating the current and emerging treatment strategies for the management of this condition.

Okay. So here we will start off with a question that requires your input. So what is the advantage of the long-acting once-weekly growth hormone preparation versus the daily preparation? Is it improved efficacy, improved adherence, improved side effect profile, less costly, or, I don't know? So please cast your votes now.

Excellent. So most of you got it right, over almost 90%. So the whole point of the use of long-acting growth hormone preparations is to address the issue with adherence that is often a big issue when using daily growth hormone. So you're absolutely right. Great job.

So just to recap those two cases that I presented to you earlier, so on the left-hand side is the typical case of an growth hormone deficient patient, and on your right-hand side, you have the transition patient. Again, I'm putting up this slide just to remind you the two different case scenarios that you may encounter if you're treating these kinds of patients, and that hopefully will factor in into the way you will consider treating these patients. But again, coming back to the treatment landscapes, and also the fact that there is also a few questions about long-acting, so I guess the question is why do we even consider long-acting preparations?

We do know that daily injections can be problematic for both the patient and also for the caregiver who is administering the injections daily. As you know, injecting yourself with injections can be inconvenient, painful, and sometimes distressing. And that is often the reason why patients decide not to continue with these injections on a daily basis, especially when, over time, when the patient has other distractions, life gets busy, non-adherence has been shown time and again to be a big issue with daily injections.

So the whole point of considering long-acting growth hormone preparations, the hypothesis is that when you decrease the number of injections from 365 injections a year to, say, if you're doing it weekly or 52 injections a year, these preparations may hopefully improve the adherence, and by doing so, hopefully it will improve clinical outcomes, although these two factors here need to be proven, obviously, when long-acting growth hormone preparations become available.

So how do we actually prolong the action of growth hormone? And in the studies, you can see here, there are different technologies that are being used, and they have been studied. Some have been successful. Some have been less successful. And in fact, if you look at the way or the technology in which the growth hormone action is prolonged, you see that there are five major technologies. You have the deeper preparation, which actually acts to delay the absorption. It actually is deposited in a subcutaneous space by a reduction or a slow release of the hormone. It actually delays the absorption and is often incorporated into microspheres. And then you have the PEGylation method. Some of you may know how PEGylation works. We use that in patients with acromegaly when we are using pegvisomant, which is also PEGylated technology.

Kevin Yuen:

So this PEGylation technology essentially slows the clearance from the circulation. So it hangs around longer, and it typically can be in the form of polyethylene glycol, which is a permanent, or it can be a reversible PEGylation. Then there's also the pro-drug formulation, which actually has the technology of converting or allows the conversion of the pro-drug over time into the actual drug, and by doing so, the action is actually prolonged. The non-covalent albumin binding is another way of doing that, and the native growth hormone molecule in the circulation is bound reversibly to the patient's endogenous albumin. And the reversibility in the binding of the albumin increases the molecular structure and therefore reduces the clearance of this compound. So again, that's another way of doing so, of increasing the growth hormone action. And finally, there's also growth hormone fusion proteins, which are synthetic polypeptides. These are naturally occurring proteins, which are either HCG albumin or immunoglobulin chains.

So to talk about the long-acting growth hormone, so this is an example. Somapacitan, which is FDA approved, although yet to be made commercially available, it is a long-acting growth hormone administered once a week. It's a novel reversible growth hormone molecular structure, and the way it works is that it binds via the albumin binder, which has a 1.3 kilodaltons in terms of molecular weight, and it's irreversibly bound so that once it's bound to the endogenous albumin, it prolongs the action, it reduces its clearance over in the kidneys, and therefore, it prolongs the action. And these are some data that was published about couple of years ago, where they looked at patients being treated either with somapacitan or daily growth hormone.

And you can see here on the left-hand side, the table, these are the outcomes that we look for in patients who are treated with growth hormone deficiency, particularly body composition, lipid profile, glycemia, adverse events, and drug antibodies, and you can see here that the body composition improves as compared to the daily growth hormone. Bone parameters is comparable. So is the lipid profile. And there's also very minimal effects on glycemia, which is good and something that often we're concerned about in case it actually increases the fasting glucose and A1C. But it doesn't appear to be the case. The adverse events are pretty comparable to daily growth hormone, and in fact, there are no antibodies found in this study.

