Difficult-to-Control Diabetes: Is Cortisol at Play?

This review captures highlights from a roundtable discussion that took place on May 30, 2023.

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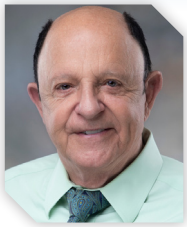

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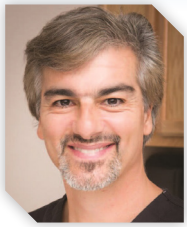

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Summary

- Almost a quarter of patients with T2DM require 3 or more medications to manage their disease, and even then, many patients have difficulty getting their diabetes under control
- Elevated cortisol activity can exacerbate the pathophysiology of T2DM and can counter the impact of traditional anti-diabetic medications, making diabetes control challenging
- Studies emerging over the last two decades suggest that up to 10% of patients with T2DM may have hypercortisolism
- Patients with treatment-resistant T2DM should therefore be evaluated for hypercortisolism
- Treating the underlying hypercortisolism is important in these patients because managing comorbidities alone has been shown to be less effective at significantly reducing morbidity and mortality

Current State of Diabetes Management

Despite the significant advances in diabetes therapies over the last few decades, there still remains a portion of patients who are not well-controlled on currently available therapies. *"You know who these patients are – they are the tough patients who are frustrated (and frustrating to clinicians) because nothing seems to be working to control their diabetes,"* said Dr. Daniel Einhorn. For example, a 64-year-old man with HbA1c of 9.7% despite attention to lifestyle modifications and numerous anti-diabetic therapies, such as metformin, SGLT-2 inhibitors, GLP-1 agonists, and/or long-acting insulin. He also has multiple comorbidities, including hypertension, dyslipidemia, and class III obesity. Patients like these are common in a busy medical practice.

A cross-sectional analysis of data from adults with diabetes in the United States participating in the National Health and Nutrition Examination Survey showed that between 2015 and 2018, 22.2% of patients with HbA1c of 7% or higher required 3 or more medications and the percentage of patients with diabetes in whom glycemic control was achieved declined in recent years.[1]

"Unfortunately, the first suspicion with these patients is medication non-compliance. For years, my approach with these patients was to first check for compliance and then intensify their therapy by adding one more anti-diabetic agent. However, with the new research coming out on the role of underlying hypercortisolism on hyperglycemia, we now know that just increasing these patients' anti-diabetic medications may not be sufficient," said Dr. Juan Pablo Frias.

Ominous Octet and the Role of Elevated Cortisol

It is well-known that hyperglycemia results from a combination of systemic dysfunctions, often called the "ominous octet," which describes abnormalities in 8 organs and tissues, including beta cells and alpha cells of the pancreas, the liver, the kidney, skeletal muscle, adipose tissue, the gut, and the brain, which ultimately lead to glucose intolerance.[2] Many studies over the last decade suggest that elevated cortisol can worsen 7 of the 8 tissues and cells that lead to hyperglycemia and T2DM,[3-7] as shown in **Figure 1**.

"Hypercortisolism affects multiple pathophysiologies in T2DM, but the two I tend to focus on are the muscle insulin resistance and the beta-cells defect, because cortisol inhibits the Wingless/Integrated (Wnt) signaling pathway, and Wnt dysregulation has been shown to play a role in the development and progression of T2DM," said Dr. Ralph DeFronzo.

"In addition to beta-cell dysfunction and insulin resistance, the incretin effect is also important. Excess cortisol impairs GLP-1 signaling and therefore counteracts the beneficial effects of the GLP-1 agonist class of anti-diabetic medications. So, when we put a patient on our multi-drug combination protocol, which has been shown to treat most of the core defects and also reduce the CV risk, if they do not achieve glycemic control or lose at least some weight, we suspect hypercortisolism," added Dr. Christopher Lucci.

When to Suspect Hypercortisolism

Traditionally, hypercortisolism, also known as Cushing's syndrome, has been associated with certain phenotypic characteristics, such as easy bruising, facial plethora, proximal myopathy, and striae.[8,9]

However, evolving data describe a significant subset of patients who are unlikely to ever develop these more obvious and discriminatory features. Instead, they present with many of the typical features seen in patients in diabetes clinics, such as T2DM, mild to moderate obesity, hypertension, osteoporosis, and depression.[9,10] Hence, identifying these patients can be challenging. *"When patients have multiple comorbidities and they are not achieving diabetes control despite trying all the appropriate multiple therapies, it is likely that they have underlying hypercortisolism,"* said Dr. Einhorn.

