Medscape EDUCATION

Call to Action: Additional Screening of Patients With Difficult-to-Control T2D and Other Metabolic Abnormalities

Difficult-to-Control T2D Can Be Caused By Hypercortisolism

Cushing syndrome (hypercortisolism), although rare, disproportionately affects patients with chronic diseases that are potentially mediated by cortisol excess, including type 2 diabetes (T2D).[1,2] Hypercortisolism leads to metabolic disturbances, including hyperglycemia and insulin resistance; thus, there is a clear relationship between Cushing syndrome and T2D.[3] Even in patients with mild hypercortisolism (less clinically apparent hypercortisolism), cortisol excess is associated with increased morbidity and mortality.[1]

Data from the CATALYST study recently presented at the American Diabetes Association's 84th Scientific Sessions in June 2024 showed that in a population of over 1000 patients with difficult-to-control T2D, the prevalence of hypercortisolism was 24% (defined as post 1-mg overnight dexamethasone test > 1.8 µg/dL).[4,5] But, due to its clinical overlap with other metabolic conditions, delays in diagnosis of hypercortisolism are common.[6]

For people with diabetes, people with hypertension, or more importantly, people with combined resistant hypertension and difficult-to-control diabetes, the prevalence increases quite dramatically. The incidence of endogenous Cushing syndrome is 2% to 5% higher in special populations (ie, those with hypertension and diabetes)[7] than in the general population.[8]

Early recognition of hypercortisolism as a potential cause for poorly-controlled glucose in patients with T2D and/or resistant or recently worsening hypertension can aid with timely diagnosis and treatment, as well as improve patient outcomes.

Comorbidities and Hypercortisolism

When comparing cortisol-producing adrenal adenomas to nonfunctioning adrenal adenomas, patients with hypercortisolism due to an adrenal source have higher rates of cardiometabolic comorbidities.[9] Pharmacologic treatment of the comorbidities without treating hypercortisolism is ineffective at improving long-term cardiovascular survival. Patients with adrenal autonomous cortisol secretion who do not receive treatment targeting their hypercortisolism are at increased risk for future cardiovascular events and cardiovascular mortality.[9] Hypertension occurs in 80% to 85% of individuals with Cushing syndrome[10] and, as a clinical feature, is second only to weight gain/obesity.[11]

Who to Screen for Hypercortisolism in Practice

Most patients with hypercortisolism in the general population present without the classic phenotypic features of Cushing syndrome. When patients with hypercortisolism present without classic phenotypic features, the source is usually adrenal; uncommonly, pituitary adenoma and ectopic adenoma are the source of the excess adrenocorticotropic hormone (ACTH).[1,12,13] It is important to note that most diagnoses of Cushing syndrome are made by identifying patients who have clusters of conditions prevalent in the general population. The Big Four represents less clinically apparent hypercortisolism associated with chronic disease that can be mediated by excess cortisol. When they are present in patients with difficult-to-treat T2D, it should alert the clinician to consider hypercortisolism as an underlying cause.

Figure 1. Classic Symptoms of Cushing Syndrome Vs Less Clinically Apparent Hypercortisolism[1,14-16]

CLASSIC		BIG FOUR
• Easy bruising • Facial plethora • Proximal myopathy (or proximal muscle weakness) • Striae (especially of reddish-purple and > 1 cm wide) • Dorsocervical fat pad ("buffalo hump")	• Facial fullness • Obesity • Supraclavicular fullness • Acne • Hirsutism	• Type 2 diabetes • Hypertension • Obesity • Osteoporosis/fractures

Screening Tests for Hypercortisolism[15]

- **1-mg OVERNIGHT DEXAMETHASONE SUPPRESSION TEST (DST)** (serum cortisol > 1.8 µg/dL with dexamethasone ≥ 140 ng/dL supports presence of hypercortisolism) – can be performed by non-specialists; high sensitivity
- **Urinary-free cortisol (UFC)** – low sensitivity; often normal
- **Late-night salivary cortisol (LNSC)** – low sensitivity
- **ACTH low/low normal** – supportive of ACTH-independent Cushing syndrome caused by an adrenal source
- **Dehydroepiandrosterone sulfate (DHEA-S) low** – supportive of adrenal adenoma

Medical Treatments for Hypercortisolism

Options for the treatment of hypercortisolism include managing comorbidities, surgery, and medications.

- Pharmacologic management of comorbidities: hypertension, hyperglycemia, dyslipidemia
- Medical treatments for hypercortisolism
  - Glucocorticoid receptor antagonists
    - Mifepristone (approved by the US Food and Drug Administration for hyperglycemia associated with Cushing syndrome)[17]
    - Relacorilant (in clinical development)[18]
  - Adrenal steroidogenesis inhibitors (some used off-label)
    - Ketoconazole,[19,20] levoketoconazole (17-alpha-hydroxylase inhibitor)[21]
    - Metyrapone,[20,22] osilodrostat (11-beta-hydroxylase inhibitor)[23]
    - Mitotane (adrenolytic)[24-26]
  - Somatostatin receptor ligands
    - Pasireotide[20]
  - Dopamine receptor agonists
    - Cabergoline[20]
- Surgical removal of adrenal adenoma
- Surgical removal of pituitary or ectopic ACTH-secreting tumor[20,27]

Take-Away Messages

The recognition, diagnosis, and treatment of hypercortisolism as a possible cause for difficult-to-control T2D is instrumental in improving outcomes for these patients.

Figure 2. Take-Away Messages

CALL TO ACTION:
Consider Screening For Hypercortisolism

- High level of suspicion: BIG FOUR
  - Difficult-to-treat hyperglycemia
  - Resistant hypertension
  - Obesity (especially recent or rapid weight gain)
  - Fractures, osteopenia
- Screening: 1-mg overnight DST
- Treatment:
  - Surgical removal of adenoma
  - Medical management (some used off-label)

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