And on the right-hand side, you see in the figure, when you compare the IGF-1 SDS generated compared to the daily growth hormone, you'll see that it's, again, very comparable over the study time period of 26 weeks. These patients were also given a questionnaire to ask them about how they felt when they were injecting the long-acting growth hormone compared to daily growth hormone injections. And you can see here, pretty obvious, that the convenience part of it is certainly something that patients actually like with the long-acting preparations.

The other FDA approved long-acting compound is lonapegsomatropin, which is approved for use in pediatric patients presenting with growth hormone deficiency. This in fact is a prodrug, and you can see here the pink and native molecule here is bound to a linker, a lonapegsomatropin linker, and the link actually links the lonapegsomatropin carrier. So when you have that linked and you bind that to the growth hormone, you actually prevent the degradation of the growth hormone in the circulation, and then over time, the linker is cleaved upon physiologic conditions, and once the linker is cleaved, the native growth hormone is then freed up to attach itself to the receptor, and the carrier is then gradually cleared in the kidneys.

Kevin Yuen:

And when you look at the data from the heiGHt trial, which is basically a study looking at pediatric patients, and this is the primary endpoint, which is the height SDS, you can see here the blue line represents ... On the left-hand side, the blue line in the figure represents daily, versus the green representing the weekly compound. You can see there is, in fact, a superior effect of the long-acting compound in terms of its induction of height SDS. And when you look at the IGF-1, which is often the biomarker that is used to titrate the growth hormone doses, you can see the green bars were very, very comparable. If anything, it was a little bit higher than the blue daily somatropin, indicating that the IGF-1 generation is fairly stable throughout the course, throughout the year, in fact, of the treatment, as you're indicating the stability of IGF-1 generated.

Then what they did was they also turned their attention and looked at the effects of this compound in adults with growth hormone deficiency. On your left-hand side, you see that it is compared to the daily growth hormone serum concentrations, and you can see they are also very comparable in terms of the long-acting with the daily preparations. And on the right-hand side, IGF-1 generation is also very comparable throughout the study, then indicating that there wasn't actually an overstimulation of IGF-1 over long periods of time, which is one of the safety parameters that we look for when we are testing for long-acting compounds.

One of the questions that is often asked is that when you're using a long-acting compound, unlike the daily compound, where you can actually measure the IGF-1 pretty much any time, is that how do you factor in the timing of when do you actually measure the growth IGF-1, when you're trying to see how you're going to titrate the dose of the compound? So it really depends on the time of when the injection takes place. So obviously, as you can see here, this is a study where it looks at somapacitan. And if you measure the IGF-1, particularly in children where higher doses tends to be used, you get a greater amplitude in the IGF-1 generation, slightly more than the adults. You'll see that in day two would represent roughly the peak of where the IGF-1 would be generated, whereas at day four is more of the average, and then at day seven is where the trough is. Whereas in adults, you probably don't see as much of a variability because there's a lesser peak, simply because I suspect this is because the lower doses of growth hormone is used typically in adults compared to children.

So you might ask the question that when these preparations become available, at least when it's commercially available, what types of patients would you consider using them in? And I would say if the patient is sitting in front of you, especially if they're likely to be nonadherent, especially if they're on many other types of injections, particularly if they're also on testosterone injections, they're also on insulin injections, it's unlikely that they would be adherent to another injection of daily growth hormone, and so maybe those patients may be good candidates for consideration of long-acting.

Patients who are not able to self-inject, but in fact, they're willing to adhere or willing to use the growth hormone simply because they have found them beneficial, but they may be a little bit apprehensive about the daily injections because they may not be very comfortable in injection injecting themselves, so these are the types of patients as well. And patients are already on daily growth hormone injections, but are clearly struggling, and they're not able to keep up with the daily injections. And if they're being honest with you, they will tell you know, "Doc, I just can't keep up with the daily injections." So they may be considered for the long-acting preparations.

