Difficult-to-Control Type 2 Diabetes: Hypercortisolism Might be the Underlying Factor

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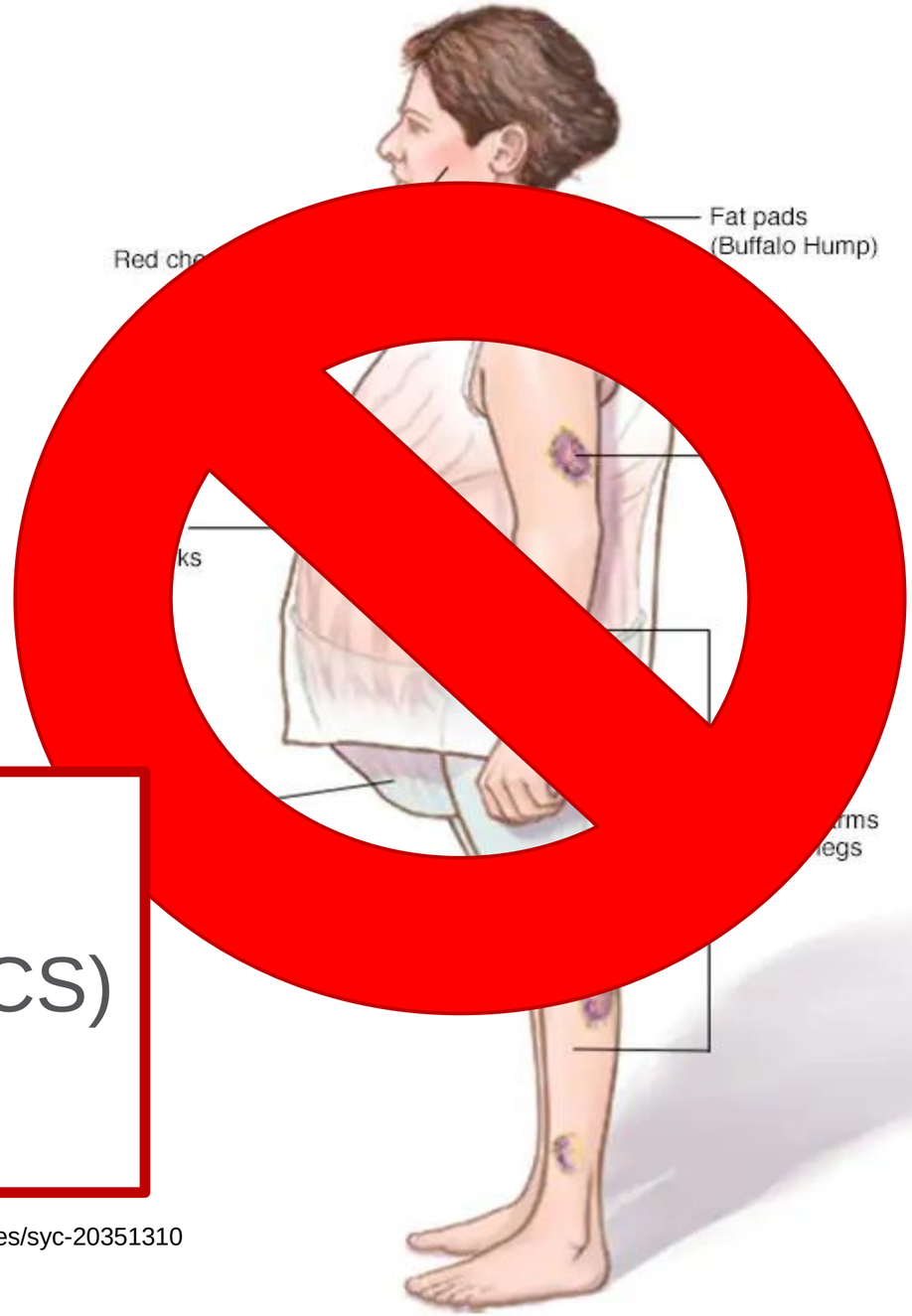
November 21, 2025

NOT about the Classic Cushing Syndrome



“Subclinical” hypercortisolism
Mild autonomous cortisol secretion (MACS)
Hidden hypercortisolism

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Image: https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310

Agenda

A. Introduction: Overview of Hypercortisolism and Type 2 Diabetes

B. Pathophysiology: Cortisol’s Impact on Glucose Metabolism

C. Clinical Manifestations and Red Flags: Screening & Diagnosing

D. Treating Hypercortisolism in T2DM: A Re-Surfaced Management Approach

E. Case Discussion & Conclusion

Learning Objectives

- ***Explain*** the pathophysiology of hypercortisolism and its role as a secondary cause of difficult-to-control type 2 diabetes.
- ***Identify*** the clinical manifestations and red flags that warrant screening for hypercortisolism in patients with type 2 diabetes.
- ***Describe*** the appropriate steps for screening, diagnosing, and interpreting initial test results for hypercortisolism in a clinical setting.
- ***Discuss*** evidence-based management approaches for hypercortisolism in patients with type 2 diabetes, including pharmacological option(s) and preparation for specialist referral.
- ***Apply*** knowledge of hypercortisolism screening to a patient case study to determine an appropriate course of action.

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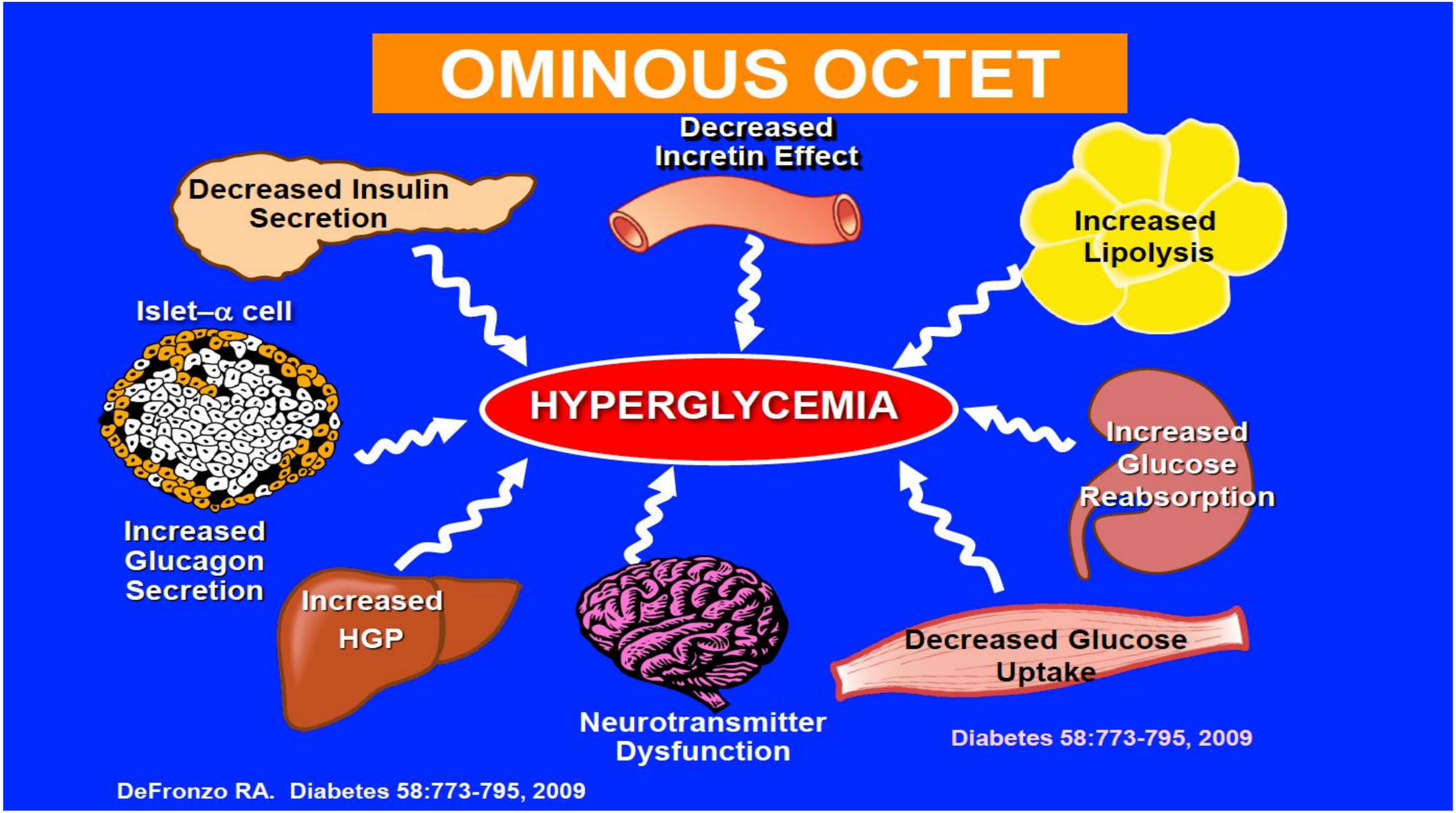
A. Introduction:
Overview of Hypercortisolism and Type 2 Diabetes



DeFronzo RA. Expanding Evidence for the Impact of Hypercortisolism on People with Difficult-to-Control Type 2 Diabetes. American Diabetes Association 85th Scientific Sessions. June 23, 2025; Chicago, IL.

