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Identifying a Key Cause of Hard to Control Diabetes

Announcer:
Welcome to CME on ReachMD. This activity titled *Identifying a Key Cause of Hard-to-Control Diabetes*, is provided by Primary Care Education Consortium in collaboration with the Primary Care Metabolic Group. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Brunton:
Well, welcome to *Identifying a Key Cause of Hard-to-Control Diabetes.* I'm Stephen Brunton. I'm a family physician who practices in South Carolina, and I'll be the moderator of today's program. I also work with the Primary Care Metabolic Group.

This is an exciting topic, because there have been many cases of very hard-to-control diabetes. We really haven't understood what the underlying cause is, and today we're going to discuss that. And I think it'll provide some insights into why these patients are hard to identify, but a prospect of how we might control and help these patients get better control of their diabetes.

I'm joined by three panelists: Dr. John Buse—he is a Verne Caviness Distinguished Professor at the UNC School of Medicine; Dr. Jennifer Goldman—she's Professor of Pharmacy Practice at the Massachusetts College of Pharmacy and Health Sciences; and Dr. Eden Miller with Diabetes and Obesity Care in Bend, Oregon.

So, let's talk about the objectives today. We hope that you'll be able to increase your awareness of hypercortisolism as a potential cause of hard-to-control diabetes. We'll also describe new and emerging data for hypercortisolism treatments, including the impact on patients within their practice who have difficult-to-control diabetes. We'll also implement methods for working with the healthcare team, including initiating effective referrals to endocrinology for patients with evidence of hypercortisolism. And then lastly, collaborate with members of the healthcare team to implement multidisciplinary management of hypercortisolism and achieve optimal patient outcomes.

So, let's talk about how common this problem is in primary care practice. And what is it? Well, it's referred to previously as Cushing syndrome or endogenous hypercortisolism. And we'll talk about that as a prolonged excessive cortisol activity that is not due to a normal physiological etiology.

Now, often it goes undiagnosed or it's misdiagnosed, and that results in progression of the morbidity as well as increased cardiovascular-related mortality. So, let's look at the classification of hypercortisolism. And it can be classified into two main categories. There's the ACTH-dependent hypercortisolism—that includes excessive adrenocorticotrophic hormone secretion by pituitary tumors. This is known as Cushing syndrome. Or non-pituitary tumors, where this results from ectopic ACTH secretion. There's also ACTH-independent hypercortisolism—that includes autonomous cortisol secretion by one or both adrenal glands.

So, what is the impact of hypercortisolism on type 2 diabetes? Well, many patients with type 2 diabetes don't reach their treatment goals. It is despite effective therapies and the best efforts from clinicians as well as the patients. And this may be because of excess cortisol that increases insulin resistance and decreases insulin sensitivity, and that negatively impacts the metabolic defects underlying type 2 diabetes. So you get a contribution to a form of type 2 diabetes that's difficult to control with our standard therapies.

With our role as primary care clinicians in managing hypercortisolism, there's an increased focus now on identifying and appropriately

managing clinically inapparent hypercortisolism. As primary care clinicians, we can play a key role. Frequently, these patients are seen in primary care, and we have a critical role in ensuring optimal treatment outcomes for these patients. Many of these patients are missed or have a delayed diagnosis and may not have access to endocrinology care. As primary care clinicians, we can identify these patients at risk for hypercortisolism and use effective screening tools to identify the disease. We can also initiate effective referrals to endocrinology as part of the healthcare team using specific approaches.

Let me introduce Dr. Jennifer Goldman. She'll talk about screening and diagnosis with hypercortisolism.

Dr. Goldman:
Let's think about how hypercortisolism presents. While classic Cushing features like moon face, central obesity, purple striae, they are well known; many patients today present with subtle or non-specific symptoms: fatigue, hypertension, glucose intolerance, or unexplained weight gain. This variability means cases are often missed, so we must maintain a high suspicion, even without textbook signs.

A delayed diagnosis can be serious. It may take up to 10 years from symptom onset to diagnose, resulting in prolonged cortisol exposure that worsens metabolic disease, bone loss, or cardiovascular risk. Untreated hypercortisolism raises mortality 2 to 5 times above the general population. Early detection is crucial.

Hypercortisolism exists on a spectrum. Even patients without classic symptoms face increased cardiometabolic risks such as dyslipidemia, hypertension, or insulin resistance. Early identification and management are key to reducing these risks. If we identify and treat it appropriately, we have the potential to alter the trajectory of patients' overall cardiometabolic health. While hypercortisolism is rare in the general population, its prevalence is higher in those with certain risk factors, such as poorly controlled diabetes or hypertension. Screening is recommended for patients with multiple comorbidities, unusual features for their age, such as osteoporosis or type 2 diabetes in young adults, or adrenal masses. And importantly, if the clinical suspicion is high, we shouldn't dismiss normal screening results. Even a normal test might warrant further evaluation depending on the context. Clinical judgment remains essential.

Endocrine Society guidelines outline specific patient groups who should be screened for hypercortisolism: screen patients with unusual features for their age, like osteoporosis, type 2 diabetes, or hypertension in young adults; multiple unexplained progressive features like worsening type 2 diabetes outside of normal progression; or unexplained weight gain or adrenal masses. Prevalence in these groups can reach up to 50%.