Kevin Yuen:

Just like any new medications, there are no long-term safety data on these compounds. Most of the studies are within a year or two years. So as you know, the safety parameters of these compounds require much longer assessment and much longer studies. So it's difficult to tell you, actually, what long-term safety profile of these compounds are. But certainly, I've compiled a list of the many types of questions that actually we can ask about this compound. And certainly, over time, will tell as to how we can improve or use these compounds effectively with minimal side effects. So I guess it's time for discussion, but I don't know, maybe I can just turn the discussion over to Mark. How do you feel about long-acting growth hormone? And if you had a patient, how would you start the patient and adjust the dosing?

Mark Molitch:

I think the first thing, as you mentioned, is to see whether they're happy with their current injections or whether they want to give it a try to use the long-acting preparation, and I suspect that we would probably offer it to many of the patients and see what their response might be and then just go ahead and switch them over. Again, the exact titration schedule for switching, I think still needs to be worked out a little bit. We'll see how that comes out when it finally actually becomes available for use.

Kevin Yuen:

Yes. And also, I think one important point, also, is different long-acting compounds have different molecular structures, as I've shown you. So we still don't quite know the tissue penetration of each compound. They may behave slightly differently. And again, only time will tell. What about you, Julie? Are you comfortable with long-acting?

Julie Silverstein:

Yes, I think one of the places where this will have a huge role is in the transition patients. I find a lot of them don't want to continue on growth hormone, take it, because they don't want to do anymore injections. They're traumatized from doing it as a child, maybe. So that's often a reason why I'll have patients not want to continue or resume growth hormones. So I feel like it's going to be something we can really use in that population.

Kevin Yuen:

Yes, yes.

Julie Silverstein:

Yes.

Kevin Yuen:

Okay. Anyway, so what we will do is before we get to our Q&A section, I'd like to offer a few SMART goals, SMART meaning specific, measurable, attainable, relevant, and timely. So these goals include evaluating patients with possible adult-onset GH deficiency, or patients transitioning from pediatric to adult care, using the best evidence to consider the most appropriate diagnostic tests when you're trying to confirm the diagnosis, follow guideline-based treatment pathways for treating and monitoring patients with GHD, when available to consider long-acting growth hormone preparations to hopefully improve the convenience and adherence to therapy. Although, again, as I had alluded to in my previous slide, many questions are still yet to be answered in this compound, and certainly over time will tell to help us improve our understandings of how each individual compound behaves and also keep up with current and emerging data and real-world experience in treating growth hormone deficiency in adults.

So I think for the remaining time, we will devote ourselves to the questions and answers. And I will look here into the iPad to see the types of questions we have, and maybe we can hopefully answer them as we go along. So question is if a patient had been treated with GH for a long time and is recently diagnosed with cancer ... It always comes up, this question, right? Mark is smiling there. Such as breast cancer, as an example, what do we do with the growth hormone and how do we counsel the patient?

Mark Molitch:

Yes, that's a tough question. I think we stop it. The question is why do we stop it? The data to show that treatment with growth hormone will make cancers worse really don't exist, and we stop at more for a theoretical reason that we don't want to give a growth factor to somebody where stimulating growth of cells might be important. And so we stop at more on the basis of theory than in practice. We know in acromegaly, even the incidence of cancers, maybe colon cancer, some others, plus or minus depending upon the study, but it's really pretty modest. So I think if our treatment really causes cancer, I doubt it, but nobody's going to do it.

Kevin Yuen:

Yes.

Julie Silverstein:

Can I ask a follow-up to that?

Mark Molitch:

Sure.

Julie Silverstein:

So what about someone with a history of cancer, breast cancer, colon cancer?

Mark Molitch:

I mean, I think the rule of thumb now is if it's five years in the past and totally silent, that it's probably okay to go ahead. Things like squamous cell skin cancers, I don't think people are going to worry too much about, even thyroid if it was a papillary from years ago, I don't think people will worry about that. But if it's something less than five years and you're still uncertain about whether somebody's truly in remission or not, I think most of us would avoid giving growth to them under those circumstances.

Julie Silverstein:

I agree.

Kevin Yuen:

What about childhood cancer survivors?

