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The Cortisol Clue: Diagnosing Hypercortisolism in People with Difficult-to-Control Cardiometabolic Conditions

Announcer:
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Dr. Yau:
This is CME on ReachMD, and I'm Dr. Hanford Yau. Joining me to explore strategies for screening and diagnosing hypercortisolism today is Dr. Eden Miller, a board-certified family medicine physician who has also completed fellowship in obesity medicine and diabetology. Dr. Miller, thanks for being here today.

Dr. Miller:
Well, thanks so much for having me discuss in this really innovative condition, and we're going to learn a lot today.

Dr. Yau:
For some background, Dr. Miller, could you explain what hypercortisolism is for those clinicians who aren't as familiar with hypercortisolism, or sometimes referred to as Cushing syndrome?

Dr. Miller:
Yeah, hypercortisolism at a 30,000-foot view is going to be this prolonged excessive cortisol exposure. It's beyond normal physiological things. After all, cortisol is really something we need in life. We get ill, we have different stressors, but it's really when the body gets bathed at an aberrant level. Now, oftentimes we think of this as more its end clinical state, right? It's advanced, prolonged, decade after decade exposure, which is really the Cushing syndrome. But like with all disease states, there is a subclinical type of state, in other words the early manifestation of high cortisol, where we get this significant morbidity and mortality associated with it. We often get very challenging to control disease states, and it goes beyond what we think of as just kind of a typical issue of high blood pressure or cholesterol. It's really that condition that is just magnified.

We don't talk a lot about the end-stage hypothyroidism, which is myxedema coma. So that's where I really want to distinguish here, that Cushing syndrome is end-stage hypercortisolism at its worst, metastatically kind of, whereas there's a preclinical or subclinical state that occurs before the overt Cushing syndrome, and a lot of it goes unnoticed. In fact, it can take years for this diagnosis to come to the forefront in many individuals.

So many of us are familiar with the overt state of hypercortisolism, the purple striae, the buffalo hump, the central obesity, the wasting, right, the muscle wasting. That's really it as it's been there and had its way with the body.

But there's also this group of individuals that we need to be aware of and need to put at the forefront of our mind, and that is individuals with multiple anti-hypertensives, non-responders to GLP-1s when it comes to obesity or diabetes treatment, multiple oral anti-diabetic

agents or high insulin levels, osteoporosis. You see osteoporosis, especially in males in the presence of type 2 diabetes, you might have high cortisol. Of course, we see excessive weight gain and sometimes kidney stones. There's a lot of depression and anxiety. And so many of you are kind of saying, 'Oh my gosh, that's a lot of my patients in clinical practice,' but we're really trying to tease out those with those conditions that aren't responding to those standards of care, conventional therapy, and you're scratching your head, going could there be something at the center that is fueling this difficult disease state?

Dr. Yau I've been talking a lot about subclinical hypercortisolism in my practice. Can you tell me a little bit about the prevalence of hypercortisolism and what we've learned in the last few years?

Dr. Yau:
Resistant hypertension is something that often gets sort of overrecognized—or underrecognized, I should say—and proper screening for secondary causes of hypertension is really underperformed. But relevant to resistant hypertension, hypercortisolism as a cause of resistant hypertension has been cited historically as up to about 8%. And in patients with diabetes, the prevalence of hypercortisolism has been cited around 3.4%. Some studies have cited up to about 15%.

But really all of these studies are very retrospective in nature, and they all have their respective variations in how they biochemically define hypercortisolism. Not until recently did we have a prospective study that really looked at patients with difficult-to-control type 2 diabetes in the United States and what the true prevalence of hypercortisolism is in these patients.

And this study was the CATALYST study that was published in *Diabetes Care*, the official journal of the American Diabetes Association. And what we found in the first ever prospective phase 4 clinical trial study of screening patients with difficult-to-control type 2 diabetes in the United States, screening over 1,000 patients using current guidelines and recommendations of using the overnight dexamethasone suppression test with the standard cutoffs of 1.8 or greater, with an adequate dex suppression level of greater than 140, what we find is that almost 24% of patients with difficult-to-control type 2 diabetes have biochemical evidence of hypercortisolism. And as you mentioned earlier, oftentimes these patients are struggling despite being prescribed multiple contemporary diabetes medications. And I really view these patients as having resistant diabetes due to unrecognized hypercortisolism.

So I think moving forward we really need to change our approach as to which type of patients that we should consider screening.

And this is reflected in the new AACE guidelines on diabetes, talking about the cause of secondary diabetes as a result of hypercortisolism or Cushing syndrome, and therefore it is now recognized in updated guidelines and recommendations as to the types of patients that we should be screening in our clinics.