Definition – Subclinical Hypercortisolism

- *"Subclinical" Hypercortisolism* = the body produces excessive cortisol ***without*** the classic signs & symptoms of Cushing Syndrome
- *Clinical Suspicion*
  - *"… patients with type 2 diabetes struggling to [manage] their blood glucose levels for some time despite being adherent to the traditionally ideal and successful therapeutic and lifestyle intervention…"*
- *Clinical Impact*
  - People with diabetes have chronically elevated levels of cortisol →
  - *Resistant hyperglycemia* →
  - *Overcoming the most potent T2D medications* (other than insulin), e.g., GLP-1 & GLP-1 + GIP receptor agonist agents

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Abichandani VK. Hypercortisolism and Type 2 Diabetes: The sinister duo! *Clinical Diabetology*. 2024;13(5):243-245. doi:10.5603/cd.103172.

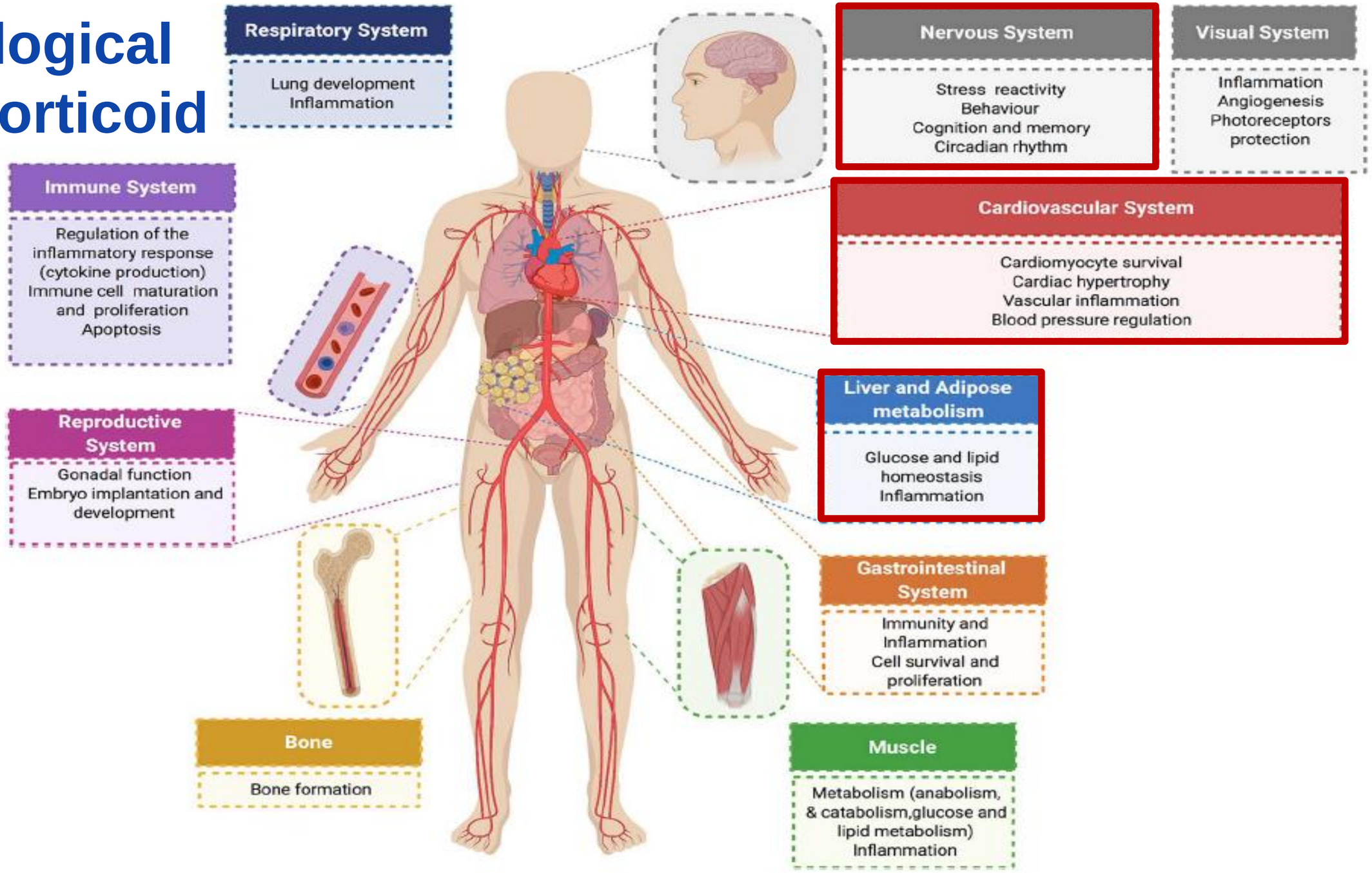
Why It Matters

- **Cortisol** (a glucocorticoid hormone): associated with *inflammation* in patients with T2D +
  - Retinopathy
  - Polyneuropathy
  - Kidney Disease

  } chronic microvascular complications and macrovascular complications
- Cortisol → exerts ***counter-regulatory*** effects on insulin via
  - Induction of hepatic gluconeogenesis
  - Inhibition of the peripheral uptake of glucose (muscle)

Abichandani VK. Hypercortisolism and Type 2 Diabetes: The sinister duo! *Clinical Diabetology*. 2024;13(5):243-245. doi:10.5603/cd.103172.

Physiological Glucocorticoid Effects



Cruz-Topete D, Oakley RH, Cidlowski JA. Glucocorticoid signaling and the aging heart. *Front Endocrinol (Lausanne).* 2020;11:347. doi:10.3389/fendo.2020.00347.

Detrimental Effects of a Delayed Diagnosis

- The *wide range* of potential clinical signs and symptoms associated with this condition – or lack thereof -- can make diagnosis challenging.[1,2]
  - The diagnosis could be delayed by up to ***10*** years or more.
- Delayed diagnosis can have *serious* consequences.[3]
  - Extended exposure to high cortisol levels greatly raises the risk of developing ***cardiometabolic disorders***.
- Untreated hypercortisolism is associated with a ***mortality rate of 2 – 5 times higher*** than that of the general population.[4]
- Highlights the need for greater awareness and prompt action in primary care settings.[5]

1. Valassi E, et al. *Endocr Connect*. 2022;11O7P: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):e3724-e3730.
4. Dekkers OM, et al. *J Clin Endocrinol Metab*. 2013;98(6):2277-2284.
5. Yorke E, et al. *Int J Endocrinol*. 2017;2017:1-6.

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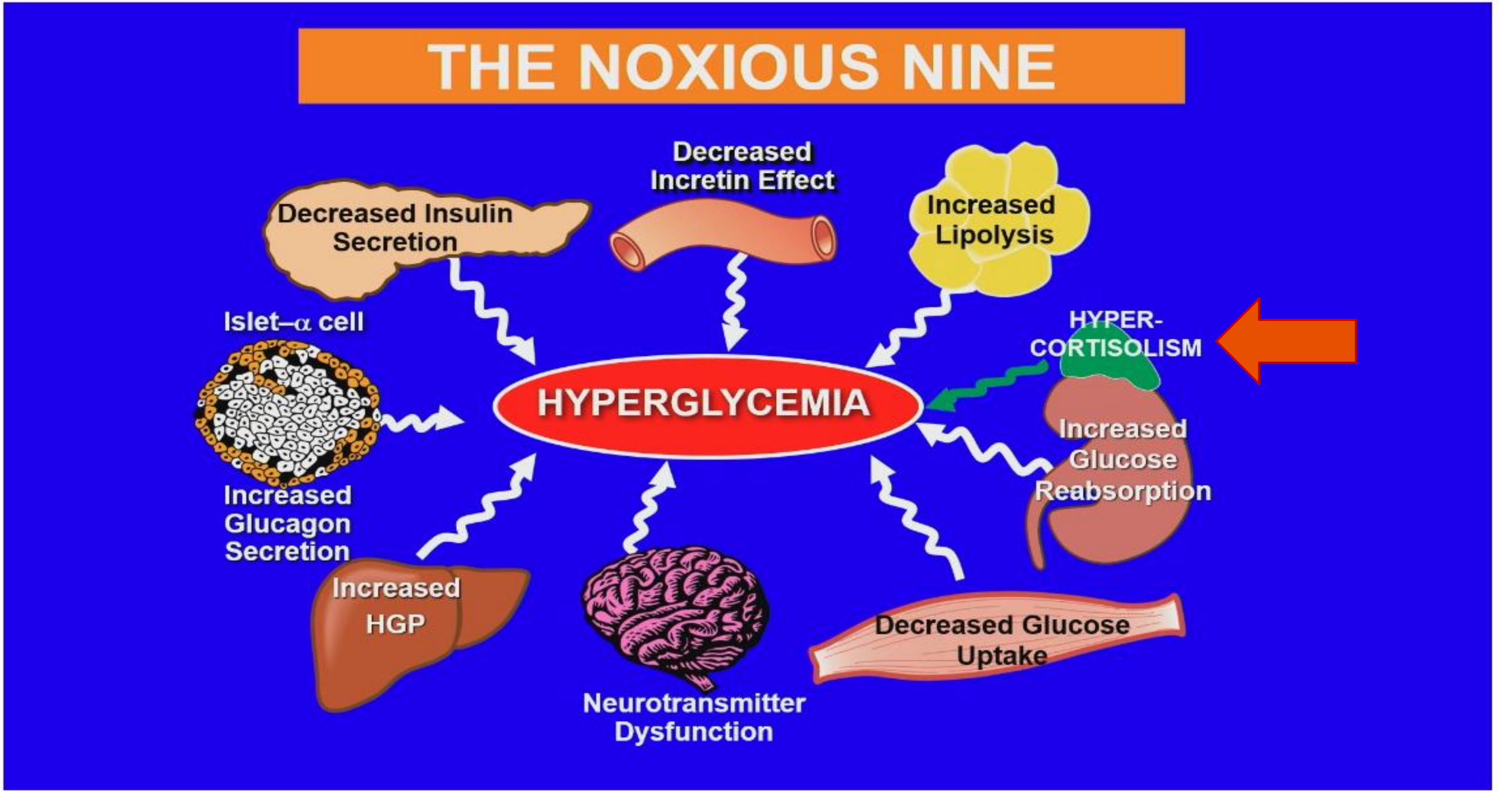

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A Cascade of Effects: Recap

Prolonged **stress** and inadequate regulation of the stress system

Chronic hypercortisolism

(a blunted cortisol response to stress)

- Subclinical inflammation
- Insulin resistance
- Increased adiposity
- Dyslipidemia
- More severe hypertension
- Type 2 diabetes

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Abichandani VK. Hypercortisolism and Type 2 Diabetes: The sinister duo! *Clinical Diabetology*. 2024;13(5):243-245. doi:10.5603/cd.103172.