Mark Molitch:

Yes, there's a lot of data on that. And the data for childhood cancers is that there really is no increase in recurrence of those cancers with growth hormone therapy. So that seems to be a pretty safe thing, and that should encourage us that in adults it's probably okay as well, But it's just this reluctance in somebody with recent cancer to go ahead.

Kevin Yuen:

Yes. I think a lot of the data about cancers and growth hormone is based on the in vitro data.

Mark Molitch:

Oh.

Kevin Yuen:

And the mouse models, the knockout mouse models where it actually does show quite good evidence that actually does cause cancers. But in terms of the clinical trials, particularly the retrospective data that we've had over many years, the signal is actually not very strong at all.

Mark Molitch:

Right. I agree.

Kevin Yuen:

Yes. A question for Julie, maybe. Why do we tend to use higher doses of growth hormone in kids? So, again, another question about long-term side effects and safety for kids.

Julie Silverstein:

Well, as an adult endocrinologist, I must say I don't have any experience in pediatrics, but I think Dr. Molitch touched on, I think, that we need higher doses to stimulate growth in children maybe. And our goals, really, in adults are to maintain IGF-1 level within the normal range, between negative two to two plus standard deviations, basically. I don't know if you have any other kind of input for that.

Mark Molitch:

I don't have any good explanation either. I mean, I aim for the middle of the normal-

Julie Silverstein:

Middle. Right, yes.

Mark Molitch:

... rather than the lower part, but we're not interested in height anymore.

Julie Silverstein:

Right.

Mark Molitch:

And that's the only good explanation I can think of. I mean, there may be some resistance to the growth hormone action in kids, I suppose, but I don't really have a good answer.

Julie Silverstein:

The other thing is we want to avoid side effects in adults. So we tend to start lower. As you said, we're not concerned about growth, and then we slowly adjust up.

Kevin Yuen:

Yes. So generally, kids tend to be higher doses because we want to mimic the physiology. So growth hormone tends to be higher in terms of when they're younger. So you try and mimic what they should be producing, and they're not producing. And as they get older, then you try and mimic that because of aging.

We have another question here, which is we sometimes see in practice completely healthy person seeking use of GH therapy on the basis of what they know from websites, about its benefits for reducing central obesity. They seek commercial labs, they do a random GH and IGF-1 level. Have you actually dealt with such patients in such a condition, and what do you actually do when you see such a condition in terms of what you tell them?

Julie Silverstein:

Well ... Oh, go ahead.

Mark Molitch:

I try to avoid those patients as much as possible. And I certainly try to avoid having to do a stimulation test in those people because every once in a while, you're going to find somebody who will have a low growth hormone response.

Julie Silverstein:

Yes.

Kevin Yuen:

Absolutely.

Mark Molitch:

And then you will end up treating them.

Julie Silverstein:

Yes.

Mark Molitch:

Even though you think that they really aren't growth hormone deficient, and that I have actually done on occasion with great reluctance. But if you do a stimulation test and their numbers are low, and they really want to have growth hormone therapy, I mean, you can't really say no. But I'm not happy about it.

Julie Silverstein:

Yes. I actually was recently referred a patient who was concerned about growth hormone deficiency, so went to their primary care who ordered a growth hormone. And it was like, I don't know, 0.3. So then referred to endocrinology for the low growth hormone. So the patient was very, very fixated on the growth hormone level. I checked an IGF-1. It was perfectly normal, and I just explained without any pituitary disease, any history to suggest that you should have growth hormone, we don't need any further testing. He's aware of stimulation tests, and so I'm waiting for the message to come back, "Well, what about a growth hormone stimulation test?" And yes, I probably will end up saying okay.

Mark Molitch:

Yes.

Julie Silverstein:

Yes.

Kevin Yuen:

Probably best at the early onset to say no and just reduce the expectations that they're not the most suitable candidates rather dig yourself into a rabbit hole-

Julie Silverstein:

Right. Yes.

Mark Molitch:

I agree.

Kevin Yuen:

... and not coming out of it, though. Yes. Okay. Great. A couple of more questions. So one question, if a patient has secondary hypogonadism and GH deficiency that you've diagnosed, do you always start on testosterone and then GH, or can you start both of these hormones pretty much at the same time?