So for those tuning in, you're listening to CME on ReachMD. I'm Dr. Hanford Yau, and today I'm speaking with Dr. Eden Miller about updates in the prevalence of hypercortisolism.

Dr. Miller, let's think about these findings in a real-world context. Can you tell me about a recent patient you saw in your clinic and how you went about identifying and diagnosing them?

Dr. Miller:
Yeah, I had this really great case. She was a 55-year-old female, and she'd come to my office because she had had diabetes for about 15 years. She wasn't doing good even though she was trying really hard. A lot of her A1c values were between about 10 and 12, and when she came to my appointment her A1c was 8.9, and she says, 'That's the best I've had in 10 years.' She had been put on a lot of different medications. She had failed some. She went to insulin. She had all of her other comorbidities treated. She had hypertension and high cholesterol, even depression, extensive family history. She had had some dysfunctional uterine bleeding.

And when I looked at her, she had central adiposity, she had a little bit of puffy eyelid edema. She had the signs of acanthosis nigricans, insulin resistance, but I didn't see any striae. I didn't see a buffalo hump. And she really said to me, 'I am trying everything to control my diabetes.' She had recently been maxed out on her GLP-1, and it didn't seem to make a difference for her. And I could tell that she was desperate. She really seemed compliant with her treatment, and even despite all that, she just wasn't succeeding in getting herself to goal.

I really started thinking, ah, there's a high level of clinical suspicion here kind of when your own internal kind of sensory goes off that you're like, I wonder if she may have a high cortisol. So I asked her, have you ever had a dexamethasone suppression test? I explained it to her taking the 1-mg tablet, you got to take it at nighttime between about 11 and 12. I made sure she had a sheet because it's important. It's a timed test, and you got to get those levels done of the cortisol and the dexamethasone before about 9:00 AM, so I made sure that she had all the instructions and I gave her the tablet, and we found a day that we were going to do it.

I told her that this was the best test in looking for this because it's really going to deal with that inhibition of the central pituitary. We're going to see if there's any—how should I say—endogenous excessive cortisol production. It's going to be way better than a late-night

salivary, which is hard to collect, and that's going to be a different kind of condition. And 24-hour urine is if you're producing so much cortisol that we're going to be able to see it there. So those other two tests are not what we call the gold standard, especially in my opinion in primary care. Not kind of at the leading edge because of the complications.

Now, I also had to make sure that she didn't have any other conditions that may cause a false negative or false positive. She wasn't on birth control, she wasn't taking any steroid, her kidneys were good, her liver was good, she didn't work night shift kind of stuff, and so I knew that was like, okay, we're probably going to have a really good screening test for her.

And guess what? Her serum cortisol level was 5.2 mcg/dL, which is above that threshold of 1.8. Her dexamethasone was 315, definitely high enough for the confirmation that she had taken the pill. Because you want to make sure if that level is not high enough that they hadn't taken it or absorbed it. At our lab her DHEA was normal and her ACTH was less than 5.

And so I brought her back in the office, and I said, guess what? You had a positive dexamethasone suppression test, and I need to do a CT of the adrenal glands. And she's like, 'Oh yeah, I had one of those 10 years ago.' And I was like, what? No way. Like, what do you mean? You have an adenoma? She goes, 'Yeah, I had this non-cancerous tumor in my adrenal glands.' I'm like, did they work it up? And she said, 'Yeah, they did a 24-hour urine, but they said it was normal.' And I was like, you've got to be kidding me. Here is this individual who had been seen by a specialist who found this incidental adenoma and worked it up, but because of the type of testing they did, she'd had a delayed diagnosis for like 13 years. And so it was quite an illuminating case that really had all of the different barriers and challenges that we see that can accompany hypercortisolism.

But if you can do me just a favor, Dr. Yau, what are some of the ways we can differentiate it? Because I know in primary care we're at the frontlines, and I want us to be looking for this and screening it, but I don't want it to feel complex, because there are other causes of hypercortisol, but how do you distill it down so we can make sense of where it's coming from?

Dr. Yau:
ACTH and DHEAS, and the reason for that is this combination of tests with the cutoff of 10 or less for ACTH and 40 or less for DHEAS really has the same sensitivity and specificity and positive predictive value equivalent to an overnight dexamethasone suppression test.

On top of that, after you do this baseline morning ACTH and DHEAS, performing an overnight dex suppression test, just like you did with your 55-year-old patient with the resistant diabetes and resistant hypertension, provides that second additional diagnostic.

So before we wrap up, Dr. Miller, can you tell us about how you ended up caring for the patient and what was their outcome? And what might have happened if you had diagnosing and treating hypercortisolism in a patient like this just like she's been missed for over 10 years?

