Panelists

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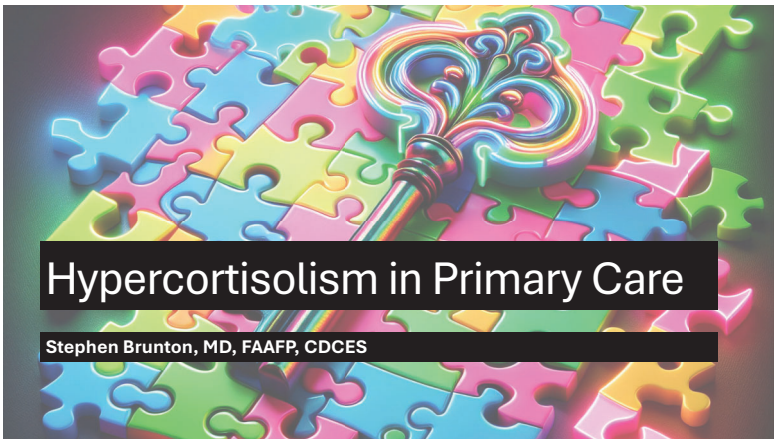
Learning Objectives

Participants in this presentation should be able to ...
Increase awareness of hypercortisolism as a potential cause of hard-tocontrol diabetes.
Describe new and emerging data for hypercortisolism treatments, including the impact on patients within the practice who have difficult-to-control diabetes.
Implement methods for working with the health care team, including initiating effective referrals to endocrinology, for patients with evidence of hypercortisolism.
Collaborate with members of the health care team to implement multidisciplinary management of hypercortisolism and achieve optimal patient outcomes.



What is Hypercortisolism?

Also referred to as Cushing syndrome, endogenous hypercortisolism is:

"Prolonged, excessive cortisol activity that is not due to a normal physiological etiology."[1]

- Often goes undiagnosed or is misdiagnosed, resulting in progression of morbidity and increased CV-related mortality.[1-3]

CV, cardiovascular

1. Reincke M, et al. *JAMA*. 2023;330(2):170. 2. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022;107(9):e3723-e3730. 4. Limumpornpetch P, et al. *J Clin Endocrinol Metab*. 2022;107(8):2377-2388.

Classification of Hypercortisolism

Hypercortisolism can be classified into two main categories[1]:

ACTH-Dependent Hypercortisolism	ACTH-Independent Hypercortisolism
Includes: • Excess adrenocorticotropic hormone (ACTH) secretion by pituitary tumors (Cushing syndrome) • Non-pituitary tumors (ectopic ACTH secretion)	Includes autonomous cortisol secretion by one or both adrenal glands

1. Reincke M, et al. *JAMA*. 2023;330(2):170.

Impact of Hypercortisolism on T2D

- **Many patients with T2D do not reach treatment goals**[1]
  - Despite effective therapies and best efforts from clinicians and patients
- Excess cortisol **increases insulin resistance** and **decreases insulin sensitivity**, negatively impacting the metabolic defects underlying T2D[1]
  - Contributes to a form of T2D that is difficult to control with standard therapies

1. DeFronzo RA, et al. *BMJ Open*. 2024;14(7):e081121. 2. Morelli V, et al. *Front Endocrinol*. 2022;13:898084. 3. Petramala L, et al. *Endocrine*. 2020;70(1):150-163.

The Primary Care Clinician's (PCC's) Role in Managing Hypercortisolism

With an increasing focus on identifying and appropriately managing clinically inapparent hypercortisolism, **PCCs can play a key role**[1]:

Patients with T2D are frequently treated in primary care—PCCs play a crucial role in ensuring optimal treatment outcomes for these patients[2]
Many patients with hypercortisolism are missed or have a delayed diagnosis and may not have access to endocrinology care
PCCs can identify patients at risk for hypercortisolism and use effective screening tools to identify the disease
PCCs can initiate effective referrals to endocrinology as part of the health care team using specific approaches

1. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401. 2. Rushforth B, et al. *Br J Gen Pract*. 2016;66(643):e114-127.

Screening and Diagnosis of Hypercortisolism

A Brief Review

Jennifer Goldman, PharmD, CDCES, BC-ADM-FCCP
John Buse, MD, PhD

Hypercortisolism: Multisystemic, Heterogeneous Presentation

- Overt symptoms of hypercortisolism include those clearly identifiable in the "index case" of Cushing's syndrome described by Dr. Cushing's in 1912[1,2]
- However, many patients with clinically significant hypercortisolism do not exhibit all of the classical overt symptoms and typically have a variety of nonspecific features[2,3]

Overt Symptoms of Hypercortisolism	Nonspecific Features of Hypercortisolism
Central obesity	Weight gain
Wasting of extremities	Diabetes
Easy bruising	Hypertension
Purple striae	Hypokalemia
Rounded "moon" face	Dyslipidemia
	Osteoporosis
	Kidney stones
	Reproductive and psychiatric disorders

1. Reincke M, et al. *JAMA*. 2023;330(2):170. 2. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401. 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022;107(9):e3723-e3730.

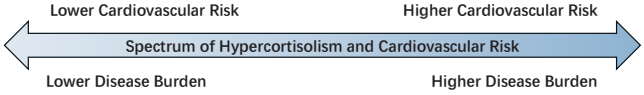
Detrimental Consequences of a Delayed Diagnosis

- Variable spectrum of clinical signs and symptoms can complicate diagnosis[1,2]
  - Diagnosis may be **delayed up to 10 years**
- The consequences of delayed diagnosis can be detrimental[3]
  - **Prolonged exposure to elevated cortisol** leads to an increased risk of cardiometabolic issues
- **Mortality 2–5 times higher** than the general population is reported in untreated hypercortisolism[4]
- Underscores the need for a **heightened awareness and timely intervention** in primary care settings[5]

1. Valassi E, et al. *Endocr Connect*. 2022;11(7):e220027. 2. Page-Wilson G, et al. *Pituitary*. 2023;26(4):364-374. 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022;107(9):e3723-e3730. 4. Dekkers OM, et al. *J Clin Endocr Metab*. 2013;98(6):2277-2284. 5. Yorke E, et al. *Int J Endocrinol*. 2017;2017:1-6.

A Continuum of Cardiovascular Risk

- Patients with hypercortisolism experience increased cardiometabolic comorbidities and mortality across the spectrum of disease[1]
- Even patients with less clinically apparent disease, lacking classically described overt features, have increased cardiometabolic comorbidities and mortality[1]
- Early detection and management are critical to mitigate these risks



1. Araujo-Castro M, et al. *Annales d'Endocrinologie*. 2023;84(2):272-284.

Certain Populations Have Higher Rates of Hypercortisolism

- While incidence of hypercortisolism in the general population is low, recent data suggest a higher prevalence in those with certain risk factors[1]
- Screening for hypercortisolism should occur in patients who have multiple risk factors[2]
  - Increased pre-test probability of hypercortisolism
  - Better positive predictive value of the screen
- If pre-test probability for hypercortisolism is high, further evaluation is recommended even with normal results[2]

1. Fonseca V. Results of the CATALYST Trial Part 1. Presented at the 84th American Diabetes Association (ADA) Scientific Sessions, June 21–24, 2024, Orlando FL. 2. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540.

Enriched Population for Screening

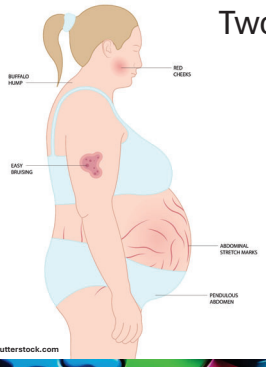
According to the 2008 Endocrine Society Clinical Practice Guideline, screening should include (but not be limited to) the following[1]:

- Patients with unusual features for their age, such as osteoporosis/fragility fracture, T2D or hypertension in young individuals
- Patients with multiple and unexplained/progressive features, like worsening T2D outside of the normal progression or unexplained recent weight gain
- All patients with adrenal mass

An observational study using a prospective hypercortisolism registry identified a prevalence of up to 50% using these screening criteria.[2]

1. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 2. Braun LT, et al. *J Clin Endocrinol Metab*. 2022;107(9):e3723-e3730.

Two "Faces" of Hypercortisolism



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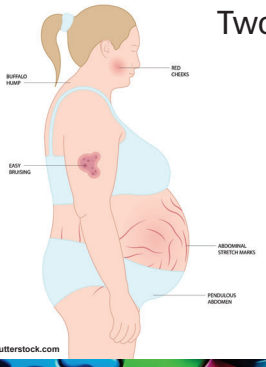
Two "Faces" of Hypercortisolism



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Subtle physical features

Multiple comorbidities

Usually ACTH-independent, autonomous adrenal production

More common than previously imagined

Photograph from Dr. Richard Auchus
University of Michigan, Ann Arbor
Shared with permission

CATALYST Rationale[1]

Diabetes mellitus
1. Stimulation of hepatic gluconeogenesis
2. Inhibition of hepatic & skeletal muscle insulin sensitivity
3. Coexistence of metabolic syndrome, dyslipidemia, & impairment of protein metabolism

Osteoporosis
1. ↓ Osteoblast number & function
2. Osteoclast stimulation → ↑ bone resorption
3. Osteocyte impairment & apoptosis
4. Coexistence of hypogonadism, inhibition of calcium resorption in the intestine, & increased calcium excretion in the kidneys

Obesity
1. ↑ Pre-adipocyte to adipocyte differentiation
2. ↓ Amino acid uptake
3. ↓ GLUT4 translocation
4. ↓ Lipogenesis & ↑ lipolysis
5. ↑ Appetite

High blood pressure
1. High cortisol levels saturate renal 11ß-HSD2 → cortisol can bind to the MR, leading to hypertension
2. ↑ Pressor response to angiotensin II
3. ↑ Sensitivity of ß-adrenoreceptor to catecholamines
4. ↑ Endothelin-1 levels

Hypercortisolism

Dyslipidemia
1. ↑ Gluconeogenesis
2. ↑ Lipoprotein secretion & fatty acid synthesis
3. ↑ Hepatic glucose output & insulin resistance
4. ↑ Liver steatosis

Cardiovascular disease
1. ↑ Number of carotid plaques
2. Worse mid-wall systolic movement, left ventricular hypertrophy, & concentric remodeling
3. High prevalence of high blood pressure and other cardiovascular risk factors

1. Araujo-Castro M, et al. *Ann Endocrinol (Paris)*. 2023;84(2):272-284.

CATALYST

Hypercortisolism in patients with difficult-to-control T2D despite receiving standard-of-care therapies: prevalence and treatment with mifepristone

A 2-part phase 4 study conducted at 36 sites in the US aiming to screen >1000 patients (NCT05772169)

Part 1 Prevalence Phase

Persons with difficult-to-control T2D

↓

1-mg overnight DST

↓

Hypercortisolism
(post-DST cortisol >1.8 µg/dL with dexamethasone level ≥140 ng/dL)

↓

Further evaluation:
- Labs (ACTH, DHEAS, cortisol)
- Adrenal CT scan

Study Population: Key Inclusion

Protocol-defined "difficult-to-control type 2 diabetes:"

HbA1c 7.5–11.5% despite taking:
- ≥3 anti-hyperglycemic medications and/or
- Insulin and any other anti-hyperglycemic medications and/or
- ≥2 anti-hyperglycemic medications and presence of ≥1 micro- or macro-vascular complications and/or
- ≥2 anti-hyperglycemic and ≥2 anti-hypertensive medications

Study Population: Key Exclusion

Exclude common causes of false positive DST:
- Systemic glucocorticoids
- Pregnancy or lactation
- Use of oral contraceptives
- Hemodialysis or end-stage renal disease
- Severe untreated sleep apnea
- Excessive alcohol consumption
- Severe medical, surgical, or psychiatric illness
- Night shift worker

Primary aim of the prevalence phase: Assess the prevalence of hypercortisolism in a population with difficult-to-control T2D despite receiving standard-of-care therapies

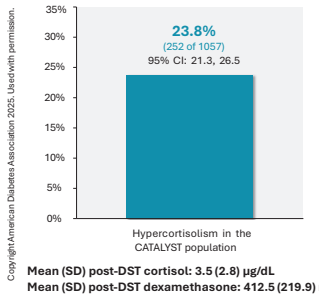
ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test;

1. Buse JB, et al. *Diabetes Care*. 2025;48(00):1-9.

Prevalence of Hypercortisolism in CATALYST

Screening Phase

Hypercortisolism defined as post-DST cortisol >1.8 µg/dL with dexamethasone ≥140 ng/dL in this population, which has a high pre-test probability of hypercortisolism and excludes known causes of false-positives



DST, dexamethasone suppression test; SD, standard deviation.

Mean (SD) post-DST cortisol: 3.5 (2.8) µg/dL
Mean (SD) post-DST dexamethasone: 412.5 (219.9) ng/dL

1. Buse JB, et al. *Diabetes Care*. 2025;48(00):1-9.

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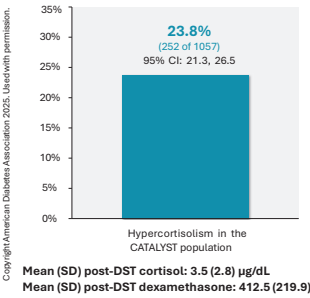


34.7% had an adrenal imaging abnormality on abdominal CT

Baseline characteristics increasing the odds of having hypercortisolism, included ethnicity, age, lower BMI, higher medication burden for hypertension, taking analgesics or fibrates, and taking SGLT2 inhibitors, tirzepatide and high-dose GLP-1 receptor agonists

Prevalence of hypercortisolism was 36.6% among those who took ≥3 blood pressure-lowering medications

Hypercortisolism prevalence was 33% in those with cardiovascular disease

DST, dexamethasone suppression test; SD, standard deviation.

Mean (SD) post-DST cortisol: 3.5 (2.8) µg/dL
Mean (SD) post-DST dexamethasone: 412.5 (219.9) ng/dL

1. Buse JB, et al. *Diabetes Care*. 2025;48(00):1-9.

Summary – CATALYST Screening Phase

- Hypercortisolism prevalence was 23.8% among the 1057 CATALYST participants with "difficult-to-control" T2D
- Very common phenotype, not based on appearance, but based on multimorbidity and medication burden
- In one third of participants with hypercortisolism, a standard abdominal CT scan revealed an adrenal abnormality
- Screening was easy to perform. A single 1-mg overnight dexamethasone suppression test with AM cortisol >1.8 µg/dL (50 nmol/L) and simultaneous dexamethasone level ≥140 ng/dL (with subsequent morning ACTH and DHEA-S) is sufficient testing to establish ACTH-independent hypercortisolism
- An adrenal CT should be performed to establish whether there is potentially surgically remediable disease
- Common causes of false positive tests need to be excluded

1. Buse JB, et al. *Diabetes Care*. 2025;48(00):1-9.

How to Screen for Hypercortisolism

Three tests commonly used to screen for hypercortisolism[1,2]:

1. 1-mg overnight dexamethasone suppression test (DST)
2. Late-night salivary cortisol (LNSC)
3. 24-hour urine-free cortisol (UFC)

- While each has strengths and limitations, the **DST is recommended as the most sensitive** first line screening test—up to 95% sensitivity[1]
- 24-hour UFC and LNSC tests are less sensitive in patients with less prominent symptoms.[3]
  - Abnormally high results with these tests strongly indicates hypercortisolism.
- When interpreting test results, accounting for clinical index of suspicion and the patient's history and comorbidities is essential.

1. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 2. Galm BP, et al. *J Clin Endocrinol Metab*. 2020;105(6):dgaa105. 3. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401.

Overnight Dexamethasone Suppression Test (DST)

Performing the test	Interpreting results
1 mg oral dexamethasone at 11 pm	<1.8 mcg/dL serum cortisol with >140 ng/dL dexamethasone level: hypercortisolism not likely
Blood sample at 8 am (~9 hours after dose) for serum cortisol and dexamethasone levels	≥1.8 mcg/dL serum cortisol with >140 ng/dL dexamethasone level: consult endocrinologist

1. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401.

Overnight Dexamethasone Suppression Test (DST)

Testing considerations

Potential Factors for False Positive	*Potential Factors for False Negative*
• Estrogen-containing medications • Pregnancy • Genetic causes of rapid dexamethasone metabolism • Dexamethasone malabsorption, failure to take dexamethasone • Undisclosed use of exogenous glucocorticoids • Secondary hypercortisolism due to non-adrenal disease • Chronic renal disease	• Chronic renal disease • Chronic liver disease • Concomitant medications that inhibit CYP3A4 leading to very high dexamethasone levels • Cyclic hypercortisolism

CYP3A4, cytochrome P450 isoform 3A4

1. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401.

Effective Screening for Hypercortisolism-Summary

- Appropriate Patient Selection
  - Signs and symptoms suggestive of hypercortisolism
  - High pre-test probability of hypercortisolism
- Sensitive Screening Tests
  - Use a sensitive screening test (1-mg overnight DST)
- Clinical Context
  - Interpret test results in the context of the patient's medical history and presentation
  - Avoid false positives and negatives

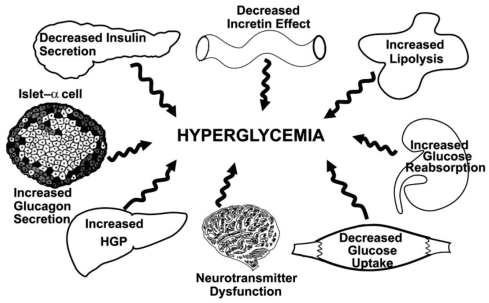
1. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 2. Scoffings K, et al. *Br J Gen Pract*. 2022;72(721):399-401.

Impact of Hypercortisolism on T2D

- Studies have shown the **benefits of addressing excess cortisol** for glycemic control in T2D, and for other comorbidities such as hypertension[1,2]
- **Assessing for hypercortisolism in patients with difficult-to-treat T2D** may be a rational strategy for identifying those who would benefit from treatment of hypercortisolism

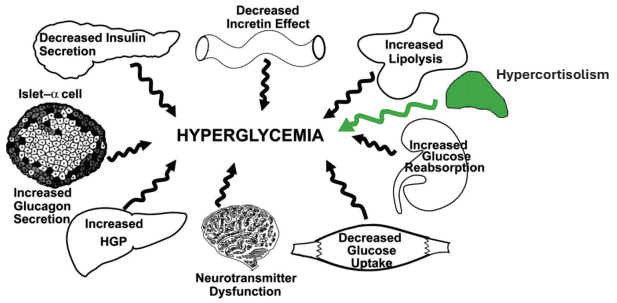
1. Morelli V, et al. *Front Endocrinol*. 2022;13:898084. 2. Petramala L, et al. *Endocrine*. 2020;70(1):150-163.

The Ominous Octet[1]



1. DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Now ... the Noxious Nine[1,2]



1. DeFronzo RA. *Diabetes*. 2009;58(4):773-795. 2. DeFronzo RA. Presented at the 85th American Diabetes Association (ADA) Scientific Sessions, June 20–23, 2025, Chicago, IL. Used with the permission of Ralph A. DeFronzo

Overview of Hypercortisolism Treatment

Surgery: Resection of the causal tumor, where possible[1,2]

- First-line treatment

Radiation Therapy[1,2]

- If surgery is not appropriate, feasible, or preferred

Medical Therapy[1,2]

- If surgery is not appropriate, feasible, or preferred
- Manage comorbidities[3]
- Use of cortisol-directed pharmacotherapies[3]

Selected Pharmacologic Agents for Treating Hypercortisolism[1-3]

Drug Class	Agents
Glucocorticoid receptor antagonists	Mifepristone Relacorilant (investigational)
Steroid synthesis inhibitors	Metyrapone Ketoconazole (off-label) Levoketoconazole Osilodrostat
Pituitary-directed agents	Pasireotide Cabergoline (off-label)

1. Nieman LK, et al. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831. 2. Favero V, et al. *IJMS*. 2021;22(21):11521. 3. DeFronzo RA, et al. *BMJ Open*. 2024;14(7):e081121.

A Case Study in T2D and Hypercortisolism

Eden Miller, DO, D-ACD, D-ABOM

New Patient Consult: Poorly Controlled T2D

- 55-year-old Caucasian female
- Duration of diabetes: 15 years
- BMI 45.58 kg/m^2, BP 130/67 mmHg
- HbA1c 8.9% (previous HbA1c 10.4%)

"That is the best A1c I have had in the last 10 years!"

- Medications
  - Insulin glargine U300 180 units SQ daily
  - Insulin aspart U100 30 units 3-4 times per day
  - Semaglutide 2 mg weekly (initiated 4 months prior)
  - Rosuvastatin 20 mg
  - Spironolactone 25mg
  - Propranolol 120mg
  - Irbesartan 150mg
  - CGM (recently restarted)
    - Current AGP in chart: TIR 21%, hypoglycemia 0%

AGP, ambulatory glucose profile; BMI, body mass index; BP, blood pressure; CGM, continuous glucose monitoring; SQ, subcutaneous; TIR, time in range

Diving Into Her History

- PMH: diabetes (unsure of which type), HTN, hyperlipidemia, migraines, GERD, and depression
- Surgical History: TAH due to dysfunctional bleeding
- Physical Exam: central obesity, upper eye lid edema mild, skin tags, acanthosis, no significant striae, or buffalo hump
- Family History: Father – T2D, CAD; Mother – good health, HTN, normal BMI
- Mentioned her challenging diabetes control and lack of significant improvement with recent max dose GLP-1 RA
  - Asked if she had ever had a DST; she was unable to remember and did not mention anything about an adrenal mass

CAD, coronary artery disease; GERD, gastroesophageal reflux disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; TAH, total abdominal hysterectomy

Hypercortisolism Work Up (Primary Care)

- UACR 65, eGFR >60 mL/min/1.73 m^2; stage 2A2 kidney disease
- LDL-C 90 mg/dL (pretty good)
- TSH 1.57 mIU/l (normal)
- 1 mg DST lab results:
  - Serum Cortisol 5.2 µg/dL (<1.8 µg/dL is the new normal range)
  - Dexamethasone level 315 ng/dL (range >140 ng/dL for adequate cortisol suppression)
  - DHEAS 55 (normal)
  - ACTH less than 5 (low as it should be)

DHEAS, dehydroepiandrosterone sulfate; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; UACR, urine albumin-creatinine ratio

Patient Returns for DST Lab Review

- Discussion of elevated cortisol that wasn't suppressed with dexamethasone
- Patient was advised she needed to get a CT of her adrenal gland to look for an adenoma

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"Oh, I have an adrenal mass – they found it 10 years ago."

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"What!!! Did they work it up?"

Patient Returns for DST Lab Review

- Discussion of elevated cortisol that wasn't suppressed with dexamethasone
- Patient was advised she needed to get a CT of her adrenal gland to look for an adenoma

"Oh, I have an adrenal mass – they found it 10 years ago."

"What!!! Did they work it up?"

"Yeah, they did a 24-hour urine cortisol and said it was normal."