Julie Silverstein:

Well, I mean, so in general, we say that you should have all the hormone deficiencies adequately treated before you start growth hormone, but that's more the thyroid and the cortisol. So I don't think there's really a problem starting both. The only thing I'd say is you wouldn't .... I mean, for me, you won't know what patient, if they're benefiting what they're benefiting from. So if that's something you're trying to tease out, it might be a reason to start the testosterone, see how they're feeling, and then talk about the growth hormone and start that. I don't know.

Mark Molitch:

No, I agree. I mean, it's a little bit different in children because then you're dealing with growth hormone and closing of the epiphysis. But in the adults, it's not really an issue. No real reason that you couldn't start both, but you're right, you wouldn't know which was causing what, as far as any clinical improvement.

Kevin Yuen:

Yes. Yes. I agree. So you probably want to start one first, and usually growth hormone tends to be the last hormone anyway. Any comments on the differences in the IGF assays? That's a very common question we get asked.

Mark Molitch:

IGF-1 assays vary from one lab to another.

Julie Silverstein:

As do growth hormone.

Mark Molitch:

And growth hormone, too, especially an IGF-1. I raise one question about the people who are good candidates for growth hormone, and at least in my own experience I'm interested in yours, is that if somebody's panhypopit for 15 years, and then they come in and say, "Oh, I wonder if you should try growth hormone after a 15-year hiatus," and you do try it, I found that most of those people don't really feel much different. On the other hand, if somebody's been growth hormone deficient for six months or a year after surgery, and then you give them growth hormone, they're the ones who respond much better. I don't know if you've found the same difference between recent versus long-lasting hypopit.

Kevin Yuen:

Yes. I think partly, or at least in my experience, I agree, is that I think they got used to the idea, and they probably don't feel so different if they have been 15 years, whereas with surgery and then, boom, they're growth home deficient, and then they're probably a little bit more cognizant of the changes, or they're more aware of the changes.

Julie Silverstein:

Yes, no, I agree. I think when you have someone who just developed hypopit and just had surgery, so they have lots of different symptoms that could be from different things, they're starting at a lower level in terms of where they're feeling than someone who's been on other replacements for many years.

Kevin Yuen:

There's a question on transition. I know, Mark, you touched on it in your talk. So do you have to treat patients transitioning from peds to adults with inadequate stimulation, or can you monitor them for a period of time to see if they eventually develop symptoms before you consider treating them or even testing them?

Mark Molitch:

Well, I think what we, in general, like to do is prevent the symptoms from developing, and again, some of it may be relatively subtle in that time period from, say, age 18 or 19 to age 25, where you really haven't reached peak bone mass until your mid 20s. And you really decrease that if you don't continue the growth hormone. So I think that it's important to test them at age 17, 18, 19. And if they're deficient, then they should be treated to make sure they get peak bone mass and that their relative muscle fat mass really changes as well. So I wouldn't wait till they have symptomatic changes. I would try to prevent that from occurring.

Kevin Yuen:

Julie?

Julie Silverstein:

I agree. Yes. I think that's a period where patients often don't end up being put back on growth hormone, though. So I think we do need to work on that transition period.

Mark Molitch:

Yes. It's an important period.

Julie Silverstein:

Yes.

Kevin Yuen:

Yes. Certainly, the bone maturation tends to occur around that crucial age, and although they're not growing, I tell my patients, if they're not growing, but certainly there's still things happening within the bone, that's important, if you miss out that period, that window period, you might end up having issues with your bones as you get older. So perhaps also a good reason that time to not miss the window. A question about does any of us in here have any experience with illicit use of growth hormone stimulatory peptides as athletic performance enhancers?

Mark Molitch:

I don't have any experience with that. And if somebody brings it up, I try to tell them to stop doing that.

Kevin Yuen:

As simple as that.

Mark Molitch:

Because it's costly and it doesn't do any good.

Kevin Yuen:

And it's illegal.

Mark Molitch:

And illegal.

Kevin Yuen:

Yes.

Mark Molitch:

That part doesn't bother me as much.