Dr. John Buse is going to take a closer look at some of the clinical features of hypercortisolism and introduce the CATALYST trial.

Dr. Buse:
Thank you, Jennifer. It's a pleasure to get to talk about the CATALYST prevalence phase of the study. But just first as background, you know, our classic teaching when we were students around hypercortisolism is based on the original observation by Dr. Harvey Cushing, I think, in 1932 about Cushing's disease. And the classical features we have in our mind are these abdominal striae—purple, violaceous striae, a centimeter wide—central obesity, easy bruising, dorsocervical fat pad, red cheeks, moon facies. That is the classic look.

But we now understand that today, the vast majority of cases of hypercortisolism, you know, have really subtle physical features, perhaps nothing at all. When you look at this picture, maybe the one thing that you would say is her face is a little round, but otherwise she has none of the stigmata of hypercortisolism. What she has is multiple comorbidities associated with hypercortisolism. And the method by which she's gotten this hypercortisolism is a so-called ACTH-independent autonomous adrenal production of cortisol, and this is much more common than previously imagined.

So, the rationale for the prevalence phase of the CATALYST study came from the recognition that hypercortisolism has very broad effects, not only on diabetes, but also dyslipidemia, cardiovascular disease, central obesity, hypertension, and osteoporosis. And frankly, of those manifestations, in some ways, diabetes might even be the least common of them.

There are multiple mechanisms by which cortisol contributes to the pathophysiology of all these conditions. And in the CATALYST study, we sought to see what was the prevalence of hypercortisolism in people with difficult-to-control type 2 diabetes who were receiving standard-of-care therapies.

The test that we used was a so-called 1-mg overnight dexamethasone suppression test—1 mg of dexamethasone at 11 pm, a single morning blood draw for cortisol and simultaneous dexamethasone level; the dexamethasone level being just to confirm the participant had taken the tablet and observed that it wasn't one of these rare hypermetabolizers of dexamethasone.

And if that test was positive—the cortisol level was greater than 1.8—we did some further evaluation: subsequently a morning ACTH and DHEA, a sulfate to confirm that it was ACTH-independent hypercortisolism, and then adrenal CT scan to evaluate whether there are adrenal structural abnormalities.

The inclusion criteria—or how we define difficult-to-control type 2 diabetes—was a hemoglobin A1c between 7.5 and 11.5% despite taking three glucose-lowering medications, or insulin plus at least one other glucose-lowering medication, or two glucose-lowering medications and having a complication of diabetes, or two glucose-lowering medications and at least two blood pressure-lowering medications.

And then we excluded things that are associated with false-positive dexamethasone suppression tests. So, most importantly, people who were taking systemic glucocorticoids, pregnant or lactating women, use of oral contraceptions, hemodialysis or end-stage renal disease, severe untreated sleep apnea, or excessive alcohol consumption. And also, in general, severe—you know, clinically severe—medical, surgical, or psychiatric illnesses, and then being a night shift worker.

What we found was that of the people with difficult-to-control diabetes, 23.8%—or 252 out of 1,057—had hypercortisolism as defined by a post-dex cortisol of greater than 1.8. In fact, the median value was 3.5.

And there were groups that had even higher prevalences. So these included people of non-white ethnicity and race, older patients who had more, people with lower BMIs had more, people on more blood pressure medications had a higher prevalence of hypercortisolism, as did people who were taking analgesics, SGLT2 inhibitors, tirzepatide, high-dose GLP-1 receptor agonists. People with 3 or more blood pressure medicines, it was 36% had hypercortisolism. People with cardiovascular disease, it was 33%. And overall, about 1/3 of the patients had an adrenal imaging abnormality on abdominal CT scan.

So, to summarize, the prevalence was 23.8%. It's a very common phenotype—not based on how people look, but based on their multimorbidity and their medication burden. About 1/3 of people had an abdominal CT scan abnormality in the adrenal glands. The screening was easy to do—a 1-mg overnight dexamethasone suppression test with a simultaneous dexamethasone level. And on a separate day, measuring a morning ACTH and DHEA-S to confirm that the source was ACTH-independent hypercortisolism. And the common causes of false-positive tests do need to be excluded in this context.

Back to you, Jennifer.

Dr. Goldman:
We have three non-invasive screening tests: the 1-mg overnight dexamethasone suppression test, late-night salivary cortisol, and 24-hour urine-free cortisol. The 1-mg overnight dexamethasone suppression test is the easiest and most sensitive at about 95%. This means it's the best option for picking up cases of hypercortisolism, especially early on.

It's important to interpret these test results in the context of the patient's overall clinical picture, including the history and any comorbidities, since no test is perfect on its own. For the overnight DST, the patient takes 1 mg of oral dexamethasone at 11 pm. The next morning—about 9 hours later—a blood sample is drawn at 8 am to measure both serum cortisol and dexamethasone levels. So, it's important to explain to patients how to prepare for that test. Timing is critical.

When interpreting the results, if the serum cortisol is less than 1.8 and the dexamethasone level is above 140, hypercortisolism is not likely. However, if the serum cortisol is 1.8 or higher with an adequate dexamethasone level, this suggests possible hypercortisolism, and an endocrinologist should be consulted for further evaluation.

