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AACE Guidance in Action: When to Suspect and Treat Hypercortisolism in Adults with Diabetes

Announcer:
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Dr. Samson:
Hi. I'm Susan Sampson, an endocrinologist at Mayo Clinic, Florida. I had the honor of chairing the Task Force for the 2026 AACE Consensus Statement: The Algorithm for Management of Adults with Type 2 Diabetes. I would like to introduce my colleague for this activity, Dr. Lawrence Blonde.

Dr. Blonde:
I'm Larry Blonde, an endocrinologist at Ochsner Medical Center in New Orleans, Louisiana. I was a member of the Algorithm Task Force for the 2026 AACE Consensus Statement, and I also had the honor of chairing the AACE Diabetes Guideline in 2022.

Dr. Samson:
Dr. Blonde, one of the unique updates to the AACE 2026 Algorithm was the addition of a diabetes classification algorithm. And I'm wondering if you can kind of walk us through how this came to be and the intent.

Dr. Blonde:
So this very valuable part of the algorithm looked at how one confirms type 2 diabetes phenotype; for example, overweight, obesity, adjusted to race and ethnicity, family history with social determinants of health consistent with type 2 diabetes, personal history of gestational diabetes, signs of acanthosis nigricans, skin tags, elevated triglycerides and low HDL, but also the ability to look for other types of diabetes besides type 1 and type 2. So that features suggesting type 1 diabetes, like DKA, autoimmunity, thyroid, celiac, and vitiligo, phenotype without insulin resistance, lean body habitus, family history of type 1 diabetes, and checkpoint inhibitors. And then, very importantly, features suggesting other types of diabetes that are neither type 1 or type 2 diabetes, and particularly issues where one should consider referral to an endocrinologist. So for example, endocrinopathies, phenotypic features of other endocrinopathy, hypercortisolism, growth hormone excess, endocrinopathy workup, and anatomic pancreatic disease, including chronic pancreatitis, pancreatic cancer, pancreatectomy, cystic fibrosis, hemochromatosis, those with monogenic diabetes, a family history of diabetes over three generations, diagnosis at less than 6 months of age, medication induced including glucocorticoids, post-transplant diabetes, checkpoint inhibitors, and other conditions as well.

Dr. Samson:
Right. And one of the key ones here that's on topic for today is thinking about endocrinopathies as a cause or an exacerbator of hyperglycemia in our patients, particularly hypercortisolism.

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You know, Dr. Blonde, I know that you've reviewed the literature in this area and that there are some publications that have highlighted how prevalent hypercortisolism is in the diabetes clinic.

Dr. Blonde:
So looking at the literature, there have been a number of publications which have reported on the prevalence of hypercortisolism in diabetes outpatient clinics. And the testing methodology for hypercortisolism is highly variable among these reports, so the prevalence also is variable, ranging from a low of 0% through to nearly 10%.

However, when the criteria for testing is narrow to those individuals with poorly controlled diabetes, the prevalence is higher in the range of 3 to 9%.

A recent meta-analysis also looked at the prevalence of hypercortisolism in patients with a diagnosis of type 2 diabetes combined with hypertension or those requiring insulin therapy, or what was termed advanced type 2 diabetes, microvascular or macrovascular complications, the need for insulin therapy, antihypertensive therapy, or those with hypertension on three or more antihypertensives; this latter category of individuals showed a significant odds ratio of 3.6 for hypercortisolism.

Dr. Samson:
Well, that certainly leads us into discussing the more newly published CATALYST study, which you were one of the coauthors of the study design, I know, and also a site. And this did take a more systematic approach to testing for hypercortisolism in patients with what was termed difficult-to-control type 2 diabetes in that study. From my reading, the enrollment criteria included patients that had to have an A1c of 7.5 to 11.5%, and difficult-to-control was defined as three or more diabetes agents, the need for insulin plus any other antihyperglycemic agent, or two or more agents with micro or macrovascular disease, or two or more antihyperglycemic agents on two or more antihypertensives. I think many of our patients in the diabetes clinic could actually meet these criteria. And so those were the CATALYST criteria.

Can you tell us a little more about the study?

Dr. Blonde:
Yes. The protocol excluded patients that could have false-positive testing, including those on estrogen-containing birth control pills, severe or untreated obstructive sleep apnea, those with end-stage kidney disease, those with an altered circadian rhythm like night shift workers, those with severe illness or excessive alcohol use. Over 1,000 patients were enrolled meeting the inclusion criteria, and they were screened with a 1-mg overnight dexamethasone test, which was considered positive if the cortisol was greater than 1.8 mg/dL.

Using this approach, 23.8% of patients had non-suppressed cortisol, 33% of patients with cardiovascular disease, and 36.6% of patients with hypertension on three or more antihypertensive medications, so a much higher prevalence than seen in previous publications.

Dr. Samson:
Yeah, so those criteria really kind of enriched the population for those that might have hypercortisolism. And I mean, with that finding of high cortisol after dexamethasone in the study, they went on to obtain abdominal imaging. And what

was intriguing is that over 1/3 of those patients that had imaging had some type of adrenal abnormality, including the majority as unilateral nodules. There could be bilateral nodules, or in some cases enlargement of one or both adrenals. So very interesting that over 1/3 of patients had something on adrenal imaging, and that would have been about 7% in the original enrolled population.