Clinical Case Vignette: Jayden

- 74-year-old Indian man
- Medical History: type 2 diabetes, chronic kidney disease, hypertension, hyperlipidemia, asthma, osteoarthritis, atrial fibrillation, GERD, erectile dysfunction, BPH
- A1c Trend:
  - 7.6% (9/10/2025)
  - 7.5% (6/10/2025)
  - 7.3% (3/27/2025)

- eGFR: 51 (9/10/2025)
- FIB-4 Score: 1.46 (1/24/2025)
- 10-Year ASCVD Risk: 33%
- CGM Data
  Data from 9/24/25 to 10/7/25
  Overall mean glucose: 193
  TAR: 60%
  TIR: 40%
  TBR <70: 0%
  TBR <54: 0%
  GMI: 7.9%

TAR = Time Above Range
TIR = Time In Range

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Clinical Case Vignette: Jayden

Type 2 Diabetes

- Tirzepatide 7.5 mg SQ once weekly on Fridays
- Insulin Glargine-yfgn 25 units SQ once daily at bedtime
- Empagliflozin 25 mg 1 tablet PO daily QAM

HTN

- Amlodipine 10 mg 1 tablet PO daily QAM
- Losartan 100 mg 1 tablet PO daily QAM
- Carvedilol 25 mg 1 tablet PO 2 times daily with a meal
- Triamterene-HCTZ 37.5 mg/25 mg 1 tablet PO daily

HLD

- Atorvastatin 40 mg 1 tablet PO daily
- Omega-3-FA 1,000 mg 2 capsules PO daily

Asthma

- Albuterol HFA 90 mcg/actuation inhaler - inhale 2 puffs Q4-6 hours PRN for shortness of breath or wheezing
- Montelukast 10 mg 1 tablet PO daily (patient takes PRN)
- Trelegy Ellipta (200-62.5-25 mcg) 1 puff into the lungs QAM

Pain

- Gabapentin 100 mg 2 capsules PO at bedtime (patient takes PRN)

BPH

- Tamsulosin 0.4 mg 2 capsules PO with the same meal (patient does not take as directed, PRN)

Other

- Centrum 50+ 1 tab PO daily
- Eliquis 5 mg 1 tab PO BID

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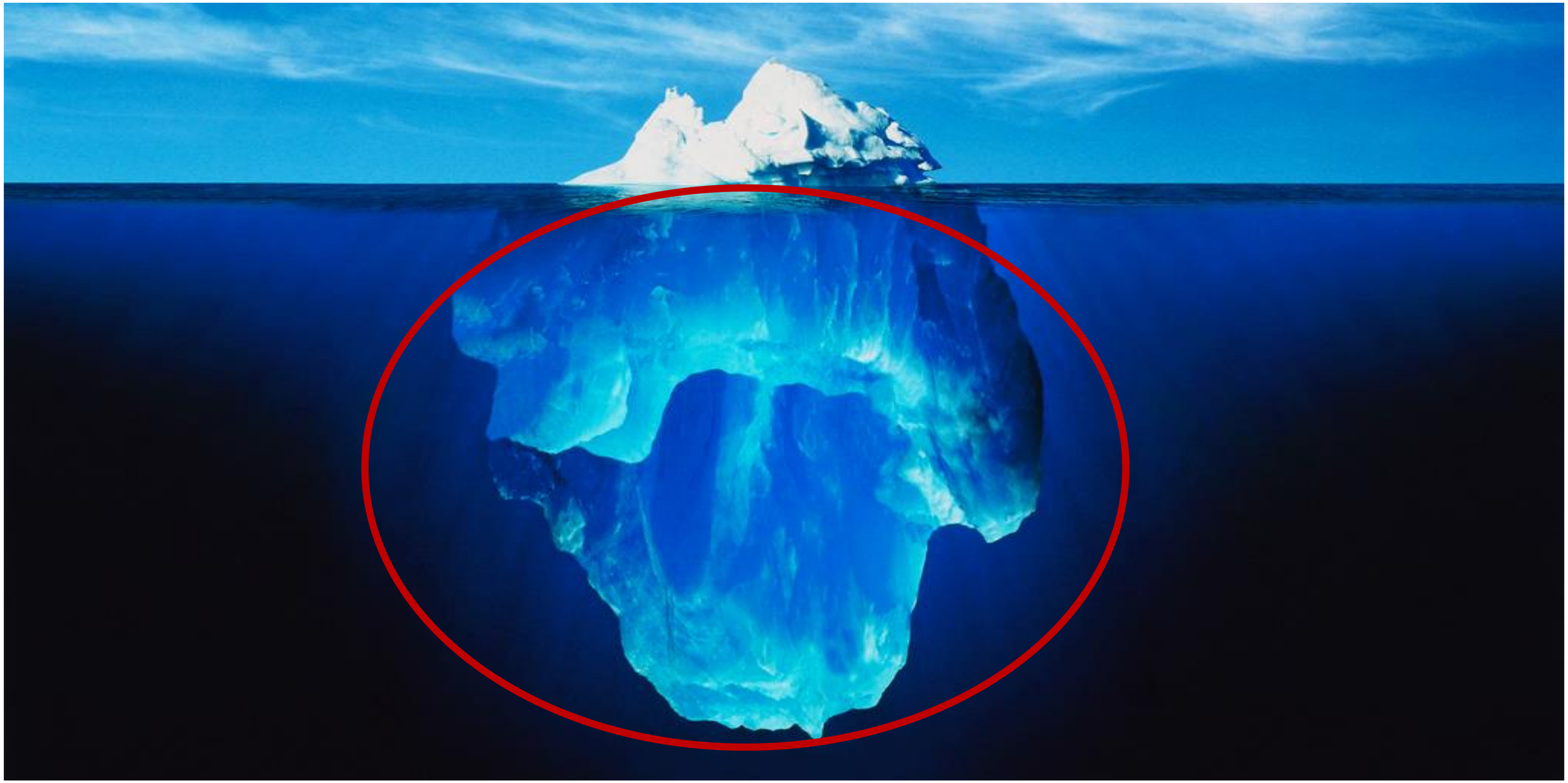

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Epidemiology of Hypercortisolism: Pre-CATALYST Trial

Patients with Difficult-to-Control Type 2 Diabetes and Hypertension

- Italy[1]
  - Case-control, hospitalized patients
    - 294 T2D patients vs. 189 matched patients without diabetes
    - Prevalence: **9.4%** “ascertained subclinical hypercortisolism” in T2D vs. 2.1% in controls
- Brazil[2]
  - 393 T2D outpatient cohort screened: **8.6%** had confirmed subclinical hypercortisolism
- France[3]
  - 200 overweight T2D patients with A1c >8%: 26% screened positive on initial DST
  - **2%** had definitive occult Cushing Syndrome (CS)
  - 3.5% had probable/mild occult CS pending definitive diagnosis

1. Chiodini I, Torlontano M, Scillitani A, et al. Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. Eur J Endocrinol 2005;153:837–844
2. Costa DS, Conceiç~ao FL, Leite NC, Ferreira MT, Salles GF, Cardoso CRL. Prevalence of subclinical hypercortisolism in type 2 diabetic patients from the Rio de Janeiro Type 2 Diabetes Cohort Study. J Diabetes Complications 2016; 30:1032–1038
3. Catargi B, Rigalleau V, Poussin A, et al. Occult Cushing’s syndrome in type-2 diabetes. J Clin Endocrinol Metab 2003;88:5808–5813

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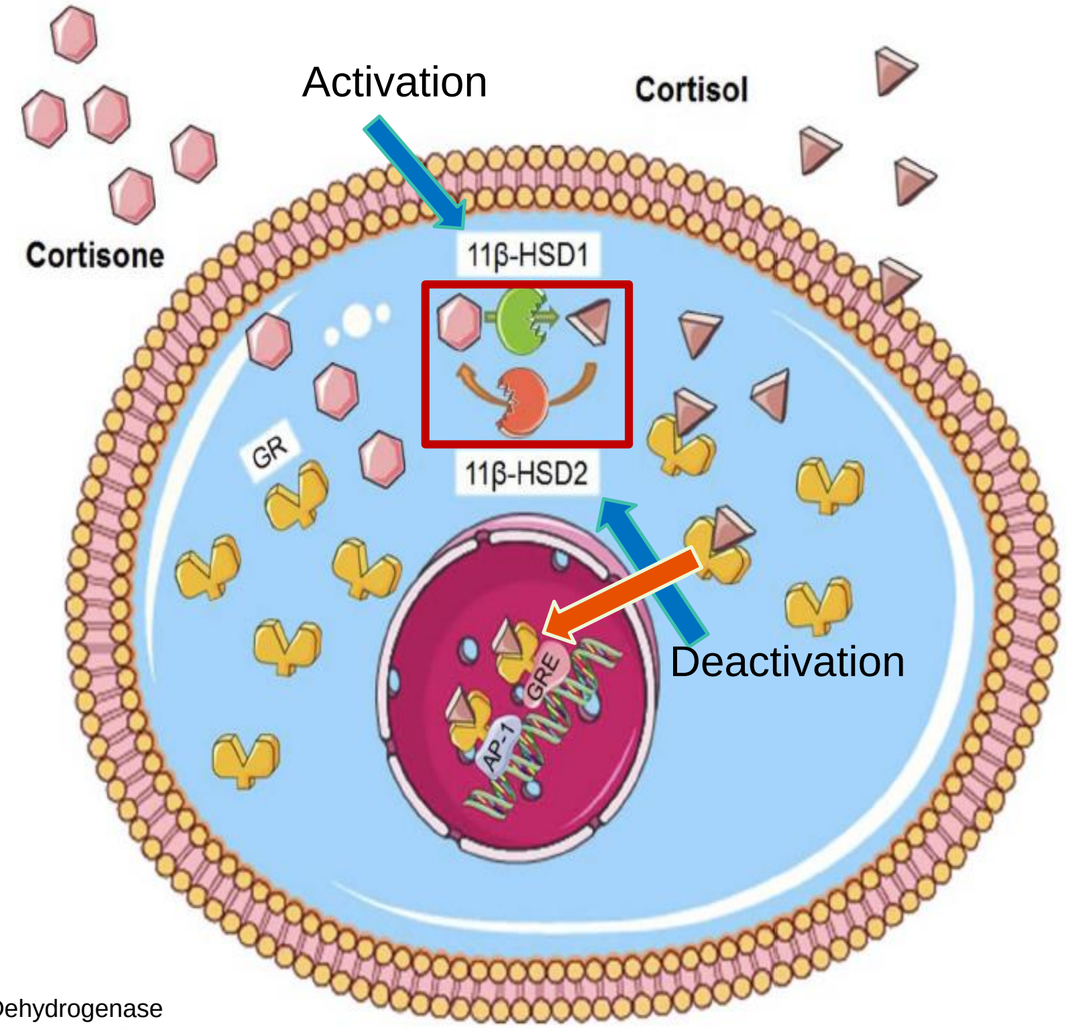
B. Pathophysiology: Cortisol’s Impact on Glucose Metabolism & Physiological Effects

Glucocorticoid Metabolism

- ***Activation***: Cortisone → Cortisol by enzyme 11β-HSD1
- ***Inactivation***: Cortisol → Cortisone by enzyme 11β-HSD2
- Cortisol binds to the glucocorticoid receptor (GR) → Ligand-receptor complex translocates to the nucleus
  - Complex binds to GRE or other transcription factors (AP-1)



HSD = Hydroxysteroid Dehydrogenase
GRE = Glucocorticoid-Responsive Elements
AP-1 = Activator Protein-1

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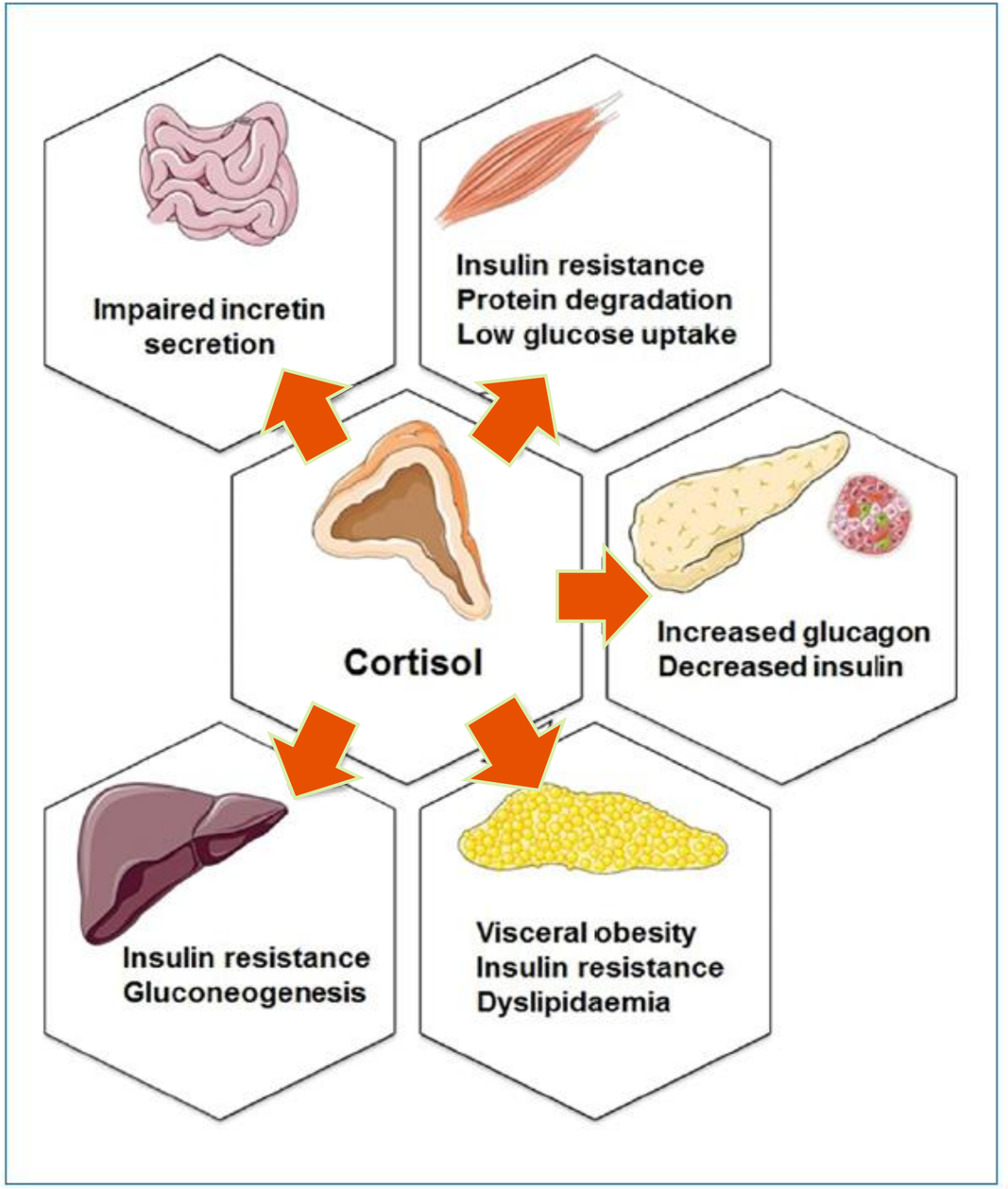
Glucocorticoid Metabolism in Obesity and Following Weight Loss", by E. Akalestou E., L. Genser, G Rutter, Front Endocrinol (Lausanne), 2020;11:59 [1].

Metabolic Functions of Glucocorticoids

- The effects of ***increased*** cortisol secretion on
  - Endocrine pancreas
  - Adipose tissue
  - Liver
  - Muscle
  - Gastrointestinal system



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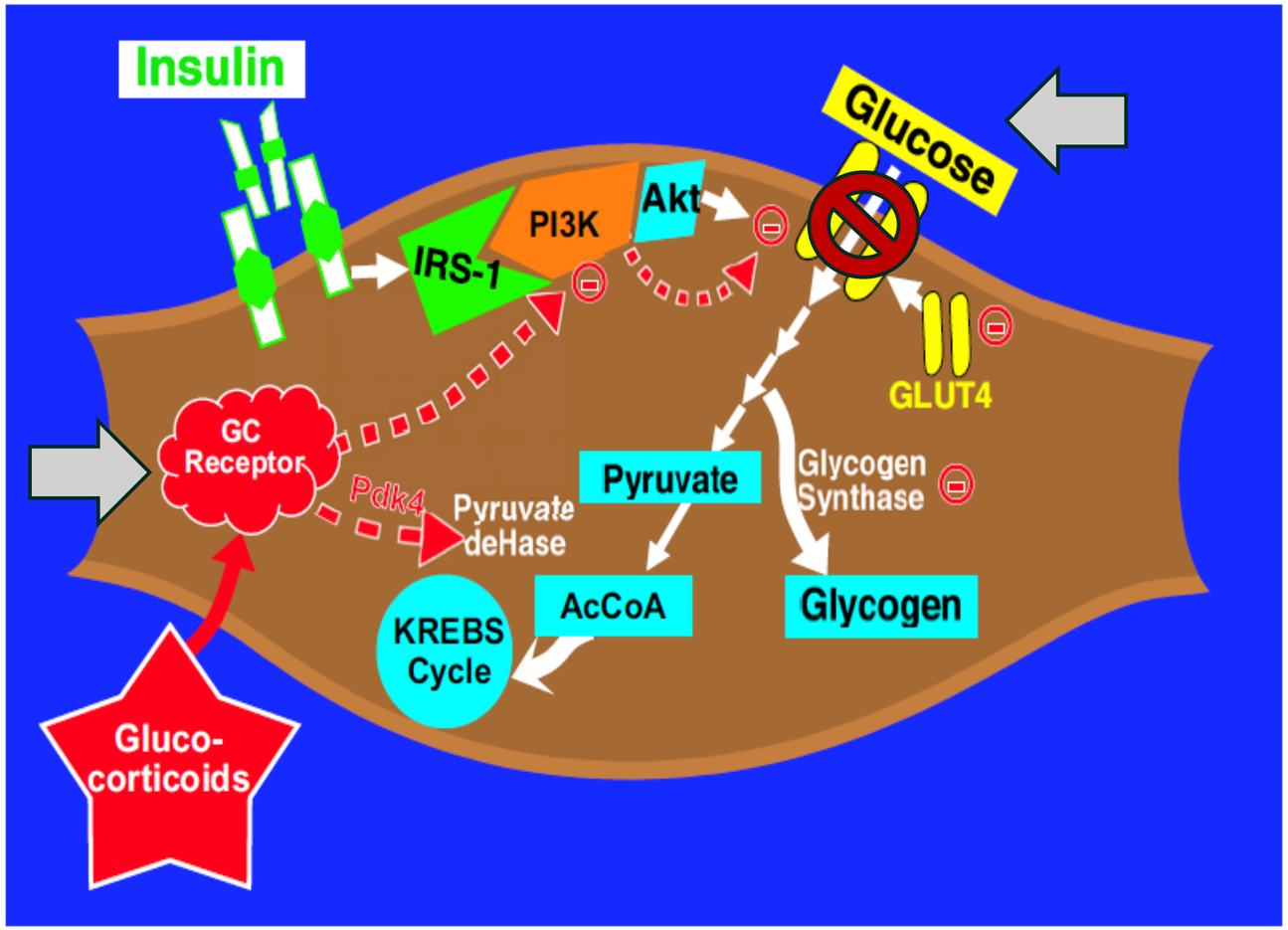
Glucocorticoid Metabolism in Obesity and Following Weight Loss", by E. Akalestou E., L. Genser, G Rutter, Front Endocrinol (Lausanne), 2020;11:59 [1].

Cellular Mechanisms Causing Insulin Resistance in Muscle

Upon entry into the myocyte:

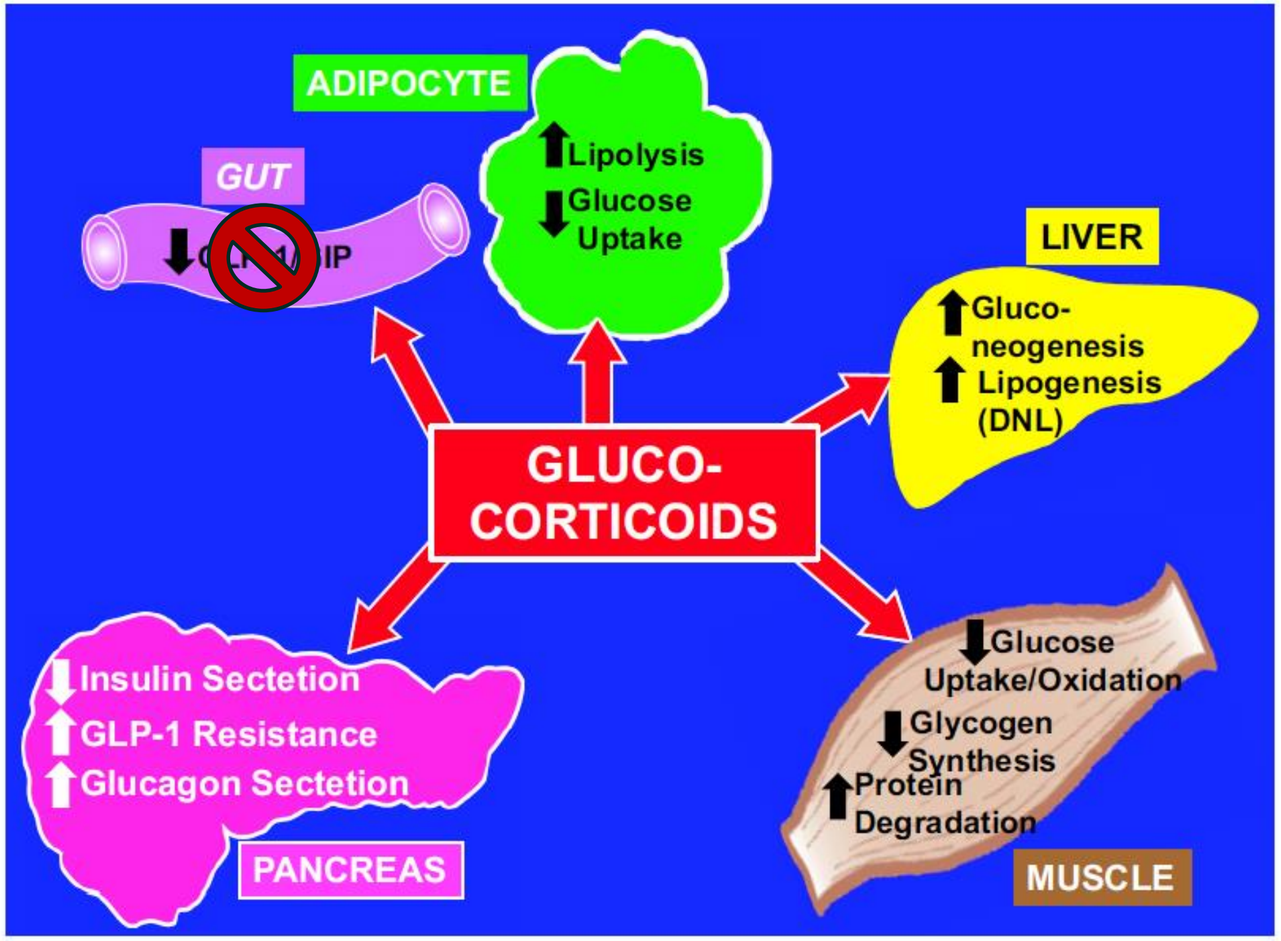
- Cortisol binds to the glucocorticoid receptor (GC) →
- Inhibition of the ***insulin*** signal transduction system
- GCs also independently inhibit
  - GLUT4
  - Glycogen synthase
  - Pyruvate dehydrogenase



DeFronzo RA, Auchus RJ. Cushing Syndrome, Hypercortisolism, and Glucose Homeostasis: A Review. *Diabetes*. Published online July 15, 2025. doi:10.2337/db25-0120

GCs Inhibit Insulin Secretion at Multiple Sites

- GCs also inhibit the ability of ***GLP-1 and GIP*** to amplify glucose-stimulated insulin secretion.



DeFronzo RA, Auchus RJ. Cushing Syndrome, Hypercortisolism, and Glucose Homeostasis: A Review. *Diabetes*. Published online July 15, 2025. doi:10.2337/db25-0120

C. Clinical Manifestations and Red Flags: Screening & Diagnosing

Who Should Be Screened?

TABLE. At-risk patient population to screen for hypercortisolism

Population	Prevalence of hypercortisolism	Examples of clinical presentation
Patients with adrenal incidentaloma	Up to 50%[6]	Patients with unsuspected tumors discovered in one or both of their adrenal glands
Patients with poorly controlled T2D	Up to 24%[17,19,23-25]	Difficult-to-control T2D with HbA1c >7.5% despite multiple antihyperglycemic medications
		T2D with poor glucose control despite insulin treatment and other comorbidities, including obesity, hypertension, hyperlipidemia, and CVD
		T2D with high insulin dose requirements, especially prandial insulin
		Patients with T2D onset before 40 years of age
		Patients with both diabetes and hypertension, requiring 2 or more drugs to control blood pressure
		Patients with both diabetes and hypertension, requiring insulin to control blood sugar
		Patients with T2D and microvascular or macrovascular complications
Patients with osteoporosis/ fragility fractures	Up to 10.8%[20]	Premenopausal women with fragility fracture
		Eugonadal men with fragility fracture
		Patients with very low or rapidly declining bone density, not responding to osteoporosis treatment
		Patients with a history of vertebral fracture, especially obese patients with vertebral fracture
Patients with hypertension	Up to 8%[21,22]	Treatment-resistant hypertension (on 3 or more antihypertensive drugs, including a diuretic)
		Patients with hypertension onset before 30 years of age

Abbreviations: CVD, cardiovascular disease; HbA1c, glycated hemoglobin A1C; T2D, type 2 diabetes.

Kushner, P., Brown, D. R., & Busch, R. S. (2024). Hypercortisolism is more common than you think—Here's how to find it. *Federal Practitioner*, 41(Suppl 6), S23–S28.

How to Perform the Screening & Diagnosing?

FIGURE 1. Screening tests for hypercortisolism: process and considerations

Overnight Dexamethasone Suppression Test (DST)

Performing the test

Interpreting results

Within reference range:
<1.8 µg/dL serum cortisol level with >140 ng/dL dexamethasone levels. Hypercortisolism is not very likely.

Consult endocrinologists if above reference range:
≥1.8 µg/dL serum cortisol level with >140 ng/dL dexamethasone levels.

Testing considerations

Potential factors for false positive

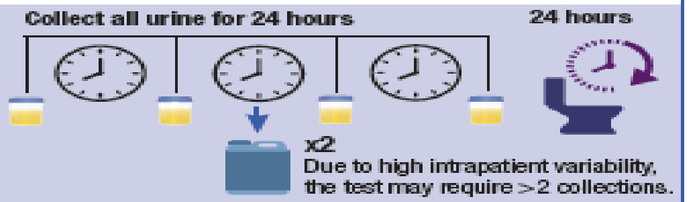
- Estrogen-containing medications
- Pregnancy
- Rapid dexamethasone metabolism, CYP3A4 inducers
- Dexamethasone malabsorption, failure to take dexamethasone
- Use of exogenous glucocorticoids
- Chronic renal disease

Potential factors for false negative

- Chronic renal disease
- Chronic liver disease
- Concomitant medications that inhibit CYP3A4 leading to very high dexamethasone levels
- Cyclic hypercortisolism

24-Hour Urine-Free Cortisol (UFC)

Performing the test



Interpreting results

Within reference range:
Due to low sensitivity, hypercortisolism cannot be dismissed, especially with high index of clinical suspicion.

Consult endocrinologists if above reference range.

Testing considerations

- UFC is insensitive because free cortisol does not become detectable in the urine until serum cortisol levels are high enough to saturate serum CBG.
- UFC is often normal in cases of less clinically apparent hypercortisolism than typical of primary adrenal disease.

Potential factors for false positive

- High level of fluid intake

Potential factors for false negative

- Incomplete urine collection
- eGFR <60 mL/min/1.73 m^2
- Cyclic hypercortisolism

Late Night Salivary Cortisol (LNSC)

Performing the test

Interpreting results

Within reference range:
Due to low sensitivity, hypercortisolism cannot be dismissed, especially with high index of clinical suspicion.

Consult endocrinologists if above reference range.

Testing considerations

- LNSC is insensitive.
  - Salivary glands contain a high level of the enzyme 11-beta HSD2 that oxidizes cortisol to inactive cortisone.
  - LNSC levels are often normal in autonomous primary adrenal disease.
- LNSC is useful to detect early signs of recurrent Cushing disease.

Potential factors for false positive

- Any blood contamination of the sample (eg, associated with brushing teeth, flossing, toothpicks, etc.)
- Smoking, use of chewing tobacco
- Eating licorice
- Use of a steroid inhaler, steroid eye drops, or steroid lip balm
- Abnormal sleep-wake cycle (eg, night shift worker or sleep-wake cycle disorder)
- Hypercortisolism due to non-adrenal disease

Potential factors for false negative

- Insufficient specimen volume

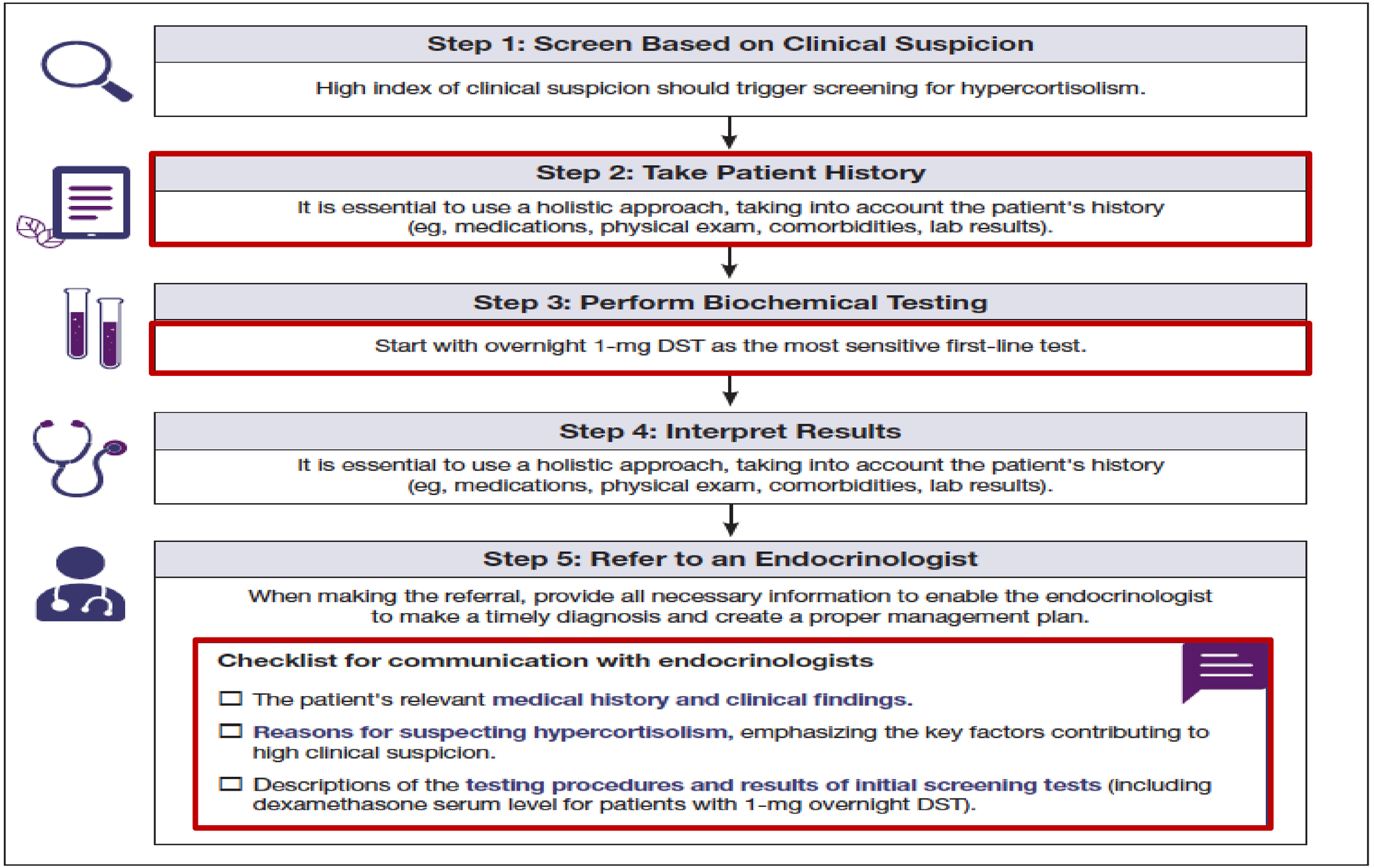
Kushner, P., Brown, D. R., & Busch, R. S. (2024). Hypercortisolism is more common than you think—Here's how to find it. *Federal Practitioner*, 41(Suppl 6), S23–S28.

Sensitivity & Specificity

	Sensitivity	Specificity
Overnight Dexamethasone Suppression Test	98.6%	90.6%
24-Hour Urine-Free Cortisol	94%	93%
Late Night Salivary Cortisol	95.8%	93.4%

Galm BP, Qiao N, Klibanski A, Biller BMK, Tritos NA. Diagnostic Tests for Cushing Syndrome. *J Clin Endocrinol Metab.* 2020;105(6):dgaa105. doi:10.1210/clinem/dgaa105.

FIGURE 2. Process and considerations for screening, workup, and referral for hypercortisolism in primary care



Abbreviation: DST, dexamethasone suppression test.

Kushner, P., Brown, D. R., & Busch, R. S. (2024). Hypercortisolism is more common than you think—Here's how to find it. *Federal Practitioner*, 41(Suppl 6), S23–S28.

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Diabetes Care®
American Diabetes Association®

Prevalence of Hypercortisolism in Difficult-to-Control Type 2 Diabetes

John B. Buse, Steven E. Kahn, Vanita R. Aroda, Richard J. Auchus, Timothy Bailey, Irina Bancos, Robert S. Busch, Elena A. Christofides, Ralph A. DeFronzo, Bradley Eilerman, James W. Findling, Vivian Fonseca, Oksana Hamidi, Yehuda Handelsman, Harold J. Miller, Jonathan G. Ownby, John C. Parker, Athena Philis-Tsimikas, Richard Pratley, Julio Rosenstock, Michael H. Shanik, Lance L. Sloan Guillermo Umpierrez, Iulia Cristina Tudor, Tina K. Schlafly, Daniel Einhorn, for the CATALYST Investigators

Diabetes Care 2025;48(00):1–9 | https://doi.org/10.2337/dc24-2841

CATALYST
Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

Prevalence of hypercortisolism in patients with difficult-to-control type 2 diabetes

CATALYST Part 1 Study Design (NCT05772169)

Adults with difficult-to-control type 2 diabetes (*N* = 1,057)

1-mg DST

Primary end point

Hypercortisolism prevalence

Post-DST cortisol >1.8 µg/dL[a]

Known causes of false-positive DSTs excluded

Further evaluation

- Clinical and laboratory characteristics
- Adrenal CT scan

"Difficult-to-control" type 2 diabetes defined as:

HbA_{1c} 7.5 –11.5% and at least 1 of:

- Taking ≥3 DM drugs
- Taking insulin & other DM drugs
- Taking ≥2 DM drugs and ≥1 micro- or macrovascular complications
- Taking ≥2 DM and ≥2 BP drugs

Hypercortisolism Prevalence

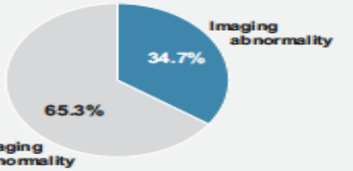
Overall population

Prevalence among participants taking ≥3 BP drugs: 36.6%

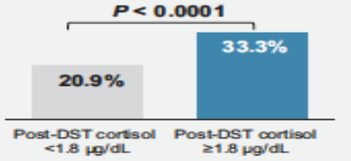
Key Takeaway: The prevalence of hypercortisolism in this population is higher than generally recognized

Other Key Findings

Adrenal imaging abnormality on CT scan[b]



More cardiac disorders in participants with hypercortisolism



Factors independently associated with hypercortisolism

- Older age
- BMI <30 kg/m²
- Non-Hispanic/Latino ethnicity
- Taking SGLT2 inhibitors, maximum-dose GLP-1 analogs, or tirzepatide
- Taking more BP drugs
- Taking fibrates or analgesics

[a]With dexamethasone ≥140 ng/dL. [b]In patients with hypercortisolism. BP, blood pressure; CT, computed tomography; DM drug, glucose-lowering drug; DST, dexamethasone suppression test; GLP-1, glucagon-like peptide 1.

Methods

Participant Population

Inclusion Criteria

- Adult aged 18 – 80 years with "*difficult-to-control*" type 2 diabetes
  - HbA1c 7.5% to 11.5%
- Despite multiple standard-of-care therapies:
  1. Taking ≥ 3 glucose-lowering medications
  2. Take insulin and any other glucose-lowering medications
  3. Taking ≥ 2 glucose-lowering medications and having at least one microvascular or macrovascular complication
  4. Take ≥ 2 glucose-lowering medications and ≥ 2 blood pressure-lowering medications

Exclusion Criteria

Designed to avoid the most common causes of a *false-positive* dexamethasone suppression test (DST):

- Use of oral contraceptive pills
- Excessive alcohol consumption
- Severe untreated sleep apnea
- Severe psychiatric, medical, or surgical illness
- Night shift work
- Hemodialysis/end-stage renal disease

Clinical Suspicion

CATALYST Part 1 Study Design (NCT05772169)

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1-mg DST

Primary end point

Hypercortisolism prevalence

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HbA_{1c} 7.5 –11.5% and at least 1 of:

- Taking ≥3 DM drugs
- Taking insulin & other DM drugs
- Taking ≥2 DM drugs and ≥1 micro- or macrovascular complications
- Taking ≥2 DM and ≥2 BP drugs

concomitant dexamethasone levels **≥ 140 ng/dL** to ensure adherence with and *absorption of the dexamethasone for adequate cortisol suppression*

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Results

Table 1—Baseline demographics, characteristics, and medication use

	All participants (N = 1,057)	Post-DST cortisol >1.8 µg/dL (hypercortisolism) (n = 252)	Post-DST cortisol ≤1.8 µg/dL (n = 805)	P value for association with hypercortisolism[a]
Age, years	60.7 (10.4)	63.8 (9.6)	59.8 (10.5)	<0.0001
Female, n (%)	479 (45.3)	109 (43.3)	370 (46.0)	NS
BMI, kg/m^2	33.5 (7.2)	33.1 (7.7)	33.7 (7.1)	NS
Waist circumference, cm	112.7 (17.0)	113.5 (17.7)	112.5 (16.8)	NS
Ethnicity, n (%)				
Hispanic/Latino	255 (24.1)	21 (8.3)	234 (29.1)	<0.0001[c]
Non-Hispanic/Latino[b]	802 (75.9)	231 (91.7)	571 (70.9)	
Race, n (%)				NS[e]
White	748 (70.8)	187 (74.2)	561 (69.7)	
Black or African American	201 (19.0)	55 (21.8)	146 (18.1)	
Asian	47 (4.4)	5 (2.0)	42 (5.2)	
Other[d]	61 (5.8)	5 (2.0)	56 (7.0)	
HbA_{1c}, %	8.8 (1.0)	8.8 (1.1)	8.8 (1.0)	NS
Systolic blood pressure, mmHg	127.6 (16.1)	127.4 (16.4)	127.6 (16.1)	NS
Diastolic blood pressure, mmHg	75.3 (9.8)	74.8 (9.5)	75.5 (9.9)	NS

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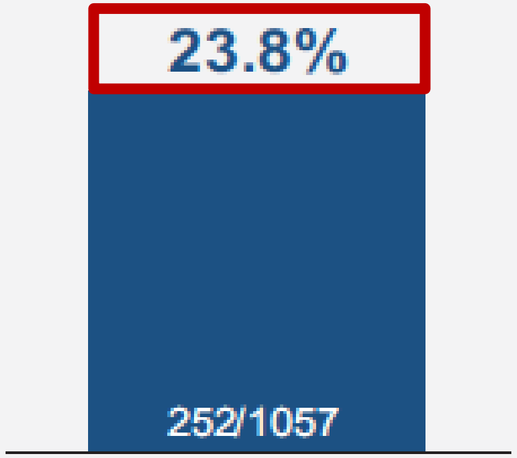
Hypercortisolism Prevalence

Overall population

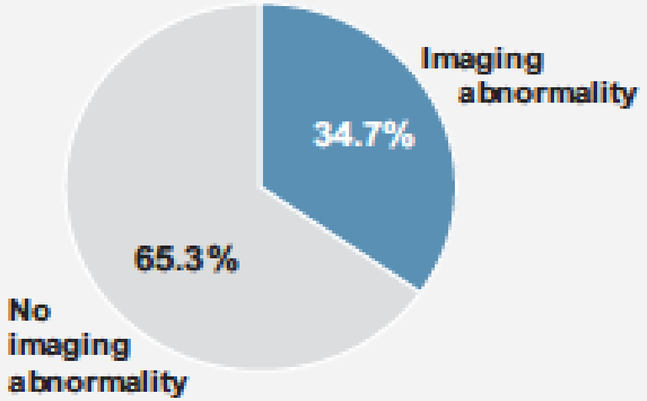


Prevalence among participants taking ≥3 BP drugs: 36.6%

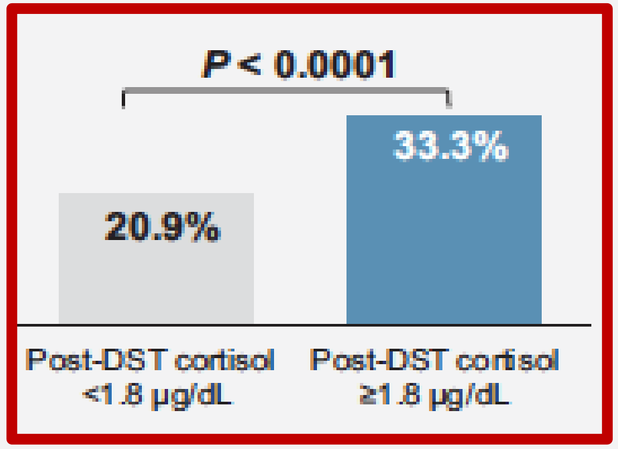
Key Takeaway: The prevalence of hypercortisolism in this population is higher than generally recognized

Other Key Findings

Adrenal imaging abnormality on CT scan[b]

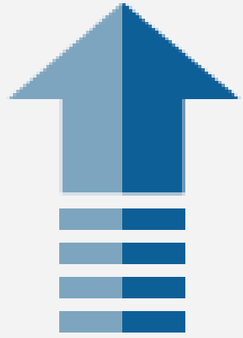


More cardiac disorders in participants with hypercortisolism



Factors independently associated with hypercortisolism

- Older age
- BMI <30 kg/m²
- Non-Hispanic/Latino ethnicity
- Taking SGLT2 inhibitors, maximum-dose GLP-1 analogs, or tirzepatide
- Taking more BP drugs
- Taking fibrates or analgesics



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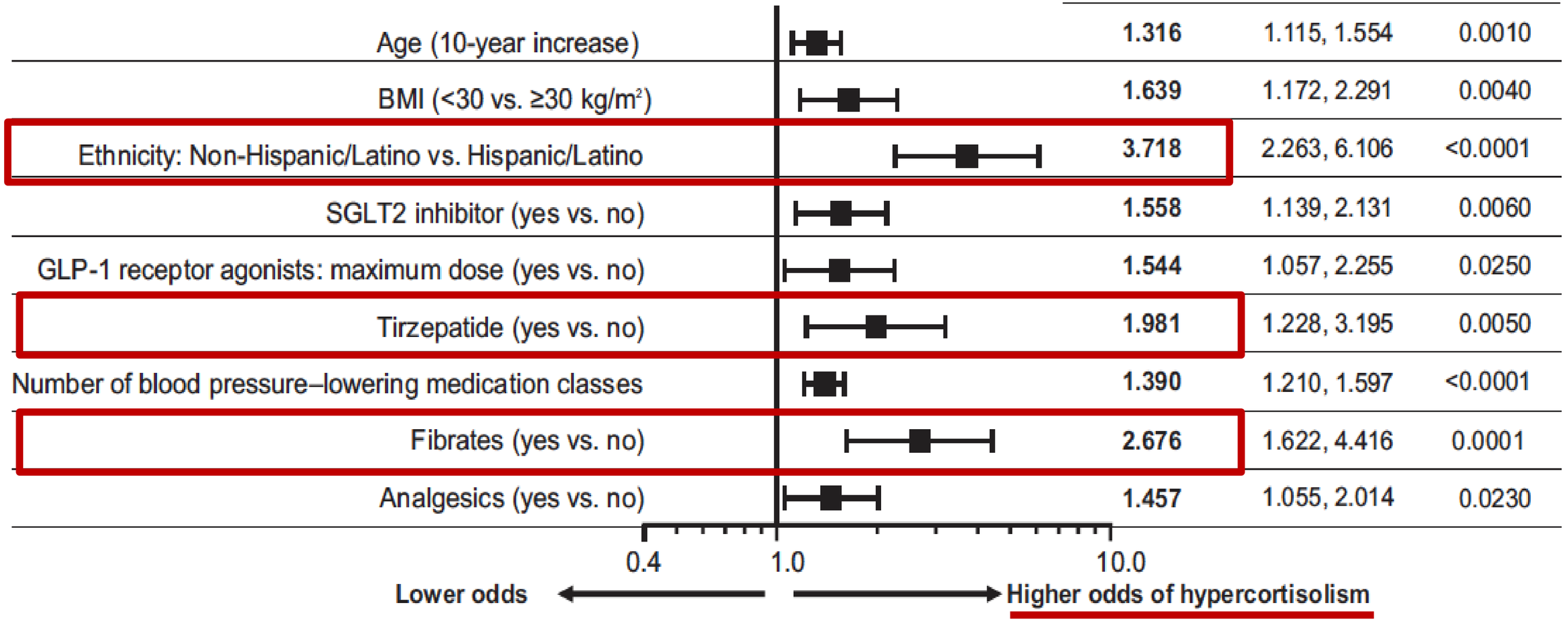
Factors Independently Associated with Hypercortisolism



	OR	95% CI	*P* value
Age (10-year increase)	1.316	1.115, 1.554	0.0010
BMI (<30 vs. ≥30 kg/m²)	1.639	1.172, 2.291	0.0040
Ethnicity: Non-Hispanic/Latino vs. Hispanic/Latino	3.718	2.263, 6.106	<0.0001
SGLT2 inhibitor (yes vs. no)	1.558	1.139, 2.131	0.0060
GLP-1 receptor agonists: maximum dose (yes vs. no)	1.544	1.057, 2.255	0.0250
Tirzepatide (yes vs. no)	1.981	1.228, 3.195	0.0050
Number of blood pressure–lowering medication classes	1.390	1.210, 1.597	<0.0001
Fibrates (yes vs. no)	2.676	1.622, 4.416	0.0001
Analgesics (yes vs. no)	1.457	1.055, 2.014	0.0230

Figure 1—Multiple logistic regression model for hypercortisolism vs. no hypercortisolism. Error bars: 95% CIs.

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Further Evaluation: ACTH Levels

ACTH = adrenocorticotropic hormone

	ACTH Levels < 10 pg/mL (suppressed)	ACTH Levels ≥ 10 pg/mL (normal or elevated)
Adrenal Computed Tomography (CT) scans	ACTH-independent or Adrenal-autonomous cause	
Pituitary Magnetic Resonance Imaging (MRI), then Whole-body Imaging (high suspicion for ectopic source)		ACTH-dependent cause

ACTH-independent cause: adrenal glands autonomously overproduce cortisol --> suppressing pituitary ACTH release through negative feedback

ACTH-dependent cause: adrenal glands are stimulated to produce cortisol by excess ACTH most common: pituitary tumor → Cushing Disease

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Diabetes Core Update: Special Edition: Hypercortisolism– May 2025, May 12, 2025
https://podcasts.apple.com/us/podcast/diabetes-core-update/id501572453?i=1000708111948&r=153

Further Evaluation: DHEAS Levels

DHEAS = dehydroepiandrosterone sulfate (adrenal androgen)

- After an abnormal 1-mg overnight DST indicated hypercortisolism
  - A separate fasting blood sample would be obtained at 8:00 AM on a later day for measurement of **DHEAS**, along with **ACTH** and **cortisol** levels.

- Low or low-normal DHEAS level + low or low-normal ACTH level
  - ACTH-**in**dependent hypercortisolism
  - The pattern suggests that the adrenal glands are *autonomously producing cortisol*.
    - → Suppresses the pituitary's release of ACTH and adrenal androgens (e.g., DHEAS)

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Further Evaluation: Imaging – Adrenal CT Scans

34.7%

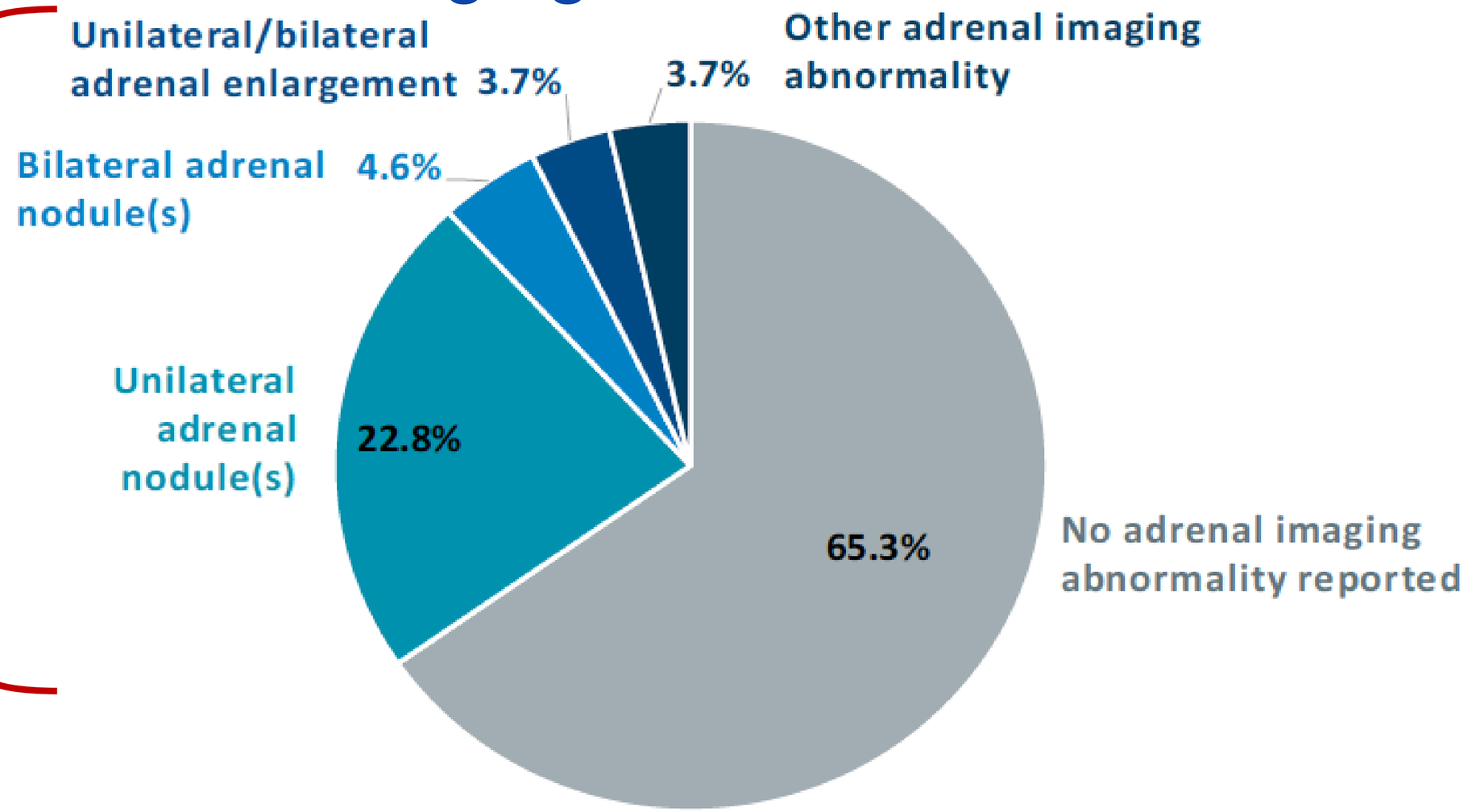

Figure 2—Results of adrenal CT scans in participants with hypercortisolism. Abdominal CT scan results were available in 219 of 252 (86.9%) participants. Reasons for not completing the CT scan included withdrawal of consent (*n* = 13), lost to follow-up (*n* = 6), physician decision (*n* = 2), and other (*n* = 12).

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Table 2—Plasma steroid-related measurements in participants with hypercortisolism with or without an adrenal imaging abnormality

	Abnormal adrenal CT scan (*N* = 76)	Normal adrenal CT scan (*N* = 143)	*P* value for association with hypercortisolism with abnormal CT scan[a]
Post-DST cortisol			
n	76	143	
Mean (SD), µg/dL	3.49 (3.27)	3.46 (2.66)	NS
Median (range), µg/dL	2.60 (1.81, 24.80)	2.55 (1.81, 23.50)	
Post-DST dexamethasone			
n	76	143	
Mean (SD), ng/dL	412.0 (264.0)	418.5 (206.0)	NS
Median (range), ng/dL	376.5 (142.8, 2,073.8)	395.1 (150.9, 1,978.7)	
ACTH			
n	73	137	
Mean (SD), ng/L	17.6 (14.9)	22.3 (14.3)	0.03
Median (range), ng/L	13.7 (2.7, 92.3)	19.2 (2.7, 82.6)	
DHEAS			
n	75	138	
Mean (SD), µg/dL	84.0 (63.9)	85.9 (75.2)	NS
Median (range), µg/dL	74.0 (7, 291)	68.5 (2, 593)	
Morning fasting cortisol			
n	70	128	
Mean (SD), µg/dL	14.0 (3.9)	14.5 (4.8)	NS
Median (range), µg/dL	13.8 (7.1, 25.5)	14.4 (4.0, 30.9)	

ACTH = adrenocorticotropic hormone
DHEAS = Dehydroepiandrosterone sulfate

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ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Despite treatment with multiple medications, glycemic targets are not met in many people with type 2 diabetes, who are at increased risk for diabetes complications. Hypercortisolism is known to promote hyperglycemia and may be a contributing factor to inadequate glucose control in some individuals.

- **What is the specific question(s) we wanted to answer?**
  What is the prevalence of hypercortisolism in people with difficult-to-control type 2 diabetes in the U.S.?

- **What did we find?**
  Approximately one-quarter of people with difficult-to-control type 2 diabetes had hypercortisolism.

- **What are the implications of our findings?**
  These results expand our understanding of why type 2 diabetes may be difficult to control in some individuals and suggest a potential role for hypercortisolism screening in this population.

Buse JB, Kahn SE, Aroda VR, et al. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes. Diabetes Care. Published online April 18, 2025. doi:10.2337/dc24-2841

D. Treating Hypercortisolism in T2DM: A Re-Surfaced Management Approach

Diabetes Care®

American Diabetes Association®

Inadequately Controlled Type 2 Diabetes and Hypercortisolism: Improved Glycemia With Mifepristone Treatment

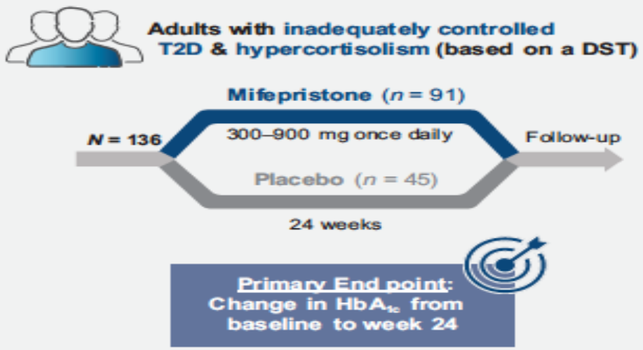
Ralph A. DeFronzo, Vivian Fonseca, Vanita R. Aroda, