Breaking Through Difficult-to-Control T2D: Targeting Hypercortisolism

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KEY TAKEAWAYS

- A diagnosis of hypercorticolism is missed or delayed in many patients, especially in those with difficult-to-control type 2 diabetes (T2D).
- In a certain group of patients with T2D, the prevalence of hypercortisolism may be as high as 24%.
- Primary care practitioners (PCPs) can identify patients at risk for hypercortisolism using effective screening tools to detect the disease.
- PCPs can initiate referrals to endocrinology as part of the healthcare team; additionally, PCPs can recommend and manage certain hypercortisolism treatments for eligible patients.
- Treatment for hypercortisolism may involve surgery for eligible patients and medical therapy for those who are not candidates, who decline surgery, or who have had unsuccessful surgeries.
- Treatment with a glucocorticoid receptor antagonist has shown significant reduction in glycated hemoglobin in patients with hypercortisolism and difficult-to-control T2D.

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INTRODUCTION

Endogenous hypercortisolism, also known as Cushing syndrome, is a multisystemic endocrine disorder characterized by prolonged excessive cortisol activity.[1] This condition often goes undiagnosed or is misdiagnosed, resulting in unnecessary progression of morbidity and increased cardiovascular-related mortality.[2-5] Hypercortisolism can be classified into 2 main categories:

- ***ACTH-dependent hypercortisolism:*** Includes excess adrenocorticotropic hormone (ACTH) secretion by pituitary tumors (Cushing disease) and nonpituitary tumors (ectopic ACTH secretion)
- ***ACTH-independent hypercortisolism:*** Includes autonomous cortisol secretion by one or both adrenal glands

Hypercortisolism presents with a broad spectrum of symptoms and comorbidities.[6] Although overt features such as a rounded face, central obesity, purple striae, and proximal muscle wasting are still observed in some cases, more common symptoms include nonspecific features that overlap with frequently occurring chronic diseases.[1,7] These common, heterogeneous, and multisystemic symptoms of hypercortisolism include weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders.[2,3,5]

The wide spectrum of clinical signs and symptoms of hypercortisolism should be considered as a continuum, with increasing rates of cardiometabolic comorbidities and mortality occurring with more severe disease.[8] Because most cases do not present with the classically described overt features and the presentation varies among patients, hypercortisolism often presents a diagnostic challenge, leading to significant diagnostic delays of up to 10 years.[9,10] Regardless of etiology, prolonged exposure to cortisol activity can lead to increased cardiometabolic comorbidities and mortality.[2-5,8] If untreated, mortality rates in patients with hypercortisolism are 2 to 5 times higher than the general population.[11-13] Thus, early detection and management are crucial to mitigate these risks.

THE RELATIONSHIP BETWEEN HYPERCORTISOLISM AND DIFFICULT-TO-CONTROL T2D

Despite the availability of effective therapies and evidence-based guidelines, many patients with T2D do not achieve treatment goals.[14,15] Patients with T2D are frequently treated in primary care, and primary care practitioners (PCPs) often play a crucial role in ensuring optimal treatment outcomes

for these patients.[15] Traditional strategies for improving glycemic control, including tailored therapy and behavior change, may be attempted but can be inadequate for some patients.[15] This presents a challenge to T2D management, especially for those patients who fail to reach glycemic targets despite best efforts from clinicians and patients to implement and adhere to optimal therapy.

Excess cortisol increases insulin resistance and decreases insulin sensitivity, negatively impacting the metabolic defects underlying T2D.[14] This contributes to a form of T2D that is difficult to control with standard therapies.[14] Clinical studies have demonstrated the benefits of addressing excess cortisol for glycemic control in T2D and for other comorbidities, such as hypertension.[16,17] Assessing hypercortisolism in patients with difficult-to-treat T2D may represent a rational strategy for identifying those who would benefit from the treatment of hypercortisolism.

SCREENING FOR AND IDENTIFYING HYPERCORTISOLISM

Best practices for screening and identifying hypercortisolism in primary care have been discussed previously.[7,18] Guidelines recommend testing for hypercortisolism in high-risk populations, such as patients with the following characteristics[18]:

- Unusual features for their age, such as osteoporosis/fragility fracture, T2D, or hypertension in young individuals
- Multiple and unexplained/progressive features, such as worsening T2D outside of the normal progression or unexplained recent weight gain
- Adrenal mass/hyperplasia

Hypercortisolism is common in patients with difficult-to-control T2D, as recently established in CATALYST, the first prospective, multicenter, US-based, large study including >1000 patients. The aims of the phase 4, two-part CATALYST trial are to (part 1) determine the prevalence of hypercortisolism in patients with difficult-to-control T2D and to (part 2) assess the safety and efficacy of mifepristone (Korlym®, Corcept Therapeutics Incorporated) to lower glycated hemoglobin (HbA1c) compared with placebo in patients with hypercortisolism identified in part 1 who have hypercortisolism.[14]

Patients were included in part 1 of the study based on the following criteria (exclusion criteria are listed in **TABLE 1**)[14]:

- Age 18-80 years
- Difficult-to-control T2D with diagnosis ≥1 year prior defined as:
  - HbA1c 7.5%-11.5% AND
  - ≥3 antihyperglycemic drugs OR
  - Insulin plus any other antihyperglycemic drugs OR
  - ≥2 antihyperglycemic drugs AND
  - The presence of ≥1 diabetes complication (eg, retinopathy, diabetic nephropathy, and chronic kidney disease [estimated glomerular filtration rate < 60 mL/min/1.73 m^2])

TABLE 1. Exclusion criteria for part 1 of the CATALYST trial.[14]

- Type 1 diabetes
- New-onset diabetes (<1 year)
- Systemic glucocorticoid medication exposure within 3 months (excluding inhalers or topical therapies)
- Pregnancy or lactation; patients of childbearing potential should have a positive pregnancy test before dexamethasone administration
- Hemodialysis or end-stage renal disease
- Severe untreated sleep apnea
- Excessive alcohol consumption (>14 drinks/week for men, >7 drinks per week for women)
- Severe medical, surgical, or psychiatric illness
- Night shift worker (awake from 23:00 to 07:00 hours)
- Has taken any investigational drug within 4 weeks prior to screening, or within less than 5 times the drug's half-life, whichever is longer
- Diagnosed with or having treatment plans for Cushing syndrome using any of the following treatments: mifepristone, metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, etomidate, octreotide, larazotide, pasireotide, long-acting octreotide, or long-acting pasireotide
- History of hypersensitivity or severe reaction to dexamethasone

Based on these criteria, 24% of patients with difficult-to-control T2D were found to have hypercortisolism, with an even higher prevalence rate (>30%) in certain at-risk patients, such as those with cardiac disorders or those taking ≥3 blood pressure–lowering medications.[19] Three tests are commonly used to screen for evidence of hypercortisolism: the 1-mg overnight dexamethasone suppression test (DST), late-night salivary cortisol (LNSC), and 24-hour urine-free cortisol (UFC).[18,20] Each test has its strengths and limitations.[18] However, the 1-mg overnight DST, using a post-DST serum cortisol cutoff of >1.8 µg/dL, is recommended as the most sensitive first-line screening method because of its high sensitivity (up to 95%).[18] Well-known causes of false-positive DST results should be excluded before DST. It is also important to ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST.[18] The 24-hour UFC and LNSC tests are less sensitive, but an abnormally high result strongly supports a hypercortisolism diagnosis.[7] UFC and LNSC should be conducted at least twice to ensure accurate results.[7] For the interpretation of biochemical test results, it is crucial to account for the clinical index of suspicion, especially in the

context of patients' medical history and comorbidities. A computed tomography (CT) scan is a routine part of the workup for patients with suspected hypercortisolism based on test results and clinical suspicion.[18]

CURRENT TREATMENT APPROACHES FOR HYPERCORTISOLISM

Although many patients with hypercortisolism can be identified—and in some cases treated—in primary care, successful management often involves the entire healthcare team.[7] This includes primary care clinic staff such as medical assistants, nurses, physician assistants/nurse practitioners (PAs/NPs), and physicians, as well as specialists—primarily endocrinologists and endocrinology NPs/PAs. By providing comprehensive and detailed referrals, PCPs can facilitate timely and effective specialist care, ultimately improving patient outcomes. Of note, some PCPs may choose to diagnose and treat certain cases of hypercortisolism in the primary care setting, especially when access to specialists is limited. Clinicians should engage in patient care as appropriate, based on their level of knowledge and comfort in managing hypercortisolism. An approach (via checklist) for managing hypercortisolism in primary care is suggested in **TABLE 2**.

TABLE 2. Checklist for managing hypercortisolism in primary care.

Screening

☐ **Determine patients at risk for hypercortisolism**
- Unusual features for their age, such as osteoporosis/fragility fracture, T2D, or hypertension in young individuals
- Patients with multiple and unexplained/progressive features, such as worsening T2D outside of the normal progression or unexplained recent weight gain
- All patients with adrenal mass
- Adults with difficult-to-control T2D; HbA1c 7.5%-11.5% and multiple antihyperglycemic and/or ≥2 antihypertension medications and/or ≥1 diabetes complication

Testing

☐ **Select appropriate test**
- Dexamethasone suppression test (DST): most sensitive
  - Use a post-DST serum cortisol cutoff of >1.8 µg/dL
  - Ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST
- Late-night salivary cortisol (LNSC): less sensitive (must perform at least twice)
- 24-hour, urine-free cortisol (UFC): less sensitive (must perform at least twice)

Diagnosis

☐ **Interpret test results in context of clinical characteristics**
- Rule out false positives and false negatives
- Medical history and exam
- Signs of hypercortisolism: weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders

Treatment

☐ **Refer patient to endocrinology or treat in primary care**

☐ **Determine whether the patient is a surgical candidate**

Contraindication or preference to avoid surgery?

☐ **If surgery is not possible or not curative, consider radiation or medical therapy**
- Options for medical therapy:
  - Glucocorticoid receptor antagonists (mifepristone)
    - Improves glycemic control in patients
  - Steroid synthesis inhibitors (metyrapone, levoketoconazole, osilodrostat)
  - Pituitary-directed agents (pasireotide, cabergoline)

☐ **Ongoing follow-up and monitoring**

First-line treatment for hypercortisolism typically involves surgical resection of the causal tumor, where possible.[21,22] For patients in whom surgery is not possible or not curative, radiation therapy or medical therapy is used.[21,22] When minimally invasive adrenalectomy is not appropriate, feasible, or preferred for treating hypercortisolism, the default approach is to manage comorbidities, such as T2D, hypertension, and hyperlipidemia.[14] However, addressing these comorbidities alone, without addressing elevated cortisol, does not lower cardiovascular risk. Certain cortisol-directed pharmacotherapies that lower the effect of cortisol in patients with hypercortisolism can potentially improve T2D, hypertension, and cardiovascular risk, including in patients who are not surgical candidates or who have failed or refused surgery.[14]

Pharmacotherapy options include ketoconazole, levoketoconazole, metyrapone, mifepristone, osilodrostat, pasireotide, and cabergoline though their approved indications and mechanisms vary (**TABLE 3**).[14,21,22] Of the approved pharmacologic agents, only mifepristone antagonizes cortisol activity directly at the glucocorticoid receptor regardless of etiology, indicating its potential for addressing comorbid conditions

TABLE 3. Characteristics of select pharmacologic treatments for hypercortisolism.[14,21,22]

Drug class	Mechanism of action	Medication	Indication	Route
Glucocorticoid receptor antagonists	Competitive glucocorticoid receptor antagonist	Mifepristone	To control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have T2D or glucose intolerance and have failed surgery or are not candidates for surgery	Oral
Steroid synthesis inhibitors	11-beta hydroxylase inhibition; also inhibits other enzymes; decreases glucocorticoid and mineralocorticoid production and secretion	Metyrapone	In combination with other diagnostic tests, for the diagnosis of adrenal insufficiency in adult and pediatric patients Treatment of Cushing syndrome (off label)	Oral
	Blocks multiple steps of steroid biosynthesis through inhibition of cytochrome P450 enzymes, including a decrease in glucocorticoid, mineralocorticoid, and adrenal androgen production and secretion	Ketoconazole	Off-label use	Oral
		Levoketoconazole	For the treatment of endogenous hypercortisolemia in adult patients with Cushing syndrome for whom surgery is not an option or has not been curative	Oral
	11-beta hydroxylase inhibition	Osilodrostat	For the treatment of endogenous hypercortisolemia in adults with Cushing syndrome for whom surgery is not an option or has not been curative	Oral
Pituitary-directed agents	Somatostatin receptor agonist; corticotroph inhibition	Pasireotide	For the treatment of adult patients with Cushing syndrome for whom pituitary surgery is not an option or has not been curative	Subcutaneous, intramuscular
	Dopamine receptor modulation; corticotroph inhibition; adrenal cortex cell stimulation	Cabergoline	Off-label use	Oral

and cardiovascular risk in patients with hypercortisolism.[14] New and emerging data highlight the potential role of pharmacotherapy to address hypercortisolism in patients with poorly controlled T2D and improve HbA1c.[14] For example, data from part 2 of the CATALYST trial showed that mifepristone reduced HbA1c at 24 weeks vs placebo in patients with hypercortisolism and difficult-to-control T2D.[23]

NEW AND EMERGING DATA FOR HYPERCORTISOLISM TREATMENT TARGETING THE GLUCOCORTICOID RECEPTOR

Within the past decade, advances in therapy for hypercortisolism have offered an increasing number of medical treatments. Moreover, there have been new data focusing on treatment of hypercortisolism through targeting glucocorticoid receptors in patients with difficult-to-control T2D.

Mifepristone is a competitive glucocorticoid receptor antagonist that has been approved since 2012 to control hyperglycemia secondary to hypercortisolism in patients with endogenous hypercortisolism who have T2D or glucose intolerance and have failed surgery or are not candidates for surgery. In part 2 of CATALYST, the safety and efficacy of mifepristone to lower HbA1c compared to placebo were assessed. Patients with hypercortisolism were enrolled in part 2 of the study if they did not require further assessment for elevated ACTH and were not candidates for, or decided against, surgery.[14] Results indicate that patients who received mifepristone had a least-squares mean change in HbA1c from baseline of –1.47% (P <.001) compared with –0.15% for those assigned to placebo (P = .92; between-group difference, –1.32%, P <.001).[23]

CASE STUDY

A 46-year-old woman with hypercortisolism, T2D, hypothyroidism, chronic kidney disease (CKD), and resistant hypertension is being managed by the care team. She currently takes metformin, dulaglutide, and empagliflozin at maximum doses, as well as 2 medications for hypertension. She is not a candidate for surgery and has not received any cortisol-targeted therapies yet (medical management of comorbidities only). Recently, her HbA1c has

increased, and the care team is considering how to adjust her treatment.

Laboratory evaluations

- Glycated hemoglobin (HbA1c): 9.3%
- Fasting glucose: 158 mg/dL
- 4-hour postprandial glucose: 270-295 mg/dL, despite dietary carbohydrate control
- Morning cortisol: 18 µg/dL (normal range 10-25 µg/dL)[24]
- Post-1 mg DST serum cortisol: 3.6 µg/dL (normal range <1.8 µg/dL)[18]
- Post-1 mg DST serum dexamethasone: 415.2 ng/dL (expected range >140 ng/dL for adequate serum cortisol suppression)[25]
- LNSC (performed twice): 3.8 nmol/L, 3.2 nmol/L (normal range <2.6 nmol/L)[26]
- 1 week after positive DST:
  - ACTH: 3 pg/mL (normal range ≥9-52 pg/mL)[27]
  - Dehydroepiandrosterone sulfate (DHEAS): 20 µg/dL (normal range 32-240 µg/dL)[28]

Clinical assessment

The patient has hypercortisolism as evidenced by the positive DST (the recommended and most sensitive test), which is a likely cause of her difficult-to-control T2D. This patient was a good candidate for DST because she met the criteria for part 1 of the CATALYST trial: HbA1c 7.5%-11.5%, ≥3 antihyperglycemic drugs, ≥1 diabetes complication, and ≥2 antihypertension medications. She did not meet any exclusion criteria (**TABLE 1**).

The diagnosis is also supported by other tests. LNSC may be preferred over UFC because of better accuracy, easier administration, and measurement of serum-free biologically active cortisol. Of note, the LNSC test is not a good option for a patient who is a shift worker or has an erratic sleep schedule. Furthermore, UFC is not an appropriate test for patients with CKD. The ACTH and DHEAS tests 1 week after the positive DST help confirm the findings and support a referral to endocrinology.

Treatment considerations

The patient was managed in primary care by her PCP, who felt comfortable diagnosing and treating hypercortisolism. However, referring the patient to endocrinology would also be an appropriate action in this scenario. The patient received a CT scan of the abdomen with adrenal protocol during workup to help determine whether she was a surgical candidate. The CT scan revealed an incidentaloma.

Because the patient prefers to avoid surgery and radiation therapy, medical management of hypercortisolism is the most likely approach to address her elevated cortisol and improve associated comorbidities. Although several medical treatment options are available, initiation of a glucocorticoid receptor antagonist such as mifepristone is the most appropriate choice because of the potential for improvement in T2D, supported by data from the recent CATALYST study. Six months after initiation of mifepristone, the patient's HbA1c improved to 7.8%, and her blood pressure also improved.

Clinical learning

This case highlights the importance of screening for hypercortisolism in patients who are at risk, particularly those with difficult-to-control T2D. Early identification and management of elevated cortisol led to improvements in the patient's T2D and hypertension. The consequences of failure to identify hypercortisolism include prolonged exposure to elevated cortisol, increasing cardiovascular risk and worsening associated comorbidities.

BOX 1. Call to action for PCPs—hypercortisolism and T2D.

- Keep in mind the effect that hypercortisolism has on blood glucose control—especially given that the prevalence of hypercortisolism in a certain group of patients with T2D is as high as 24%.
- Raise clinical suspicion of hypercortisolism when patients have difficult-to-control T2D and comorbidity despite standard-of-care treatment (multiple antihyperglycemic/ antihypertensive medications) and appropriate lifestyle adjustments.
- Screen with an overnight 1 mg DST (the most sensitive test), excluding known causes for false-positive results.
- Be prepared for proper treatment and/or referral for patients with positive test results and a high clinical suspicion for hypercortisolism.

SUMMARY

Awareness and understanding of hypercortisolism are essential for PCPs to improve the care of these patients, specifically those with difficult-to-control T2D. Recognizing the signs and symptoms, selecting patients with a high pretest probability, using appropriate screening methods, and making informed referrals can significantly impact patient health by reducing the delay in diagnosis and preventing the severe complications associated with this condition. A specific call to action for PCPs is detailed in **BOX 1**. PCPs can be empowered to increase the detection of hypercortisolism in their patients who are at risk and initiate appropriate treatments to ensure optimal patient outcomes. ●

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