Obtained Previous 10 Years of Records from Endocrinology

Type 1 diabetes (2003) Ab– ; ***All antibodies negative type 1 diabetes 2016***
C-peptide <1.0 ng/mL (actual result was 0.9 ng/mL)

HbA1c 11.7% (patient's results were typically in the 10–12% range)

Multiple daily injections of insulin with doses ranging from 150–250 units per day

CGM for about 6 months (intermittent use) – recently restarted

Prior failed medications
- Metformin (acidosis never found in the records)
- Pioglitazone (due to abnormal weight gain)
- Discontinued exenatide (ineffective)
- SGLT-2 inhibitor (genitourinary infections)

SGLT-2, sodium-glucose cotransporter-2

Additional Workup at Endocrinology in Last 10 Years

Incidental solitary adrenal mass (2.5 cm) on CT in 2015 prompted the following labs:

- 24-hour UFC 21 mcg/24 hours (normal range 3.5–45 mcg/24 hours)
- DST 2.1 µg/dL (2015) noted borderline abnormal
- Then repeated UFC in 2023 with level of 25 mcg/24 hours which is still normal

She Has Had Undiagnosed Hypercortisolism…

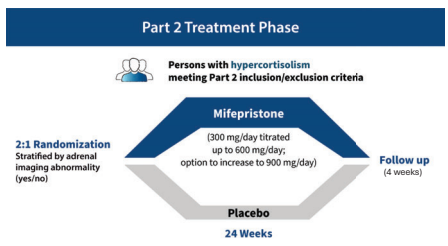
- For over 10 years
- With a known adrenal adenoma
- Positive DST previously and recently
- Significantly difficult to control diabetes and HTN
- Surgery would not take her for removal due to her poor controlled diabetes
- Mifepristone was initiated

New and Emerging Data for Hypercortisolism Treatment in T2D

John Buse, MD, PhD

CATALYST Treatment Phase Study Design[1]

Treatment Phase



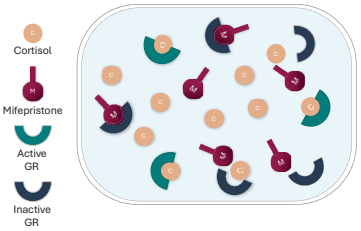
Primary Endpoint
- Change in HbA1c from baseline to week 24 in participants treated with mifepristone versus placebo

HbA1c, hemoglobin A1c
For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Treatment Phase

What Is Mifepristone and How Does it Work?



Mifepristone Is a Competitive Glucocorticoid Receptor Antagonist

- Binds to the glucocorticoid receptor, decreasing cortisol-mediated signaling[1-3] and reducing the clinical effects of hypercortisolism[4]
- FDA approved for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have T2D or glucose intolerance[5]

GR, glucocorticoid receptor; T2D, type 2 diabetes

1. Bourgeois S, et al. *EMBO J*. 1984;3(4):751-755. 2. Heikinheimo O, et al. *J Steroid Biochem*. 1987;26(2):279-284. 3. Sitruk-Ware R, Spitz IM. *Contraception*. 2003;68(6):409-420.4. Katznelson L, et al. *Clin Endocrinol (Oxf)*. 2014;80(4):562-569. 5. Korlym [prescribing information]. Redwood City, CA: Corcept Therapeutics Incorporated; September 2024.

Treatment Phase

Key Inclusion and Exclusion Criteria[1]

Rationale for ACTH criteria: Exclude patients with high ACTH from a placebo-controlled trial

Completed the prevalence phase with hypercortisolism (post-DST cortisol >1.8 µg/dL)

Adrenal abnormality on CT scan (nodule, enlargement, or other abnormality)

Eligible if
- 8 AM ACTH ≤15 pg/dL OR
- 15–30 pg/dL with DHEAS ≤100 µg/dL

+ other eligibility criteria met

No adrenal abnormality on CT scan

Eligible if
- 8 AM ACTH below the upper normal range

+ other eligibility criteria met

1. Unable to correct BP to <160/100 mmHg
2. Unable to correct potassium to ≥4.0 mEq/L
3. Unable to control hypo- or hyperthyroidism
4. Taking or at risk for taking systemic glucocorticoids due to an underlying condition (eg, asthma)
5. Liver transaminases >3× ULN or total bilirubin >1.5× ULN
6. eGFR <30 mL/min/1.73 m²
7. Taking drugs metabolized by CYP3A or CYP3A substrates with narrow therapeutic ranges
8. History of unexplained vaginal bleeding, endometrial hyperplasia, or endometrial carcinoma

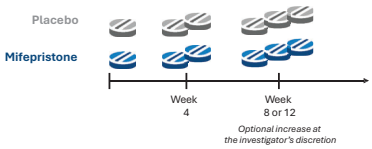
ACTH, adrenocorticotropic hormone; BP, blood pressure; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; CYP3A, Cytochrome P450, family 3, subfamily A; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Treatment Phase

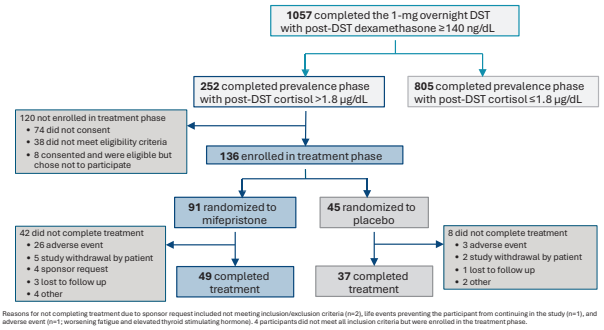
Study Medication and Management[1]

- **Mifepristone** administered as 300 mg tablet(s), identical **placebo**
  - Tablets taken once daily at approximately the same time with food
- **Dosing schedule was individualized** to allow for lower doses, slower titration, dose interruption, and dose reduction / re-escalation for safety and tolerability
- **Biweekly visits** were scheduled to monitor glucose, potassium, blood pressure, and symptoms of glucocorticoid withdrawal



1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

CATALYST | Participant Flow[1]



Reasons for not completing treatment due to sponsor request included not meeting inclusion/exclusion criteria (n=2), life events preventing the participant from continuing in the study (n=1), and adverse event (n=1; worsening fatigue and elevated thyroid stimulating hormone). 4 participants did not meet all inclusion criteria but were enrolled in the treatment phase.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Demographics and Baseline Characteristics[1]

Treatment Phase

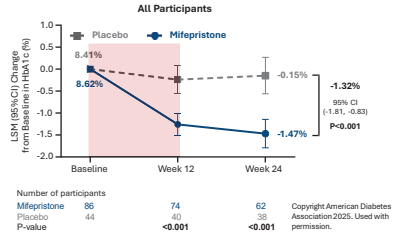
	Mifepristone (n=91)	Placebo (n=45)	Completed Prevalence Phase with Post-DST Cortisol >1.8 µg/dL but Did Not Enroll in Treatment Phase (n=118)
Age, years, mean (SD)	62.9 (8.9)	63.8 (11.5)	64.3 (9.5)
Male, n (%)	54 (59.3%)	29 (64.4%)	60 (50.8%)
Race, n (%)			
White	71 (78.0%)	39 (86.7%)	79 (66.9%)
Black or African American	16 (17.6%)	5 (11.1%)	34 (28.8%)
Other[a]	4 (4.4%)	1 (2.2%)	5 (4.2%)
Ethnicity, n (%)			
Hispanic or Latino	5 (5.5%)	4 (8.9%)	12 (10.2%)
Not Hispanic or Latino	85 (93.4%)	41 (91.1%)	106 (89.8%)
Abnormal adrenal CT scan, n (%)	25 (27.5%)	13 (28.9%)	N/A[c]
Body weight, kg, mean (SD)	99.7 (23.21)	97.4 (23.43)	95.4 (24.2)
Waist circumference, cm, mean (SD)	114.0 (17.45)	115.3 (18.24)	112.8 (17.4)
Body mass index, kg/m², mean (SD)	33.1 (7.31)	33.7 (8.21)	32.8 (7.9)
HbA1c, %, mean (SD)	8.62 (1.27)	8.41 (1.08)	8.82 (0.97)
Systolic blood pressure, mmHg, mean (SD)	125.0 (15.98)	125.4 (14.78)	128.3 (16.5)
Diastolic blood pressure, mmHg, mean (SD)	74.1 (9.12)	73.3 (9.44)	74.3 (9.5)

[a]Race category "Other" includes Asian, multiple, and other. [c]The main reasons why participants with hypercortisolism did not enroll in the treatment phase were participant did not consent (n=74), not meeting eligibility criteria for the treatment phase (n=38), and participant decision (n=8). [c]Not all participants completed the CT scan.
CT, computed tomography; HbA1c, hemoglobin A1c; SD, standard deviation

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Treatment Phase

Primary Endpoint: Statistically Significant Reduction in HbA1c Despite Medication Reductions/Discontinuation[1]



Number of participants

	Baseline	Week 12	Week 24
Mifepristone	86	74	62
Placebo	44	40	38
P-value		<0.001	<0.001

Of the 91 participants randomized to mifepristone, 65 (71%) received 600 mg and of those, 28 (31%) received 900 mg mifepristone during the study

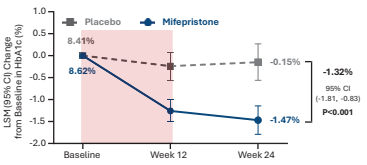
CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSM, least-squares mean; SUs, sulfonylureas
P-value for LSM difference between mifepristone and placebo shown. Dose decreases and discontinuations combined for insulin, SUs, GLP-1 RAs, and tirzepatide; discontinuations only for metformin and SGLT2 inhibitors. [N] indicates the number of participants taking a medication from the class at baseline.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Primary Endpoint: Statistically Significant Reduction in HbA1c Despite Medication Reductions/Discontinuation[1]

Treatment Phase

All Participants



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Discontinuations/Dose-reductions in Glucose-lowering Medications by Week 12

n/N= (%)	Mifepristone	Placebo
Long-acting insulin	32/65 (49.2%)	3/23 (13.0%)
Fast-acting insulin	10/33 (30.3%)	2/19 (10.5%)
Sulfonylureas	4/18 (22.2%)	2/19 (10.5%)
GLP-1 RAs	4/33 (12.1%)	0/19
Tirzepatide	2/19 (10.5%)	0/3
Metformin	1/67 (1.5%)	0/33
SGLT2 inhibitors	0/56	1/27 (3.7%)
Total	**53**	**8**

CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSM, least-squares mean; SGLT2, sodium-glucose cotransporter 2; SUs, sulfonylureas
P-value for LSM difference between mifepristone and placebo shown. Dose decreases and discontinuations combined for insulin, SUs, GLP-1 RAs, and tirzepatide; discontinuations only for metformin and SGLT2 inhibitors. *N indicates the number of participants taking a medication from the class at baseline.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

HbA1c: Subgroup Analyses Support the Primary Endpoint[1]

Treatment Phase

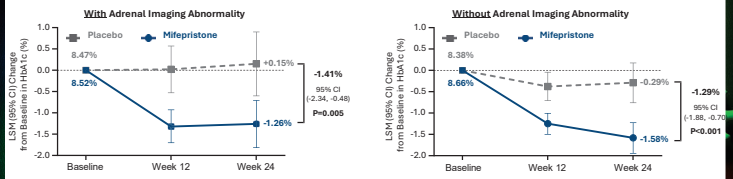
HbA1c (%)	Mifepristone	Placebo	Difference from Placebo	P-value
Participants who completed 24 weeks of treatment				
Baseline, mean (SD) [n]	8.82 (1.33) [47]	8.42 (1.02) [36]	—	—
Change from baseline to week 24, LSM (95% CI) [n]	**-1.69** (-2.09, -1.30) [47]	-0.13 (-0.58, 0.32) [36]	**-1.56** (-2.12, -1.00)	**<0.001**
Participants who received 3 tablets (900 mg mifepristone)				
Baseline, mean (SD) [n]	9.10 (1.35) [24]	8.62 (1.09) [25]	—	—
Change from baseline to week 24, LSM (95% CI) [n]	**-2.01** (-2.63, -1.39) [23]	-0.16 (-0.76, 0.45) [25]	**-1.85** (-2.67, -1.04)	**<0.001**

Analyses conducted to assess the robustness of the primary endpoint (tested in the intent-to-treat population). Analysis in participants who received 3 tablets includes those who received 3 tablets for at least consecutive 28 days. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.
CI, confidence interval; HbA1c, hemoglobin A1c; LSM, least-squares mean; SD, standard deviation

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Similar HbA1c Reductions in Participants With and Without Adrenal Imaging Abnormalities[1]

Treatment Phase



Number of participants

Mifepristone	25	22	19
Placebo	13	11	11
P-value		<0.001	0.005

Number of participants

Mifepristone	61	52	43
Placebo	31	29	27
P-value		<0.001	<0.001

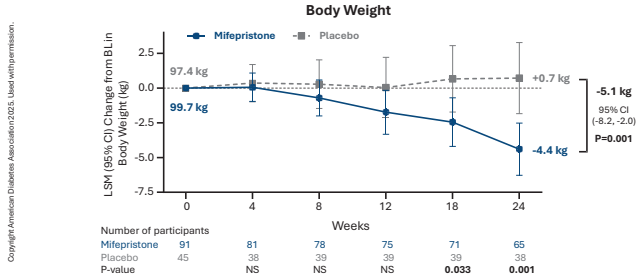
First randomized, placebo-controlled study to show that hypercortisolism without an adrenal imaging abnormality responds to cortisol-directed pharmacological treatment

CI, confidence interval; CT, computed tomography; HbA1c, hemoglobin A1c; LSM, least-squares mean. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.. DeFronzo RA, et al. Diabetes Care. 2025 Jun 23:dc251055. doi: 10.2337/dc25-1055. Online ahead of print.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Body Weight Loss With Mifepristone[1]

Treatment Phase



Number of participants

Mifepristone	91	81	78	75	71	65
Placebo	45	38	39	39	39	38
P-value		NS	NS	NS	0.033	0.001

By week 24, participants taking mifepristone had a 3.6% reduction in body weight compared to an increase of 0.3% in those taking placebo

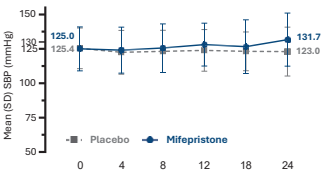
BL, baseline; CI, confidence interval; LSM, least-squares mean; NS, not significant
For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Effect of Mifepristone on Blood Pressure[1]

Treatment Phase

All participants



Number of participants

Mifepristone	91	86	80	78	72	65
Placebo	45	43	42	41	40	39

SBP remained near target in the overall population and no changes from baseline were observed in participants with baseline SBP ≥130 mmHg

SBP, systolic blood pressure; SD, standard deviation

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Treatment-emergent Adverse Events Reported in >10% of Participants[1]

Treatment Phase

Preferred Term, n (%)	Mifepristone (n=91)	Placebo (N=43)
At least one TEAE event	86 (94.5%)	36 (83.7%)
At least one treatment-related AE	56 (61.5%)	14 (32.6%)
TEAEs leading to treatment discontinuation	26 (28.6%)	1 (2.3%)
Serious TEAE	29 (31.9%)	2 (4.7%)
Most common TEAEs		
Hypokalemia	27 (29.7%)	0
Fatigue	19 (20.9%)	7 (16.3%)
Nausea	19 (20.9%)	5 (11.6%)
Vomiting	14 (15.4%)	3 (7.0%)
Peripheral edema	14 (15.4%)	1 (2.3%)
Headache	11 (12.1%)	5 (11.6%)
Diarrhea	10 (11.0%)	3 (7.0%)
Dizziness	10 (11.0%)	3 (7.0%)

Overall TEAEs were mostly mild-to-moderate in severity; no grade 4 TEAEs observed

TEAEs were manageable and consistent with mifepristone's known safety profile

TEAE, treatment-emergent adverse event

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

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Dizziness	10 (11.0%)	3 (7.0%)

Hypokalemia, a known side-effect of mifepristone, was the most common adverse event

Due to overstimulation of the mineralocorticoid receptor

TEAE, treatment-emergent adverse event

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Treatment-emergent Adverse Events Reported in >10% of Participants[1]

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Many of the most common TEAEs were consistent with glucocorticoid withdrawal, which can occur with any treatment for hypercortisolism, surgical or pharmacological

TEAE, treatment-emergent adverse event

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Summary – Treatment phase[1]

- Mifepristone therapy reduced A1c by 1.47%
  (LSM change at week 24; 95% CI, -1.79 to -1.14%; baseline A1c, 8.62%)
  - Placebo-adjusted LSM reduction in A1c was -1.32% (95% CI, -1.81 to -0.83; P<0.001)
  - Despite greater glucose-lowering medication dose reduction or discontinuation
  - No difference among those with and without adrenal imaging abnormalities
  - Sensitivity analyses (on treatment and completers) support the findings
- Mifepristone was associated with clinically meaningful changes in body weight (placebo-adjusted LSM, -5.1 kg; 95% CI, -8.2 to -2.0), BMI and waist circumference

LSM, least square mean; CI, confidence interval; BMI, body mass index

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

Summary – Treatment phase[1]

- Fewer completers in the mifepristone arm, 53.8%, compared with 82.2% in the placebo arm
  - The most common reasons for treatment discontinuation in the mifepristone arm were adverse events (61.9%)
- While mean blood pressure on mifepristone remained at or near the recommended target of less than 130/80 mmHg throughout the study, mean SBP increased from 125.0 to 131.7 mmHg in the mifepristone arm
- Serious treatment-emergent adverse events were reported more frequently in the mifepristone arm (32% versus 5%)
- Many of the most common adverse events were consistent with glucocorticoid withdrawal, which can occur with any treatment for hypercortisolism
- Hypokalemia, a know adverse event of mifepristone, may be better addressed in clinical practice by proactive use of potassium-sparing diuretics

1. DeFronzo RA, et al. *Diabetes Care*. Published online June 2025. doi:10.2337/dc25-1055

CATALYST implications

- Screen for hypercortisolism in people whose T2D is challenging to treat adequately
- The mifepristone results provide a proof of concept that identifying and addressing hypercortisolism is a novel path to improving diabetes care in millions of people worldwide
- Mifepristone for the treatment of hypercortisolism requires individual, patient-centered considerations[1]
  - Drug-drug interactions
  - Set expectations appropriately with patients regarding steroid withdrawal symptoms
  - Treat hypokalemia proactively, consider preemptively prescribing mineralocorticoid receptor antagonists
- ***Guidelines should reflect the insights from CATALYST***

1. Brown et al. *Clinical Diabetes and Endocrinology* (2020) 6:18

Working with the Multidisciplinary Health Care Team

- Many patients with hypercortisolism can be identified in primary care.
- However, the complex diagnosis and nuanced treatment necessitates long-term follow up and management involving the health care team:
  - Primary care clinic staff, including medical assistants, nurses, physician associates (PAs), nurse practitioners (NPs), physicians, social workers, and mental health clinicians
  - Specialists, primarily endocrinologists, endocrinology NPs/PAs, pharmacists

1. Scoffings K, et al. *Br J Gen Pract.* 2022;72(721):399-401. 2. Uwaifo GI, Hura DE. Hypercortisolism. *StatPearls [Internet].* Updated July 4, 2023. Accessed June 23, 2025. https://www.ncbi.nlm.nih.gov/books/NBK551526/

Role of the Health Care Team in Diagnosis and Treatment

- PCCs may be the first to recognize the possibility of a hypercortisolism diagnosis.

  By providing comprehensive and detailed referrals, PCCs can facilitate timely and effective specialist care, ultimately improving patient outcomes.
- Endocrinology is typically the first specialty sought for full evaluation and management of a patient with hypercortisolism.
- Other specialists may be involved in diagnosing and treating hypercortisolism, such as radiologists, nuclear medicine clinicians, general surgeons, and neurosurgeons.
- Pharmacists may educate patients on the need for and use of medications, drug-drug interactions.
- Patients with hypercortisolism who receive care in a structured interprofessional setting have improved outcomes.

1. Uwaifo GI, Hura DE. Hypercortisolism. *StatPearls [Internet].* Updated July 4, 2023. Accessed June 23, 2025. https://www.ncbi.nlm.nih.gov/books/NBK551526/

Components of a Successful Referral

- A successful referral is highly dependent on clear communication within the healthcare team, specifically the endocrinologist

Components of a successful referral include the following:

- Relevant clinical findings and the patient's medical history
- Reasons for suspecting hypercortisolism
  - Key factors contributing to high clinical suspicion
- Description of testing procedures and results of initial screening tests
  - Including dexamethasone serum level for patients with 1-mg overnight DST

Example Flowchart for Hypercortisolism Referral

Step 1: Clinical Suspicion
High index of clinical suspicion should trigger screening for hypercortisolism

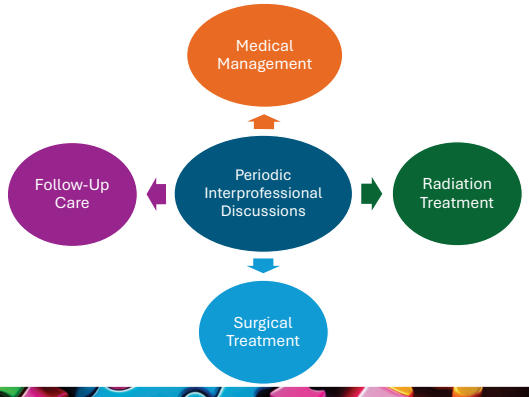
Step 2: Patient History
Review medications, physical exam, comorbidities, lab results

Step 3: Biochemical Testing
Start with overnight 1 mg DST as the most sensitive first-line test

Step 4: Interpret Results
If test results suggest hypercortisolism, proceed with referral to endocrinology.

Step 5: Refer to Endocrinology
Include all necessary information for a successful referral

Involving the Health Care Team Across Treatment Settings



1. Uwaifo GI, Hura DE. Hypercortisolism. *StatPearls [Internet].* Updated July 4, 2023. Accessed June 23, 2025. https://www.ncbi.nlm.nih.gov/books/NBK551526/

Selected Health Care Team Notes by Treatment Setting

Medical Management	• Pharmacists work with the care team to select treatment and discuss details of drugs for treatment of hypercortisolism, including optimal dosing, potential drug interactions, and other considerations. • Nurses participate in patient consultations with other members of the health care team to facilitate drug administration and monitor for treatment response and adverse reactions.
Radiation Treatment Surgical Treatment	These definitive therapies often require hospital admission. • Hospital care teams evaluate patients and administer these therapies. • Hospital care teams often include anesthesiology, nursing staff, clinical nutrition, social workers, physical rehabilitation, and mental health specialists.
Follow-Up Care	• PCCs, endocrinologists, and surgeons typically drive the structured long-term follow up plan. • Plans should include periodic evaluation to assess for recurrent or persistent hypercortisolism.

1. Uwaifo GI, Hura DE. Hypercortisolism. *StatPearls [Internet].* Updated July 4, 2023. Accessed June 23, 2025. https://www.ncbi.nlm.nih.gov/books/NBK551526/

Summary and Key Takeaways

- Hypercortisolism as a diagnosis is often delayed or missed, leading to adverse consequences for patients, including mortality and unnecessary morbidity.
- Current data, including from the recent CATALYST trial, suggest the prevalence of hypercortisolism is higher than previously estimated.
- Hypercortisolism is a heterogeneous, multisystemic disease with variable presentation along a spectrum of signs and symptoms from classically overt to clinically inapparent.
- Hypercortisolism occurs along a continuum of cardiometabolic risks that increase with disease severity and duration.

Summary and Key Takeaways

- Screening for hypercortisolism in primary care requires:
  - Appropriately selecting patients with suspected hypercortisolism
  - Using a sensitive screening test
  - Interpreting results within the patient's clinical context
- Cortisol-directed medical therapy for adults with inadequately-controlled T2D and hypercortisolism may reduce HbA1c and other markers of disease
- A successful referral to endocrinology requires communicating:
  - The patient's relevant clinical findings and medical history, reasons for suspecting hypercortisolism, screening test results
- Working with the multidisciplinary health care team is essential for optimal outcomes in hypercortisolism diagnosis and management.