Dr. Blonde:
After these patients were identified as having hypercortisolism by non-suppressed cortisol, patients had the opportunity to enter the second phase of CATALYST, which was to treat with mifepristone.

Dr. Samson:
So mifepristone is a cortisol receptor blocker that was approved by the FDA in 2012 for control of hyperglycemia secondary to endogenous Cushing syndrome, and in those patients that have type 2 diabetes and impaired glucose tolerance who couldn't have surgery or were not candidates for surgery. Our knowledge of the effects of mifepristone come from the SEISMIC trial at that time, which had enrolled patients with Cushing's disease. Those were the majority of patients, with a few patients with ectopic ACTH and adrenal carcinoma. So this is really where we get our understanding of mifepristone, its impact on glucose, and potential adverse effects.

And what's interesting when I looked at CATALYST is in order to be eligible for the treatment phase, patients with adrenal findings had to have an ACTH less than 15, in other words, mildly suppressed or on the low side. Or if they had an ACTH that was higher than that, 15 to 30, they had to have a DHEAS of 100 or below. So in other words, with adrenal findings, wanting to make sure that this was not ACTH dependent.

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And then for those without adrenal findings, the ACTH could not be above the normal range. In other words, trying to rule out those that might have elevated ACTH from a pituitary tumor, ectopic Cushing's.

And so that was the criteria they used in order for patients to move into the treatment phase.

Dr. Blonde:
So for CATALYST, 136 patients were randomized in a 2:1 design for mifepristone or placebo treatment and stratified by adrenal CT results. Patients were treated with a starting dose of 300 mg of mifepristone, which could be titrated to 600 mg at 4 weeks and 900 mg at 8 to 12 weeks, depending on tolerability. The treatment duration was 24 weeks.

Looking at the results of the A1c in patients on mifepristone and placebo, the A1c decreased significantly at week 24, although effects were already seen at 12 weeks. A1c was decreased 1.32% comparing mifepristone with placebo. But the decrease in A1c was also similar whether patients had an adrenal abnormality on imaging or not, which is intriguing. Body weight, BMI, waist circumference, cholesterol, and fasting plasma glucose all decreased on mifepristone compared to placebo, while systolic blood pressure increased.

Dr. Samson:
Yeah, that increase was about 10—an increase of 10 systolic. And we think that this is secondary to the increased action of cortisol at the aldosterone receptor. And sometimes in these patients, the mineralocorticoid antagonist spironolactone can be used to counteract that effect.

Activation of the aldosterone receptor also is the likely reason for the most common treatment adverse event that occurred in CATALYST, which was hypokalemia. This occurred in nearly 30% of participants on mifepristone, but none on placebo. The rest of the adverse events that we're seeing are really consistent with what we already know from previous data on mifepristone, and particularly from the findings of the SEISMIC trial. Use of the mifepristone to block the glucocorticoid receptor can give patients symptoms of glucocorticoid withdrawal. And certainly this makes it sometimes more challenging to use mifepristone in the clinical setting, because we have to really work to monitor our patients closely and to educate them on the symptoms that can occur on this medication.

So overall, in the CATALYST treatment phase, 54% completed 24 weeks on mifepristone, meaning that there was 46% who withdrew for a number of reasons, but for the most part, due to some symptoms, or at what we would call adverse events in the clinical trial world.

Dr. Samson:
So when I think about the differences between CATALYST and some of the patients I see in my clinic that I'm working up for overt Cushing syndrome, I think a big difference is CATALYST used the dexamethasone suppression test only with that very sensitive cortisol threshold of greater than 1.8, which can have a high false positive rate. And when we see patients in clinic that we think have overt Cushing syndrome, we do use additional tests, particularly also collecting a 24-hour urine free cortisol, or using late night salivary cortisol; several of those in order to confirm endogenous Cushing syndrome.

If we're able to confirm endogenous Cushing syndrome, we'd need further workup to determine if it's ACTH dependent or independent disease. And this requires that we measure ACTH, that we also look at DHEAS, which can also help with the diagnostics. We need to localize the disease to the adrenal or ectopic or pituitary source in order to treat the patient properly. And we have to also remember that although at overt Cushing syndrome, we may see some very important signs consistent with hypercortisolism, so facial plethora, cushingoid face or fat pads, easy bruising, striae, objective muscle weakness. But that isn't always present in patients with mild adrenal disease, and something we've come to call mild autonomous cortisol secretion, but we could still see major metabolic impacts in these patients.

Dr. Samson:
Well, Larry, it was great talking with you today about the CATALYST trial and about diabetes and hyperglycemia, and I hope to see you again soon.

Dr. Blonde:
Yes, and as usual, every time that I have the opportunity of being with you, I always learn a tremendous amount, and this is another example of that. So stay safe, well, and happy.

Dr. Samson:
Thank you.

Announcer:
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