Dr. Miller:
And then I pulled up her last CT scan that we did in 2015. I ended up repeating it anyway because I wanted to make sure, , just as good continuity of care. She did have that incidental solitary adrenal mass in 2015, and she had her 24-hour urine, which came back kind of elevated kind of thing. But then her DST came back at 2.1. So here's a case where years ago it came back at 2.1, which still would have been the threshold we have now. And it was repeated. The urinary free cortisol was repeated again, and so I was like, hey, somebody was thinking about this, right? And yet they hadn't done it.

So then for 10 years, with the known adrenal adenoma, positive DST by our standards, all the associated difficult-to-control conditions, she ends up in my office, and I'm back at that same crossroads with her.

And so you're exactly right. What I did, once I did confirm the diagnosis, I did the other ancillary tests, I made sure that's what we were dealing with, I did get the repeat CT, I actually referred her for surgical intervention because we're using the care team, right? We're using those who are dealing with it. I found an adrenal specialist. And guess what? They didn't think she was a candidate for surgery due to her poor diabetes control. And I was like, yes, there's a reason for that.

And this is a common kind of crossroads we see, because a lot of those individuals would have a curative effect with an identified adenoma. Only a third of them have adenomas. Some have unilateral, some have bilateral, some have hyperplasia. So don't always think you have to find a smoking gun, but we want to look for it because there might be a different pathway for intervention.

But in her case, we are actually going to treat her clinically. We're going to block the cortisol from binding to the receptor. We did all the appropriate screening for that. We placed her on spironolactone for this particular drug to make sure her potassium stayed stable. We had to do a lot of discussion of a reverse titration of insulin with her CGM. And I gave her a little bit of a hall pass for work if she'd had any kind of issues regarding that. Because when you start to block the cortisol, however you do it, whether it's surgically or pharmacologically, you can feel that withdrawal from it, and so you got to be mindful of that. You're pulling away this high cortisol that's

really fueling the fire.

And so that was great that we managed to go through that. We are several months out. We were monitoring her potassium level and chemistries. We gradually increased her treatment of mifepristone according to the recommendations, doing appropriate follow-up closely initially.

And now she's actually doing quite well. She's about, 6 months in. Her A1c is continuing to fall. We now have it less than 8. She is still navigating her reduction of her insulin, and her weight has started to shift. Her blood pressure was the thing we saw the first thing. That was one of the first things that we really saw changing.

And so now what I think we're doing is we're really going to the core problem.

And so imagine with an individual with a high A1c non-responder, where I'm giving a different directed treatment that's also going to go to some of the other complications she has, because she has this cardio-renal-metabolic complications that create this high level of risk, and she's had that exposure. And that's really why we're doing this. We're doing this because there's this residual risk that high cortisol lays on top of hypertension and diabetes, and so it brings her into kind of a newer category, almost like these conditions accelerated as cortisol being that fire that lights it. And so we're starting to expand our ability to look at this condition beyond just diabetes.

So if you're keeping pace with us and this whole dysfunctional metabolism and diabetes, we're also seeing it in hypertension, which really, as you mentioned, reminds me that I need to look at people with hypertension through a new lens. I need to look at them for high cortisol.

There's a great trial that's hot off the presses called the MOMENTUM trial, looking at the prevalence of endogenous hypercortisolism in patients with resistant hypertension. So if we just created a thought-provoking idea, now we're going to go beyond that, right? We're going to go beyond just hard-to-control diabetes. We're going to be saying, hey, you have high blood pressure, you have hard-to-control hypertension. Who are those individuals and should we be screening them?

I think it's going to be that list in your head of those chronic conditions that you see, or those comorbidities that don't seem to be shifting. Osteoporosis, hypertension, and excess adiposity, and I know that many of you are going to get excited. And so here's the good news and the bad news. Every person you think of is not going to have high cortisol. So we want you to know that you are going to find them if you look, but you're probably going to screen more people than not. But don't let it stop you, because for those individuals that's 100% of how we're going to impact their trajectory of their disease, reduce their risks, and start getting them the guideline-directed therapy that they need for this subclinical hypercortisolistic state.

Dr. Yau:
The prevalence of hypercortisolism in resistant hypertension found in the recent published MOMENTUM study, again, was over 25%. The data is very similar between MOMENTUM and CATALYST, even though one was looking at diabetes, the other hypertension.

So I want to thank my guest, Dr. Eden Miller, today, for helping us better understand how to use this data in practice to help improve patient care. Dr. Miller, it was great speaking with you today, and I want to thank you all for sharing your time and joining us here on ReachMD CME program.

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