Difficult-to-Manage Diabetes: Is Screening for Hypercortisolism the CATALYST for Change?

This review captures highlights from a roundtable discussion that took place on October 28, 2024.

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Summary

- Hypercortisolism is often underdiagnosed despite being a potential underlying cause of difficult-to-manage type 2 diabetes (T2D), treatment-resistant hypertension, or early-onset bone disease[1-4]
- CATALYST trial aimed to better describe the prevalence and clinical presentation of hypercortisolism in patients with difficult-to-manage T2D[5]
- 24% (n=252/1057) of CATALYST patients had endogenous hypercortisolism, underscoring the need for increased screening in clinical practice[4]
- CATALYST offers a potential roadmap to better identify and screen patients at higher risk for hypercortisolism, including those on newer antidiabetic medications and multiple antihypertensive treatments[4]

Could Hypercortisolism Be Masquerading as Another Condition?

Emerging data in recent years have shown that patients with hypercortisolism can present with a range of complications commonly encountered in everyday practice (eg, difficult-to-manage T2D, treatment-resistant hypertension, early-onset bone disease).[3,4] Recently, a group of experts in the field of endocrinology shared their perspectives on how the prevalence rate of hypercortisolism found in CATALYST, a large United States (US)-based prospective clinical trial, changes the face of hypercortisolism in a subset of patients with difficult-to-manage T2D and what clinical characteristics may help clinicians zero in on who may be at highest risk.[5]

Hypercortisolism: The Overlooked Disease Hiding in Plain Sight

Meet Sandra*—a 38-year-old woman referred to her endocrinologist by a primary care physician because of a history of uncontrolled T2D. Her HbA1c was 12.3% at referral despite taking metformin, liraglutide, and insulin, and she suffers from other comorbidities, including hypertension, dyslipidemia, and depression. During 14 months of antidiabetic treatment, which included several dose adjustments and medication changes, her HbA1c dropped to 8.2% but plateaued despite switching to tirzepatide and insulin intensification. Although studies have shown that excess cortisol can impact glucose metabolism and insulin sensitivity leading to difficult-to-manage T2D over time,[6-8] the potential of hypercortisolism is rarely considered in cases like Sandra's.

Bradley Eilerman, MD: A lot of the people who have been diagnosed with hypercortisolism struggle with this for a long time. Patients often report that the healthcare professionals (HCPs) they have consulted don't even realize that hypercortisolism is a possibility and that the process leading up to the diagnosis is discouraging.

Honey East, MD, FACP: We must recognize how frustrated patients like Sandra are. I remember a patient I had previously diagnosed with Cushing syndrome. She was crying when she first came in because she feared yet another physician would say that nothing was wrong with her and that she simply needed to watch her diet and stick to her medications. These patients are frustrated with the status quo.

Richard Pratley, MD: We are a referral center, and providers do not send patients like Sandra to us saying to work them up for hypercortisolism—it's just poorly controlled diabetes. The challenge is many providers continue to search for the classic physical features of Cushing disease (adrenocorticotropic hormone [ACTH]-dependent) before considering a diagnosis of hypercortisolism.

> *"Shifting the conversation to the cardiometabolic symptoms and broadening the diagnosis beyond just those classic physical features will help clinicians change the way they think about the disease and reduce the time it takes for patients to receive an accurate diagnosis."*

James Findling, MD: Part of the problem is with the term 'Cushing syndrome' itself because it has become a caricature. We now recognize, particularly in the last decade, that many patients with hypercortisolism, especially when it's mild, lack any of the classic physical features that Harvey Cushing described 90 years ago. Hypercortisolism may cause significant cardiometabolic, musculoskeletal, neurocognitive/neuropsychiatric problems even in the absence of overt clinical features of 'Cushing syndrome.' Cortisol excess can be cardiotoxic, so patients who have a higher probability of hypercortisolism should be screened so that appropriate treatment is not delayed.

Amy Burmesch, PA-C: Think about the long-term risk or the consequences for a patient this young if we miss this diagnosis. Not that it's inconsequential for someone in their sixties or even seventies. But think about the potential consequences for someone in their thirties if a diagnosis of hypercortisolism is missed, and then they must live with it the rest of their life.

On average, patients with hypercortisolism see more than 4 physicians over a period of up to 10 years before receiving a correct diagnosis.[2,9] Timely diagnosis and treatment for hypercortisolism are imperative as untreated hypercortisolism has been shown to contribute to poor clinical outcomes, including increased risk of cardiovascular (CV) events and CV mortality.[10] The health consequences associated with a delay in diagnosis underscore the need for a more complete understanding of the prevalence of hypercortisolism in patients with difficult-to-manage T2D to guide HCPs in their clinical decisions.

A Call to Action: Shining a Light on Hypercortisolism Prevalence

CATALYST, a Phase 4 clinical trial conducted across 36 US sites, is the largest prospective study to date investigating the prevalence of endogenous hypercortisolism in patients with difficult-to-manage T2D.[5] In the trial, patients were enrolled based on stringent inclusion and exclusion criteria, and screened for hypercortisolism, defined as a 1-mg dexamethasone suppression test (DST) level of >1.8 µg/dL and an AM dexamethasone level of ≥140 ng/dL, as shown in **Figure 1.**[5,11] Approximately 24% (n=252/1057) of patients with difficult-to-manage T2D were found to have endogenous hypercortisolism.[4]

Pratley: What CATALYST shows is that these patients aren't all that rare, especially in specialized diabetes centers, and you can do the initial hypercortisolism screening with very little difficulty. The CATALYST protocol can be implemented into clinical practice quite easily.

Findling: The overnight 1-mg DST has been around for 60 years and remains the most robust screening test due to its high sensitivity and reasonably good specificity, particularly for identifying patients with cortisol excess associated with adrenal nodular disease.

> *"In clinical practice, a 1-mg DST should be the initial screening test for patients whenever you have a high suspicion for cortisol excess."*

There is also value to measuring a dexamethasone level as was done in this study to ensure proper test execution, drug absorption, and to rule out rapid metabolic clearance.

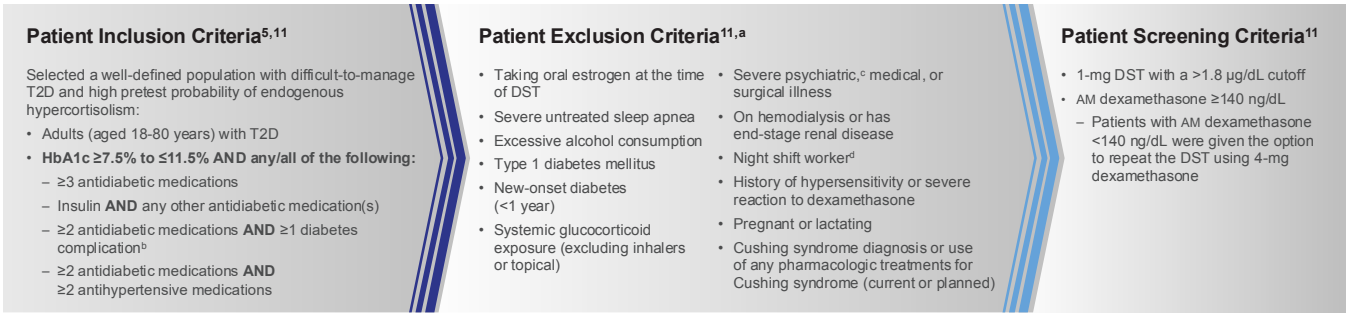

Figure 1: Patient inclusion, exclusion, and screening criteria for CATALYST trial part 1.
[a]These criteria were specifically included to reduce the risk of false-positive 1-mg DST results.[5] [b]For example, retinopathy, diabetic nephropathy and chronic kidney disease (eGFR<60 mL/min/1.73m^2), diabetic neuropathy, or atherosclerotic heart disease with diabetes.[11] [c]For example, schizophrenia or dementia.[12] [d]Awake from approximately 11 PM to 7 AM.[11]

East: What I find helpful about CATALYST is the exclusion criteria, as seen in **Figure 1,** because when we do the DST in practice, what we worry about are confounding factors that might make the DST level higher than 1.8 µg/dL other than hypercortisolism, and CATALYST accounts for these circumstances. This helps provide confidence in the data.

Findling: It is also important for referring physicians and patients to understand the interpretation of the 1-mg DST. I explain to patients that dexamethasone suppresses pituitary ACTH secretion that in turn suppresses their cortisol. I routinely measure ACTH as well as cortisol the morning after they take dexamethasone. If their ACTH level is low and the cortisol level remains inadequately suppressed (>1.8 µg/dL), there's autonomous cortisol secretion and we have something to act on.

Eilerman: Although these tests are important for a diagnosis, the diagnostic process is supposed to get you to a treatment decision point, and you can't get stuck thinking there is a capital T—Truth—to what point a test passes a particular threshold. While it is very specific in some diseases, pinpointing the threshold becomes more challenging when talking about a hormone like cortisol that naturally varies. It is important to consider the biochemical evidence in the context of the entire clinical picture and the index of suspicion.

Burmesch: We need a simple algorithm for clinicians to follow, whether it is in a primary care setting or community endocrinology. There is no single test that makes this diagnosis or excludes it, but...

> *"I think that the CATALYST protocol is perhaps the best way to begin the screening process and ensure patients do not get missed."*

Unveiling a Potential Roadmap for Better Screening

Given the high prevalence of patients with difficult-to-manage T2D, it may seem overwhelming to screen all patients in this enriched population.[4] CATALYST provides HCPs with insights that can better identify patients who are at higher risk for hypercortisolism and warrant further screening. The trial demonstrated a greater likelihood of hypercortisolism in patients taking newer classes of antidiabetic medications, those with a higher overall medication burden, those on multiple medications for hypertension and T2D, as well as individuals with concurrent CV diseases **(Figure 2)**.[4]

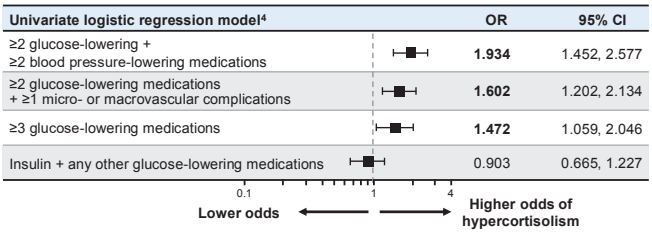

Figure 2: Likelihood of hypercortisolism vs. no hypercortisolism in those with difficult-to-manage T2D who enrolled in CATALYST based on hypertension and/or microvascular/macrovascular complications.

Pratley: There are several different potential pathways embedded within CATALYST that people could follow for their individual clinics. CATALYST is just a starting point for people to think about the problem and to raise awareness. For example, if you think about the clinical trials for tirzepatide, almost everyone got to an HbA1c of close to or below 7%, even patients who had inadequate glucose control despite taking metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and insulin. Tirzepatide is spectacularly effective. When you have a patient who doesn't respond to tirzepatide and you are reasonably assured that they are taking their medications, I think it's a sign that a secondary cause, such as hypercortisolism, might be involved, as shown in **Figure 3.**

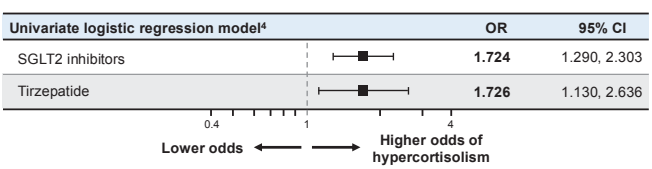

Figure 3: Likelihood of hypercortisolism vs. no hypercortisolism in those taking newer classes of antidiabetic medications.