When interpreting DST results, it's important to consider factors that can skew accuracy. False positives may occur due to estrogen-containing medications, pregnancy, rapid dexamethasone metabolism, or failure to absorb or take the medication. Use of exogenous steroids and conditions like chronic kidney disease can also contribute.

On the flip side, false negatives may result also from chronic kidney disease, or other disease, or drugs that inhibit CYP3A4. And these can elevate dexamethasone levels and suppress cortisol, even when hypercortisolism is present. Additionally, cyclic hypercortisolism may lead to normal results if cortisol happens to be low at the time of testing. Being aware of these is essential to avoid misdiagnosis and guide appropriate follow-up. Effective screening follows three steps. First, it's essential to focus on appropriate patient selection. We should screen patients who have signs or symptoms suggestive of hypercortisolism or those who have a high pretest probability based on their clinical presentation. Second, using the sensitive screening test is crucial. The 1-mg overnight dexamethasone suppression test is the first-line option because of its high sensitivity. And finally, always interpret test results within the clinical context. This means considering the patient's overall medical history and presentation to avoid misdiagnosis. By doing so, we can minimize both false positives and false negatives, ensuring patients receive the most accurate assessment and appropriate follow-up care.

When we think about difficult-to-control type 2 diabetes, we often reach for intensifying therapies. But what if cortisol is an overlooked contributor? Studies have shown that addressing hypercortisolism can improve glycemic control and blood pressure and other metabolic markers. So, for patients whose diabetes don't follow the typical trajectory or who seem resistant to standard care, it's worth considering

whether excess cortisol may be part of the problem. In those cases, screening for hypercortisolism might help us uncover an underlying, treatable contributor to their metabolic dysfunction.

To better understand how hypercortisolism impacts glucose metabolism, let's take a step back and revisit a concept that many of us know well—Dr. Ralph DeFronzo's Ominous Octet. And this model outlines the eight core defects that drive type 2 diabetes, including insulin resistance in muscle and liver, beta cell dysfunction, increased lipolysis, and more. And it's a helpful framework that reminds us that diabetes is about complex, multisystem dysfunction. Understanding this gives us a lens to appreciate how additional factors like cortisol excess may further complicate the picture. But the science doesn't stop at eight. As we learn more, we continue to refine our understanding of metabolic disease, and that brings us to the next evolution of the model.

Dr. DeFronzo recently proposed an expansion of the original model to include a ninth contributor—hypercortisolism. The addition of cortisol excess to the mix reflects what we're seeing clinically. Elevated cortisol interferes with multiple pathways involved in glucose homeostasis. It amplifies insulin resistance, increases hepatic glucose production, and worsens central adiposity. The shift from the Ominous Octet to the Noxious Nine highlights the evolving recognition that we need to look beyond traditional risk factors, especially in patients who aren't responding as expected to conventional therapy. This evolution underscores the importance of identifying and managing hypercortisolism as part of comprehensive diabetes care.

First-line treatment for hypercortisolism typically involves surgical resection of the causal tumor where possible. But for patients in whom surgery is not possible or not curative, radiation therapy or medical therapy is used. And when minimally invasive adrenalectomy is not appropriate, feasible, or preferred for treating hypercortisolism, certain cortisol-directed pharmacotherapies that lower the effect of cortisol in patients with hypercortisolism can potentially improve type 2 diabetes, hypertension, and cardiovascular risk, including patients who are not surgical candidates, who have failed or refused surgery.

Throughout treatment, managing comorbidities aggressively—hypertension, diabetes, dyslipidemia, and bone health—are critical.

Dr. Brunton:
Next, we have Dr. Eden Miller. She'll give us a case study in type 2 diabetes and hypercortisolism.

Dr. Miller:
Hi. I am so excited to present this case. This is a new patient consult that I had in my office, and I'm going to walk you through all the details to really conceptualize this concept of identifying those who may be suffering from this subclinical hypercortisolism.

So she had very poorly controlled type 2 diabetes. She was 55, Caucasian. She had diabetes for 15 years. She had struggled with excess adiposity. As you can see, her BMI and her A1c just never really got into control. It would hover between about the high 8s and the low 10%. She was on several medications that you can see on the right-hand side, a very high basal insulin use, rapid-acting insulin three times or more per day, she was on a GLP-1, all the accouterments for hypertension.

So I want to point out a little bit of kind of those at-risk factors that came top of line for me. First of all is the fact that she is on a couple antihypertensives, right? So this poorly controlled type 2 diabetes—you don't have to be on insulin, but she was a non-GLP-1 responder. What I mean by that is GLP-1s are amazing. We talked about them before. We tend to see significant improvement in glycemia. She was on the max dose of the GLP-1, and look at her total daily dose of insulin. She's like 300 units, and it's still not controlling her. Yes, I asked her all those questions—are you taking it? She was on a CGM. And she just became exceedingly frustrated because she said, 'I just don't know what to do.' And when I had just seen her recently, her A1c was 8.9, and she was excited. She was like, 'Oh my gosh, this is my best A1c yet! And I'm like, you're kidding, you know, we're still not doing very well.

So what I did is I went and took a pretty deep history. I talked with her about diabetes, what kind she was; she was unsure. And I promise you, I worked it up. She had all the associated hypertension, hyperlipidemia. She had migraines as well, which is kind of an interesting symptom that later on we're going to explore. And she suffered from depression. She had a total abdominohysterectomy due to dysfunctional bleeding, which is not uncommon.

So let's talk about her physical exam. She did have central adiposity—you know, where we get that central obesity and a thinner arm kind of appearance. She also had this upper eyelid edema. I promise you, I worked her up for thyroid, which was normal. She had the insulin resistance kind of like phenotypes—the skin tags, the acanthosis. But she didn't have any significant striae—you know, those little kind of stretch marks that we see with hypercortisolism or very advanced Cushing's disease. She didn't have a buffalo hump either.

I went for her family history, which was type 2 diabetes, coronary artery disease. And you know, I mentioned to her the challenging diabetes control and the lack of the improvement with the GLP-1. So I asked her, as a result of her pretty extensive history, has she ever had a DST—a dexamethasone suppression test? She couldn't remember that. I think maybe because I said doctor needs, and so looking back now, I might have explained it a little bit differently, but she never indicated that she had had any kind of workup that she

could remember.

And so what we did is we did the workup. So here are her kidney functions. She had a little bit of proteinuria—not surprising given her length of diabetes. Her LDL was pretty good control. But remember, we were on those particular medications. Blood pressure was decent, thyroid was good. Why? Because I want to make sure that any of that facial edema I was seeing wasn't related to that.

And so I gave her a 1-mg dexamethasone suppression test. Now remember, that's the one where you give the tablet late at night, you have them go into the lab before 9:00 a.m., they do a serum cortisol and we do a dexamethasone range. Those are the two most important tests. Why? Because we want to see if that dexamethasone suppressed her own additional cortisol production.

So first off, you have to have the dexamethasone level positive. That means it's greater than 140. That means they took the tablet, it's working, it's doing the job of doing any kind of central pituitary suppression. Then we measure the serum cortisol. That serum cortisol should be less than 1.8—that's the new normal range. You're going to get labs from the lab that show a much higher range, so do not be misled. It's 1.8.

And for us, she was at 5.2. I did all the DHEA, which was normal, looking for polycystic ovarian or other androgen production. And here's another critical thing, the ACTH was low. That means that her suppression of her pituitary signal was positive, meaning she was low and she didn't have a pituitary type of problem.

Now, you can do all those tests at the same time, you can do them separately. I'm just going through what we did for her. So I had her come back in. She came in for a follow-up, and I said, you know, you have an elevated cortisol that wasn't suppressed by the dexamethasone. And I mentioned to her, we need to get a CT of the adrenal glands to look for an adenoma, a noncancerous-producing cortisol area, or a growth. And she says to me, 'Oh, I have an adrenal mass. They found it 10 years ago.' And I was like, what? So I quickly have my staff go in there and get a copy of that CT. And lo and behold, I'm like, did they work it up? And she's like, 'Well, yeah, they worked it up. And I'm like, well, what did they do? And they said, 'Yeah, they did a 24-hour urine cortisol. I went to an endocrinologist specialist because they incidentally found this adenoma on CT, and I got referred there.' And I said, You did a 24-hour urine? Like, how long ago was this? And she was like, 'Oh, about, I don't know, 3-4 years ago.' So lo and behold, I pulled up the CT, there it was. I kind of looked at it, looked at where it was located, pulled up the old labs, and I said to her, oh my goodness, do you understand that we don't look at urinary cortisol anymore? I'm going to use an analogy so you get it. Imagine if we diagnosed diabetes by just looking for glucose in the urine, right? It has to get pretty high—like above 200. So imagine if we waited to diagnose diabetes by looking at glucose in the urine, it would be a lot more advanced. And so in this case, her early subclinical hypercortisolism wasn't picked up as a result of that 24-hour urine cortisol. It's not high enough to get there. But that doesn't mean that she's not suffering from hypercortisolism.

So just top of line—because I know I told you I would say this—I did get all of the previous records. She was negative for type 1. Remember the hard-to-control diabetes—we got to make sure that we don't miss those variants. Her A1c by her prior endocrinology visit was between 10 and 12 most of the time. She varied throughout her history between 150 and 250 units plus of insulin. Sometimes she gets near 300. And her prior failed medications—because I know you all are thinking, has she tried these meds—were below; the metformin, the pioglitazone. She had a normal weight gain and edema—no surprise, it causes sodium retention. She had been on a couple different GLP-1s, and she had failed an SGLT-2.

So we had some additional work that I was able to look up because I'm like, how did this still get missed, right? So, 2015—so that was like 10 years ago—she couldn't remember. She had a solitary adrenal mass at 2.5 cm. Now what I will tell you is I repeated that CT, and it hadn't changed. I looked back at her 24-hour urinary-free cortisol, and it was minimal—just like I said. When you have advanced metastatic Cushing's disease, that's when it'll show up in the urine.

Now, she did have a DST, so kudos to the endocrinologist who did a 1-mg dexamethasone suppression test. But he noted that it was 2.1 and that it was borderline abnormal. And the reason was because his scale—you know, the lab—was not what it is typically now regarded as elevated. Remember, 1.8—1.8—I mean, she would have been positive. And again, they repeated the urinary-free cortisol in 2023. That means somebody was questioning what was going on, rather than just working this up in the appropriate manner, and really diagnosing her with that.