Dr. Ralph DeFronzo emphasized that, "99% of my patients are obese, 80% are hypertensive, so while it is not feasible to screen all these patients for hypercortisolism, when patients are having a poor response to treatment, you really ought to be thinking about screening them for hypercortisolism."

In fact, multiple studies have shown that the prevalence of hypercortisolism in patients with T2DM ranges from approximately 5% to 10%.[11-15] *"When endocrinologists are asked about how many of their patients have Cushing's syndrome, most would generally say 1-2 patients in their entire practice. But when you see the actual data for the prevalence of hyperglycemia secondary to hypercortisolism, you realize that everyone probably sees 20-30 patients with this condition in their clinic. It's just that they are disguised as difficult-to-control diabetes patients. Bottom line is this is a lot more relevant a disease than we originally thought,"* said Dr. DeFronzo. *"Often times these patients are cast aside for being non-compliant to their treatment plan, but I believe most patients are generally quite good at following their treatment plan; so, when we see these difficult-to-control diabetes patients, perhaps we should think about an underlying hypercortisolism problem first instead of jumping to conclusions about adherence,"* added Dr. John Buse.

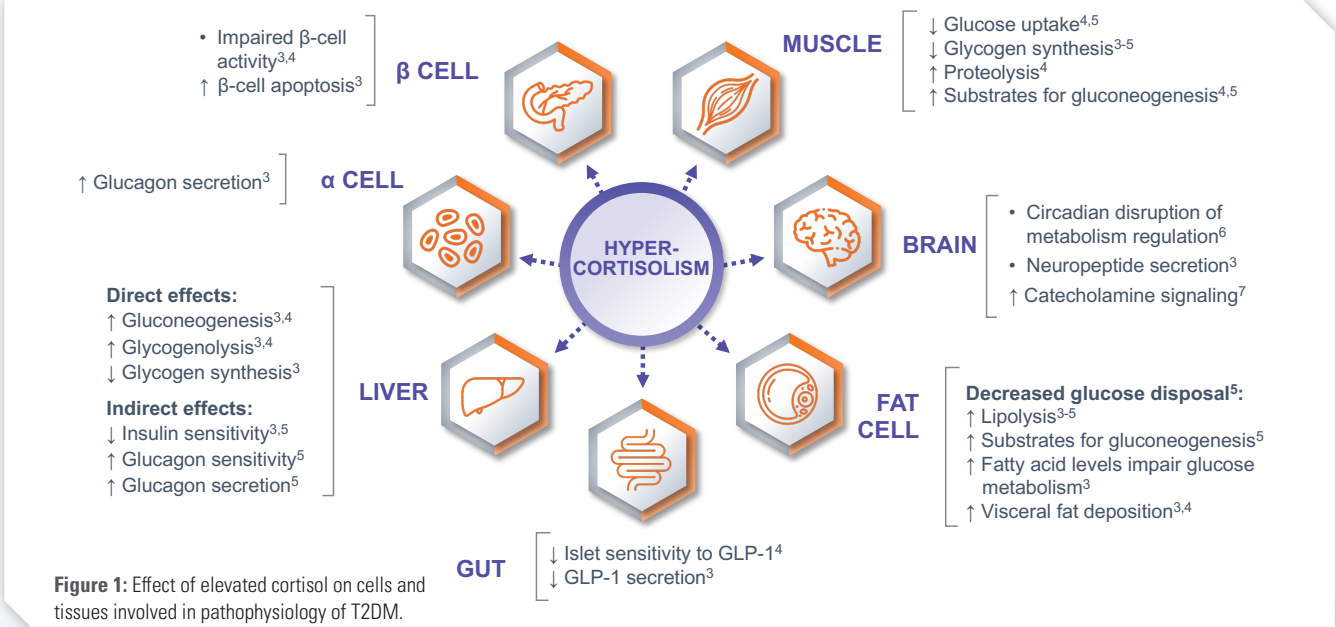


Figure 1: Effect of elevated cortisol on cells and tissues involved in pathophysiology of T2DM.