Burmesch: While CATALYST focuses on patients with difficult-to-manage T2D, I think even patients who don't have this advanced T2D should be considered for hypercortisolism screening if they have new onset T2D at a young age, particularly without a family history, or if they have had a fragility fracture.

East: I look at insulin mismatch. If their bolus requirements are disproportionate to their basal requirements, it raises my suspicion for hypercortisolism. I also like what Amy says because I have had many patients who just have pre-diabetes, but their disease presentation is unusual—those patients should be checked further. I think maybe we need to approach this the same way we do treatment-resistant hypertension where three medications along with a diuretic is typically a flag.

> *"If a patient is requiring three or more optimally used medications, along with incretin therapy perhaps, for managing their diabetes, they should be screened for hypercortisolism."*

Eilerman: My current approach focuses on identifying where the value is in terms of generating system change. Medicare flags patients when their HbA1c is greater than 9% or if their blood pressure exceeds 140/90 mmHg. Even starting with the patients who have both difficult-to-manage T2D and resistant hypertension, as shown in **Figure 4**, provides you with an enriched population that is more likely to have underlying hypercortisolism.

> *"By screening these patients, even if we get a fraction of the 24% found in CATALYST testing positive for hypercortisolism, and provide them appropriate treatment in a timely manner, that's moving the needle in a really big way."*

While this discussion emphasizes the importance of considering hypercortisolism as a driver of difficult-to-manage T2D and highlights CATALYST as a possible framework for putting people on a path toward a diagnosis, secondary testing and an appropriate differential diagnosis remain crucial for making fully informed treatment decisions.

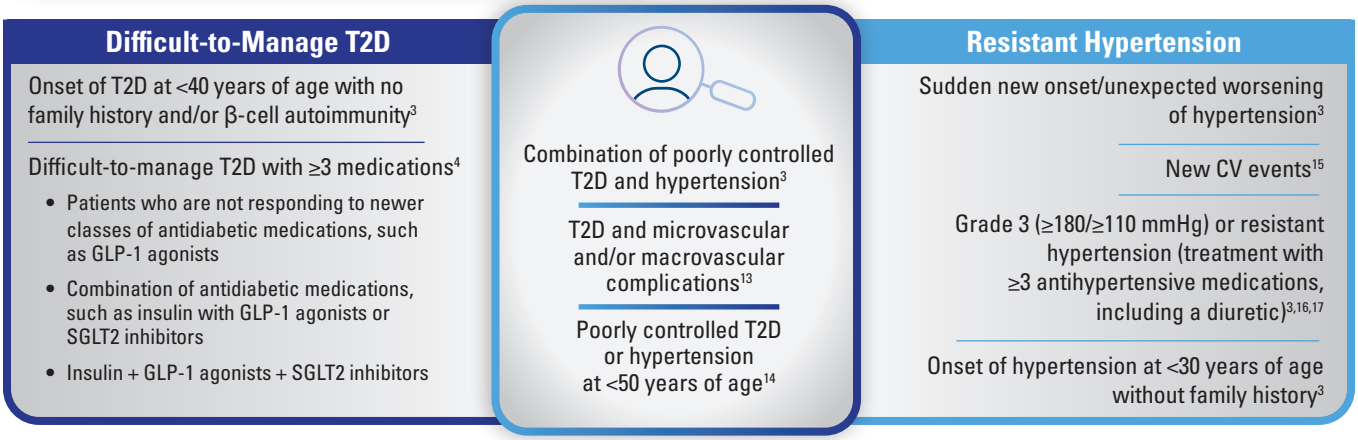

Figure 4: Clinical suspicion for hypercortisolism should be increased in patients with concurrent difficult-to-manage T2D and resistant hypertension.

Each participant engaging in this roundtable discussion is acting in their personal capacity.
The opinions expressed in this article are those of the participants and do not reflect the view of any institution or government entity.

*A real patient dealing with difficult-to-manage T2D.
Figure abbreviations: CI, confidence interval; CV, cardiovascular; DST, dexamethasone suppression test; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; OR, odds ratio; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

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