So for 10 years now, she has gone undiagnosed hypercortisolism, which, as we've reviewed in the data, has a huge cardiorenal metabolic risk associated with it. Not only that, she had a known adrenal adenoma with a positive DST and significantly hard-to-control type 2 diabetes, hypertension, plus these migraines and depression, which I am waiting to see if those improve. So I repeated the CT—no change in the adrenal mass. I sent for surgical consult, and guess what? They said she's not a candidate for surgical removal due to her fairly severe type 2 diabetes—like, you've got to be kidding me, right?

In addition, there's only a few surgeons in the country that do what are called the adrenal-sparing surgery, and they're thinking about doing a full adrenalectomy, which she may have to go on a little bit of cortisol in the future. Oh, you see how crazy this gets.

Okay, so let's summarize. She's been properly identified, screened, positive, we did additional confirmation, and we have now started the process of mifepristone. Just talked to her yesterday. She has her prescription. We have all of those baseline things we got to do—monitoring labs, watching potassium, making sure that there's no med interaction, lowering her diabetes-related drugs. And I'm so excited for her because she's due to start this next week, so maybe we'll have a follow-up to see how she's going to respond with her diabetes, her hypertension, her excess adiposity. I'm excited.

So thanks for letting me share this case with you, and we'll continue on with our education.

Dr. Brunton:
Dr. John Buse will talk about new and emerging data for hypercortisolism in the treatment of type 2 diabetes.

Dr. Buse:
So I mentioned before, 23.8% of the patients with difficult-to-control type 2 diabetes had hypercortisolism. We took those people who met the inclusion criteria for the phase 2—which I'll get to in a moment—and randomized them in a 2:1 manner to mifepristone or placebo for 24 weeks, and then followed for an additional 4 weeks off of medication.

The primary endpoint was the change in hemoglobin A1c from baseline to week 24, comparing mifepristone versus placebo. And what is mifepristone? So it's a competitive glucocorticoid receptor antagonist. It binds to the glucocorticoid receptor, thereby decreasing cortisol-mediated signaling and reducing the clinical effects of hypercortisolism. It's FDA approved for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have either type 2 diabetes or glucose intolerance.

So technically, this study was a, quote, phase 4 study to evaluate patients based on the indication for mifepristone on the aim to improve glycemic control. The key inclusion criteria were to exclude people with high ACTH or pituitary, or from another tumorous source where ACTH is sometimes made in, for instance, lung tumors. So among the people that had a cortisol level greater than 1.8 with a simultaneous dexamethasone level greater than 140, we stratified the population based on those that had adrenal abnormalities on CT scan versus no adrenal abnormality. And the eligibility criteria were around suppressed levels of ACTH and DHEA sulfate. There were slightly different cut-points for the two criteria, but this is basically a way of ensuring that patients have ACTH-independent hypercortisolism, and that is generally from an autonomous adrenal source.

The other eligibility criteria really mostly had to do with safety of the approach. So we excluded people who we were unable to correct their blood pressure to less than 160/100. We excluded people if we were unable to correct their potassium to greater than 4. We were excluding people who had uncontrolled hypo- or hyperthyroidism. We excluded people who either were taking systemic glucocorticoids or were at risk for taking systemic glucocorticoids due to an underlying condition like asthma. We excluded people with evidence of liver disease, eGFR less than 30. And very importantly, drugs metabolized by CYP3A4 or CYP3A substrates with a narrow therapeutic window—things that would have a drug–drug interaction with mifepristone. And then we excluded people with an unexplained history of vaginal bleeding, endometrial hyperplasia, or endometrial carcinoma.

The dosing schedule—again, this is a blinded study, so we didn't know who's getting drug and who's getting placebo. We started with one 300-mg tablet. After 4 weeks, we increased the dose if people were tolerating it well to two 300-mg tablets, and between week 8 and 12, and could increase the dose up to 900 mg as needed.

Here's the participant flow in the study. So there were 252 people who completed the prevalence phase and had a post-dex cortisol greater than 1.8. Of those, 120 did not enroll in the treatment phase, mostly because they didn't want to; 38 did not meet the eligibility criteria that we just went over, but 8 consented and were eligible to participate but then eventually decided not to participate. So there were a total of 136 patients—91 randomized to mifepristone and 45 randomized to placebo.

You can see that of the people randomized to mifepristone, more people did not complete treatment as compared to placebo—42 versus 8. And this non-completion was largely related to adverse events, and we'll get to that more in a moment.

Here are the demographics and baseline characteristics. So the groups were pretty well matched based on the randomization, and not very different from the overall proportion of patients who had a cortisol greater than 1.8, with the exception that there was less enrollment of eligible African American and Latino patients—perhaps related to issues about concern about participating in research. The average BMI was 33 and change, and the average A1c was 8.4 and 8.6.

So here's the primary endpoint—the reduction in hemoglobin A1c from baseline to week 24. You can see in the mifepristone-treated

patients in blue, the A1c was reduced from 8.6% by 1.5% at week 24, and the placebo-treated patients had a much smaller reduction in A1c of only about 0.15%. So the difference between arms was highly statistically significant and clinically meaningful, with a 1.3% reduction in hemoglobin A1c. And that was despite the fact that the mifepristone-treated patients had much more reduction or dose continuation of medications, including insulin, as the investigators tried to help the patients avoid hypoglycemia.