Consequences of Untreated Hypercortisolism in Patients With Difficult-to-Control Diabetes

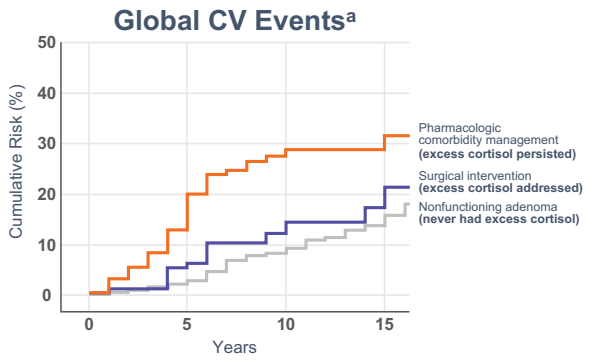
A natural history study published in 2020 compared CV events and CV survival rates for 157 patients with adrenal adenomas and autonomous cortisol secretion who either underwent an adrenalectomy or were medically managed with optimized therapy for the comorbidities alone. As shown in **Figure 2**, patients with autonomous cortisol secretion who only received treatment for their comorbidities were at greater risk for future CV events and CV mortality than those who either had their source of excess cortisol removed via surgery or never had hypercortisolism in the first place.[16]

This is important because patients with T2DM are twice as likely to develop cardiovascular disease and at a younger age.[17] Dr. Lucci emphasized, *"These data underscore the importance of screening patients for hypercortisolism. Even with the latest developed multi-drug combination regimens, yes, the CV risk is being reduced, but there is still a problem of residual risk. This study illustrates the 2- to 3-fold increased risk of CV events that may be posed by hypercortisolism even after you have implemented the most advanced standard of care therapies. Screening for this condition, and treatment when it is found, remains an unmet need."* Dr. DeFronzo agreed, and added, *"These data suggest that cortisol is independently doing some bad things to your arteries above and beyond all the other risk factors and the likelihood that you are going to correct all the comorbidities and get them all under control is probably not very high. So, early identification and treatment of underlying hypercortisolism is important."* A randomized trial published in 2022 assessed the effect of adrenalectomy versus personalized medical management of comorbidities on CV and metabolic outcomes in 62 patients with cortisol-secreting adrenal incidentalomas after 6 months of intervention. This study demonstrated a significant improvement in HbA1c and blood pressure control when surgically removing the source of abnormal cortisol secretion compared to just medically treating the comorbidities.[18]

How and When to Screen for Hypercortisolism

When patients with hypercortisolism do not present with classic Cushing's syndrome features, the source of the disease is usually adrenal.[19] This is important because it changes which tests to rely on to diagnose the disease. Historically, the common tests used to detect hypercortisolism included the 1-mg overnight DST, the LNSC, and the 24-hour UFC.[9]

"We now know that LNSC and UFC may lack the necessary sensitivity for confirming ACTH-independent hypercortisolism. So, having a normal LNSC or UFC does not rule out hypercortisolism in this population. The 1-mg DST with a cutoff of 1.8 µg/dL has come to be recognized as the most sensitive test to screen for ACTH-independent hypercortisolism," said Dr. Daniel Einhorn.



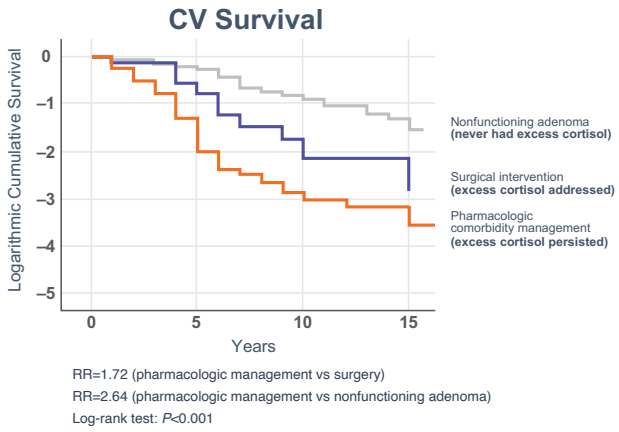


Figure 2: Patients with adrenal autonomous cortisol secretion who do not receive treatment targeting their hypercortisolism are at increased risk for future CV events and CV mortality.[16]

[a]Nonfatal acute myocardial infarction, percutaneous transluminal coronary angioplasty, and surgical bypass for ischemic heart disease, or ischemic stroke.