Kevin Yuen:

Okay. And then this is interesting. In treating patients with growth hormone deficiency, okay. We use IGF-1 as a biomarker. So where would you target your IGF-1 level for your patient?

Mark Molitch:

I mean the upper part of the middle part of the range, between 50 to 75%, is where I would be.

Julie Silverstein:

Same, mid normal range.

Kevin Yuen:

Yes. Do you tend to reduce your target if the patient is maybe diabetic or not tolerating or ...

Mark Molitch:

No.

Kevin Yuen:

No? You would push the dose? Okay. Oops.

Julie Silverstein:

But you may want to start at a lower dose, potentially, in diabetics.

Kevin Yuen:

And the follow-up question is what about patients, you asked that question earlier, Julie, is patients with, say, a distant history or cancers or where would you target the IGF-1 then?

Julie Silverstein:

We don't have any reason to think we can't target the same level we do with anybody else. So mid-range. Yes.

Kevin Yuen:

Okay. And then I think there is ... Oh, pretty much it, though. Unless ... yes. I think we've exhausted all ... Oh. Trials of growth hormone in dementia. Not that I know of. Do you?

Mark Molitch:

Say that?

Kevin Yuen:

Any trials of growth hormone on the effects on dementia, on brain?

Mark Molitch:

I'm not aware of any.

Kevin Yuen:

No aware of, no.

Mark Molitch:

Coming back to your diabetes question, I once had a patient who had type one diabetes, was very recurrent hypoglycemia, very difficult to control, who was also panhypopit. And I deliberately started her on growth hormone and kept her IGF-1 relatively high to decrease her hypoglycemia, to make her more insulin-resistant.

Julie Silverstein:

Interesting.

Mark Molitch:

And it worked.

Julie Silverstein:

Interesting.

Mark Molitch:

Yes. It really was very helpful for her.

Kevin Yuen:

So it was easier for you to manage the insulin?

Mark Molitch:

Yes. Yes.

Kevin Yuen:

Yes. Okay.

Julie Silverstein:

I have a question for you guys. Is there an age at which you wouldn't discuss growth hormone with a patient? I don't know, a seventy-year-old.

Mark Molitch:

95.

Julie Silverstein:

80-

Kevin Yuen:

90.

Julie Silverstein:

Yes. Just wondering, do you discuss it with every patient?

Mark Molitch:

I guess I probably don't do too much in people over 70 or 75. Yes.

Kevin Yuen:

Yes. I don't have a cut off. I mean, if they have a good history and if they're symptomatic, I mean ... Although I do tell them, especially for those who are above 80-some years, that there isn't good data in octogenarians in that age group. So we don't know, and we don't actually have good safety data, but if they are symptomatic, I would treat them like any other patient.

Julie Silverstein:

Yes. I agree. I don't have a cutoff. I was just curious.

Kevin Yuen:

Any questions from the floor? I think I've exhausted all the questions here, unless you have any other questions.

Julie Silverstein:

Yes.

Kevin Yuen:

Anybody?

Speaker 4:

So are you convinced some patients ... Like now I'm getting some patients in my practice from a previous endocrinologist that left the practice about seven, eight years ago but they had received growth hormone for that period. Now their primary doctor is sending them back and said, "You really need to go back on growth hormone." But I do the testing, and everything is coming back normal. But they disagree with the test. And I said ... Oh, sorry.

And they disagree with your test and say, "Well, my prior endocrinologist said I need growth hormone. The only reason I wasn't on it was because I couldn't find a provider to prescribe it." So how do you cancel them now, based on your testing, even though some of those patients, you don't really think they had the full dynamic testing initially, because there was no record of those things?

Julie Silverstein:

That's a tough situation. I'll repeat maybe the beginning. So you have a patient that's being referred to you that was previously on growth hormone by another endocrinologist, and now you're seeing the patient, repeating the testing, and it's normal. I mean, one way you could approach is to say that insurance isn't ... I mean, at least in Missouri, where I am, insurance usually won't cover it unless you have evidence of growth hormone deficiency, including provocative testing that's abnormal. So that could be one way. You could say, "Well, insurance probably isn't going to cover it," but that's a hard situation to be in.

Mark Molitch:

Yes. One thing that can always be said is that these tests aren't as precise as we would like, and you're not quite sure what occurred several years ago, but testing now seems to indicate adequate growth hormone. But you're right, we're really not allowed to give growth hormone if the insurance won't pay for it. But it's a tough situation.

Kevin Yuen:

This question in front.

Speaker 5:

Oh, related question to that situation.

Julie Silverstein:

I think they want you to have the mic.

Kevin Yuen:

Yes, the mic. The mic. Pass him the ...

Speaker 5:

Just maybe a related question. If you inherit a patient who's on growth hormone, but maybe it's not really clear whether or not, from the history, if it's actually legitimate or not, you don't really have any reason to suggest otherwise, but at the same time, maybe their provider was somewhere else, and the records, you weren't able to get records of provocative testing. Would you just stop their growth hormone and repeat dynamic testing, or is it easy just to allow the patient to just refill their meds without ... if you want to be an academic about it, then I would think maybe it's good to confirm, make sure that the diagnosis is correct.

Mark Molitch:

Yes. I think a lot depends upon the individual patient. You're sitting there, somebody who had pituitary surgery, they've got three other hormones deficient, and they're put on growth hormone because they had an abnormal test, then I think you can assume that they probably actually are deficient and just continue it on. Somebody said, "I was only growth hormone deficiency before, no other hormones are deficient," that's probably something I probably would push hard to retest.

Kevin Yuen:

And also, I think if the patient is growth hormone sufficient, and if they're taking growth hormone, I mean, you look at their IGF-1, too. I mean, if the IGF-1 on growth of one is normal or low, then clearly you think maybe you give the patient that benefit of the doubt, in a patient with appropriate history. One other question that just came up is how long do you treat patients for? Is there a time in their life where you tell them to stop?

Mark Molitch:

We have no data.

Kevin Yuen:

No date. No expiration date, I would say.

Mark Molitch:

Right. Right.

Julie Silverstein:

But that said, I think it's reasonable after a couple of years to talk to the patient about whether or not they feel like they're benefiting from it. And if they don't feel like they're benefiting from it, it's reasonable to stop, I think. And then you can bring them back and see how they're doing.

Mark Molitch:

Yes, no. Yes, after a year or two, I certainly ask how are they feeling? Do they feel better than they did before they started growth hormone? And if they say, "I feel absolutely no difference at all," I will actually stop it. But again, as I said, some people, when they stop it, three months later, they come back and say, "Oh, I really was feeling better," and they do want to restart. But not everybody.

Kevin Yuen:

Maybe the patients may not say it, but their spouse will tell you.

Mark Molitch:

Yes. True.

Speaker 6:

Excuse me. Just to follow up on the previous question, what about those who were diagnosed with growth hormone deficiency as kids and then as adults, they may stop growth hormone, will you continue that lifelong as well, or do you, at some point, decide to stop?

Mark Molitch:

I think so.

Kevin Yuen:

I think so. Yes. I mean, there's no reason to stop if the patient is doing well on it.

Mark Molitch:

Right.

Speaker 7:

Question. If somebody has a residual pituitary tumor, if they are on growth hormone, does the tumor increase in size? Are you concerned about that?

Mark Molitch:

No.

Julie Silverstein:

No, there's-

Mark Molitch:

It doesn't increase.

Julie Silverstein:

Yes.

Mark Molitch:

That's been looked at.

Julie Silverstein:

Yes.

Kevin Yuen:

I mean, it's a very reasonable question.

Julie Silverstein:

Yes.

Kevin Yuen:

But there hasn't been any suggestion that it actually causes the tumor to come back.

Mark Molitch:

There have been several studies that have looked specifically that issue, because that's what we do. The tumors don't regrow at an increased rate with growth hormone.

Kevin Yuen:

And they've also looked not only at pituitary adenomas, they have also looked at craniopharyngiomas as well.

Mark Molitch:

Right.

Kevin Yuen:

There hasn't been any negative signal there. Yes. So, good. Okay. I think ...

Mark Molitch:

Okay.

Kevin Yuen:

Thank you.

Julie Silverstein:

Thank you.

Mark Molitch:

Thank you.