If you look at the subgroup analyses for completers or people who received the 900-mg maximum dose in the study of mifepristone, that supports the primary endpoint we saw, a somewhat greater difference from placebo, 1.6% for the 24-week completers and 1.85% for those that took the maximum dose of mifepristone.

And if you look at patients with or without adrenal imaging abnormalities, you can see very little difference in the hemoglobin A1c reduction with adrenal imaging abnormalities 1.4%; without adrenal imaging abnormalities 1.3%. And this is important because this is really the first randomized placebo-controlled study that showed that hypercortisolism—even without an adrenal imaging abnormality—responds to cortisol-directed pharmacologic treatment.

There was body weight loss, so about 5 kg as compared to placebo at 24 weeks. And you can see that the weight loss is persistent and continuing at 24 weeks. So we don't know how much weight loss might eventually have ensued in these patients. And this was associated with reductions in BMI and waist circumference.

There was a small increase in blood pressure associated with mifepristone therapy. This was clinically not particularly meaningful in these patients, as they went from a baseline of 125 systolic blood pressure to 132. But there was an increase in blood pressure. This is likely due to the fact that with blockage of cortisol action, you still have cortisone which is being metabolized from cortisol, and cortisone can work on the ACTH receptor and drive an increase in blood pressure in patients that are on cortisol receptor antagonists like mifepristone.

If we look at treatment-emergent adverse events, there were more in the patients treated with mifepristone. And particularly, if you look at one treatment-related adverse event or more, it was 61.5% versus 32%. If you look at treatment-emergent adverse events leading to treatment discontinuation, 29% versus about 2%, and the series of events about 32% versus 5%.

The most common treatment-emergent adverse events were hypokalemia, and this is well known with mifepristone and again related to overstimulation of the mineralocorticoid receptor as a result of the activity of cortisol on that receptor. And the other adverse events were consistent with the glucocorticoid withdrawal syndrome, which will occur with any treatment of hypercortisolism, whether surgical or pharmacologic. Generally, it is transient, lasting a matter of weeks. Eventually, the patient adapts to the lesser cortisol activity, and the symptoms generally resolve, but they can be quite bothersome to patients.

So to summarize, the treatment phase, mifepristone therapy reduced hemoglobin A1c by 1.47% as a least square mean change at week 24. This was a reduction from a baseline of 8.62% to around 7.1%, and the difference from placebo was 1.32%. This occurred despite the fact that there was greater glucose-lowering medication dose reduction and discontinuation with mifepristone. There was no difference in the extent of the A1c lowering whether patients did or did not have an adrenal abnormality. Sensitivity analyses support the finding. And mifepristone was associated with clinically meaningful changes in body weight of about 5 kg. And again, that was still continuing at the 24-week time point.

There were fewer completers in the mifepristone arm, and the most common reason for treatment discontinuation was adverse events in nearly 2/3 of those patients. While the mean blood pressure on mifepristone remained at or near the treatment goal of 130/80, systolic blood pressure did increase from 125 to 132 in the mifepristone arm.

Serious treatment adverse events were reported more frequently with mifepristone, and many of the most common adverse events were consistent with the glucocorticoid withdrawal syndrome, which can occur with any treatment for hypercortisolism. Mifepristone is not associated with flat-out clinical adrenal insufficiency, but this can be clinically meaningful and lead to treatment withdrawals. And in clinical practice, we should counsel patients around the development of these symptoms and support them through those symptoms to achieve the benefits.

And then lastly, hypokalemia, which is a known adverse event to mifepristone, could be better addressed in clinical practice than any clinical trial by proactively using potassium-sparing diuretics, as we prescribe mifepristone or other such therapies.

So to summarize, the implications of the CATALYST study are quite broad and important. First, we should be screening for hypercortisolism in people whose type 2 diabetes is challenging to treat adequately, looking for people who have multimorbidity and are treated with multiple medications. The mifepristone results provide a proof of concept that identifying and addressing hypercortisolism is a novel path to improving diabetes care, potentially for millions of people worldwide. Mifepristone, however, is a tough drug to use, and for the treatment of hypercortisolism, it requires individual patient-centered considerations. So first, there are important drug-drug

interactions that need to be screened for. Secondly, we have to set the expectations appropriately with patients regarding the steroid withdrawal symptoms and how we can work together to try and mitigate those. And third, we should treat hypokalemia expectantly and proactively, considering preemptive prescribing of mineralocorticoid receptor antagonists like spironolactone. And we should make sure—or I guess we can't make sure, but we should look for guidelines to reflect the insights from the CATALYST study.

Dr. Brunton:
Well, let's start our faculty panel discussion. Should primary care clinicians consider treating patients for hypercortisolism? Or should we always refer to endocrinology? Eden, let's get your perspective.

Dr. Miller:
Well, first of all, I love that we're talking about this in a primary care setting, because we are on the front lines. Now, whether a clinician feels comfortable in going the full course with hypercortisol, it's really going to be an individual journey. I can also see that over time changing.

I think the biggest thing is for us to identify it's there, to screen, and maybe you could take some of the initial steps. But for sure, don't just let inertia stop there. Make sure you find a care team. Make sure you find an individual that feels comfortable in taking those next steps. And maybe in the future, those clinicians will feel more comfortable in treating the various steps of addressing hypercortisolism.

Dr. Brunton:
Well, what do primary care clinicians need to know about other treatments for hypercortisolism, like surgery or other medical therapies that are like glucocorticoid receptor antagonists? John, what are your thoughts on this as an endocrinologist?

Dr. Buse:
Yeah, I mean, the only thing that's been studied specifically in this area of difficult-to-control type 2 diabetes and managing hypercortisolism with an aim to improving glycemic control—the only thing that's been studied is mifepristone.

There are adrenal steroidogenesis inhibitors, like osilodrostat, which are indicated for the treatment of Cushing syndrome. They just haven't been studied in this specific condition, and so we don't really know what the benefit would be. You know, pituitary-directed agents we would not think would be beneficial in this setting, and then there are already sort of more adrenolytic-ish agents like ketoconazole and metyrapone. And again, they may have benefits—just hasn't been studied; not really sure where to go there.

Dr. Brunton:
Well, let's discuss the importance of the interprofessional team to screen for hypercortisolism, as well as the diagnosis and treatment. Eden, you're leading an interdisciplinary practice, share your thoughts.

Dr. Miller:
Yeah, you know, it really takes a team, especially since we have limited time. We all want to play a role. We want to be practicing at the top of our licenses. I mean, I think of an example just recently of a hypercortisolism patient, that I'm going through all the diagnosis and the journeys, and I've really had a lot of interactions with many of the team members. I have had various endocrinology NP and PAs where I have gleaned prior records. I even had a great conversation with the gynecological nurse practitioner as we were getting ready to start some of those cortisol blockers, to talk about some of the dysfunctional uterine bleeding that this individual had.

So what I tend to do is I take the person in front of me who has hypercortisolism, I go through all of their multidisciplinary teams, all their specialists, because many of them have specialists by now—remember, they're hard-to-control diabetes. And so I go through all those specialists. I make contact with them as colleagues, talk to them about what I'm doing, and make sure that everybody's on the same page and everybody's helping too. Because, you know, Jennifer is going to talk about pharmacological too; they're usually in charge of a lot of these other medications, and I want to make sure I'm having conversations as I initiate therapy regarding these individuals. So you've got to have a team effort and share that burden workload amongst all of those colleagues.

Dr. Buse:
Yeah, I think the critical issue really is communication. And one thing I need to make sure that everybody understands—there are endocrinologists, and then there are endocrinologists. I, for instance, I'm an endocrinologist, but I'm largely diabetes focused. And until this CATALYST study, had basically zero experience with mifepristone as a drug therapy or the management of hypercortisolism in general.

So there are adrenally focused endocrinologists who will have a lot of experience in the space, but a lot of endocrinologists won't. So I think it's really important as you contact someone to help you with regards to managing a patient with hypercortisolism in the context of difficult-to-control type 2 diabetes, is to go over the reasons why you thought this might be an issue, your clinical suspicion, their medical history in that regard, the testing that you've done.

And again, the 1-mg overnight dexamethasone suppression test is largely sufficient. If you get a post-dexamethasone level as well, and then on a different day, an ACTH and DHEA-S, that would be the whole workup. But if you want to refer them to the endocrinologist to continue with the workup, you may want to specifically reference the CATALYST study. And, you know, that this is the benefits that you're looking for.

Dr. Brunton:
Jennifer, as a pharmacist, you have some insights to offer us as well.

Dr. Goldman:
Sure, absolutely. And I think that obviously, periodic interprofessional discussions are certainly important, but we have to think about medical management. We're also thinking about radiation and surgical and follow-up care. But truly, as a pharmacist, we have to be involved in tailoring the dosing, potential interactions. What other drugs are patients taking? It's important to reiterate that and make sure it's identified.

Dr. Brunton:
In your practice, how do you distinguish between poorly controlled type 2 diabetes due to problems with adherence versus something else, such as hypercortisolism? John, let's begin with you.

Dr. Buse:
Yeah. You know, I think people develop a nose for problems with adherence. And what I do is primarily give people permission to be non-adherent. I tell them that, you know, when I first started the acetate medications, I rarely even completed a 7-day course of antibiotics, taking every tablet exactly how and when I was supposed to. But it's something that takes a while, and that for us to work effectively together, I just need to understand what they're doing. I don't care what they do. I'll encourage them to take the medications that we prescribe, but if they don't want to take a medicine, or they can't afford it, or you know, they can't remember how to do it, just be honest with me, and we'll work it out from there. And I think in that context, you basically have to trust the patient that if they say they're taking the medication, they probably are.

And I will tell you, this whole hypercortisolism and difficult-to-control type 2 diabetes, when you do identify it, it is such a relief to patients because, you know, they have felt terrible about not achieving their goals. Their family—you know they suspect that their family members think that, 'She's just not a very good patient. She doesn't do what she's supposed to with regards to diet and exercise, medication, and frequent monitoring.' And we as providers feel terrible that we haven't been able to help people more. So it is, in a way, quite a relief to find out that someone has hypercortisolism.

And I certainly wouldn't not screen someone for hypercortisolism because they thought it was possible that maybe they were not adhering. I find more often than not, at least my patients are adherent to their medications.

Dr. Miller:
You know, I learned a very good thing from a older physician back in the day. He says, if you give the patient long enough, they'll tell you what's wrong with them—if you give them long enough to talk. You know, many of our patient interactions—they're coming to us for our expertise in diabetes and metabolic conditions, and they say, 'I've tried everything.' And I always engage the patient to say, you know, how are they doing with their medications? But they feel hopeless and helpless.

And I love hearing about the screening. We're not expecting you to predict every person you screen for hypercortisolism that they're going to be positive, but we expect you to wonder and to dig a little bit more, to be able to look at the potential secondary causes for their difficult-to-control diabetes. I mean, we all get that kind of sense or that feel.

I often see that if they're non-GLP-1 responders, where we don't see that improvement that we would expect, this really should raise that top of line.

But screen, screen, screen, screen—it's okay to look for it. It's okay to check it out. Because if you do find it, it's going to be 100% the solution for that individual. And so I have a very low threshold for screening for this and adding that additional diagnostic tool and identifying in your own clinical practice those people who you might consider for screening, because it's easy and it's inexpensive to do.

Jen, from a pharmacist's standpoint, give us an idea of how you're kind of going out there with your colleagues and educating them about how to look for these hard-to-control people.

Dr. Goldman:
Thank you, Eden. Yeah, I'm kind of thinking about what Dr. Buse just said also in terms of adherence. And so, most patients are honest. Most of them are honest. But we can ask, can you afford your medication? And there's ways around. We know we have very,

very effective drugs now for type 2 diabetes. So if they say they're taking them and we're using CGM or A1c, and we're not getting what we're expecting, it should also be a very low threshold for testing.

But I do think that everything you just said is certainly critically important. I think pharmacists are well positioned to make sure that patients have access to medications, can make recommendations as part of the care team of when to screen if we're not seeing what we're expecting to see, and just being there to be able to help.

And also to educate to make sure—it just brought up the dexamethasone testing being easy to do—but that's another place where a pharmacist can be involved: to make sure it's important for them to take it at the right time. So they have to take it at 11 p.m. so that they're tested in the morning in order to know. Because if they don't have hypercortisolism, we're not going to expect that cortisol level to go up. So it's critical for them to take it correctly. So having another person to be able to educate a patient on when to take that and when to get tested is important.

Dr. Brunton:
Well, as we wrap up, is there anything else you'd want to add? Jennifer, do you want to begin?

Dr. Goldman:
So I would like to reiterate the value of a multidisciplinary approach—so physicians, nurses, pharmacists, other specialists working together to optimize patient outcomes. So we need to stay vigilant for at-risk patients and maintain a very high index of suspicion for hypercortisolism in those patients with difficult-to-control type 2, resistant hypertension, unexplained obesity, or other comorbidities. So we also need to stay up to date with advances in hypercortisolism and recognition and management.

Dr. Miller:
I'm actually so excited to have learned about the CATALYST data a few years ago. It really filled in this big gap that I saw in clinical practice, where I was giving individuals my best—the best meds out there, the best intervention and lifestyle—and I just couldn't seem to move the needle with them.

So reframing the way I do clinical practice with the lens of hypercortisolism—you're going to screen a lot. You're going to find a fair percentage. But go ahead and identify those individuals in your practice that you need to go that next step to try and uncover those real reasons—those real drivers—behind that metabolic, hyperglycemic, even that cardio risk with them.

And so we encourage you, with this new information, to start that journey, because it can mean the world for those patients who have been battling with this silently, not even really treating the underlying cause.

Dr. Buse:
You know, this is a revolutionary concept. You know, there are very few things in my 35-year career that have sort of jumped the shark, and this is one of them.

So I think number one is to screen for type of hypercortisolism. It's going to take a while for our communities to get used to this conceptually. You'll find that many people are going to suggest much more complicated evaluation strategies and will be, you know, down on the opportunities with regards to medical management, because these drugs are not easy drugs to use. But eventually, I think each of our communities will grow at peace with this information, will develop the expertise to be able to manage patients with mifepristone and newer agents in the pipeline—other agents that will be studied. This is going to make a big difference in a lot of people's lives. Screening is the first step. That's what you need to do today.

Dr. Brunton:
Well, let's look at some key takeaways from this program.

First of all, hypercortisolism is a diagnosis often delayed or missed, leading to adverse consequences for patients, including mortality and unnecessary morbidity. Current data, including from the recent CATALYST trial, suggests the prevalence of hypercortisolism is higher than previously estimated. This is a heterogeneous, multisystemic disease with variable presentations along the spectra of signs of symptoms, from classically overt to clinically inapparent. Hypercortisolism occurs along a continuum of cardiometabolic risks that increase with disease severity and duration.

Now, screening for hypercortisolism in primary care requires appropriately selecting patients that you might suspect as having hypercortisolism, using a sensitive screening test, and then interpreting results with the patient's clinical context. Cortisol-directed medical therapy for adults and inadequately controlled type 2 diabetes and hypercortisolism may reduce A1c, as well as other markers of disease.

A successful referral to endocrinology requires communicating the patient's relevant clinical findings and medical history and the reasons

for suspecting hypercortisolism, screen test results, and other thoughts. And then working with a multidisciplinary team to essential monitor and really develop optimal outcomes in these patients so we get appropriate diagnosis and management.

Well, thank you very much for your participation. We hope this has helped you in identifying these important patients that we've offered this before.

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