In fact, the 2023 European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas recommends that in patients with incidentally discovered adrenal adenomas who do not present with the signs and symptoms of overt Cushing's syndrome, a post-DST cortisol of >1.8 µg/dL should be considered diagnostic of autonomous cortisol secretion without requiring additional tests.[20]

Dr. Lucci agreed, and added, *"If I have a patient with a post-DST cortisol of 1.8 µg/dL or more and if they have treatment-resistant diabetes, we do not even do LNSC or UFC tests. Instead, we repeat the DST while we are setting up imaging and we ensure that there are no confounding factors that might have caused a false positive result. Ultimately, it is important to trust your clinical judgment and not rely solely on diagnostic tests and their cutoffs, as that often leads to under-treatment of diabetes patients."* Dr. DeFronzo agreed, and added, *"There needs to be some liberty in interpreting cutoffs like this. This is similar to what we see in diabetes: if your patient has HbA1c of 6.5%, they are diabetic, but if they are at 6.4%, they are prediabetic and it wouldn't make sense to ignore it. We would still treat the patient for their condition as a whole instead of relying on cutoffs like this, so a similar approach should be taken when interpreting post-DST cortisol – always look at the patient as a whole."*

Given the high burden of diabetes in the United States, clinicians may be reluctant to add yet another test to these patients' list of workups. However, data suggest that not all patients with diabetes need to get tested for hypercortisolism. A 2021 meta-analysis reviewing the prevalence of hypercortisolism in patients with T2DM suggested that patients with diabetes requiring insulin may be more than 2 times more likely to be diagnosed with hypercortisolism while patients with advanced T2DM, defined as prevalence of micro- and/or macrovascular complications, insulin treatment plus hypertension, or hypertension treated with 2 or more medications, may be approximately 3.5 times more likely to be diagnosed with hypercortisolism.[10] Hence, a specific subset of the population, such as patients with difficult-to-control diabetes, treatment-resistant hypertension, or adenomas, can benefit from hypercortisolism screening as shown in **Figure 3**.[19,21]

"I do think that we have had a blind spot for years and it is time to change behavior with regard to screening for hypercortisolism in difficult-to-control patients with diabetes, and there needs to be an update in the American Diabetes Association guidelines to indicate when to screen these patients for hypercortisolism. What makes screening for hypercortisolism worthwhile is that there are multiple treatment options available for these patients," said Dr. John Buse.

Dr. Frias agreed, and added, *"I wish I had known about this 20 years ago. I do not know how many patients I have missed over the years in my practice, but hypercortisolism screening in difficult-to-control diabetes patients is something I am now incorporating in my practice. The more we can refine the identification of patients who may be at high risk of hypercortisolism through clinical studies and meta-analyses, the easier it will be for clinics to incorporate hypercortisolism screening in their practice."*

Difficult-to-control T2DM[19]
- Poorly controlled T2DM despite medications and appropriate diet
- Combination of poorly controlled T2DM and hypertension
- Onset of T2DM aged <40 years without family history and/or β-cell autoimmunity

Resistant hypertension[19,21]
- Grade 3 or resistant hypertension
- Sudden new onset/unexpected worsening of hypertension
- Onset of hypertension aged <30 years without family history

Adenomas[19]
- Adrenal adenomas
- Adrenal incidentalomas

Figure 3: Patient populations to screen for hypercortisolism.

With the evolving understanding of Cushing's syndrome, it is now evident that many patients with ACTH-independent hypercortisolism rarely present with the classic phenotypic features and more often present with difficult-to-control diabetes and hypertension. This type of patient presentation is easy to miss in already busy medical clinics. Having difficult-to-control diabetes is frustrating for both the patient and the clinician and is often attributed to lack of adherence to therapy. However, as demonstrated by the recent studies and expert opinions in this review, these patients may have underlying hypercortisolism and therefore cannot be adequately treated with anti-diabetic therapies unless the effect of the cortisol itself is treated. It is incumbent on clinicians to be vigilant in identifying the appropriate patients with difficult-to-control diabetes and have them undergo screening for hypercortisolism. Timely treatment of hypercortisolism can help prevent significant morbidity and mortality.

ACTH, adrenocorticotropic hormone; CV, cardiovascular; DST, dexamethasone suppression test; GLP-1, glucagon-like peptide 1; LNSC, late-night salivary cortisol; SGLT-2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus; UFC, urine free cortisol.

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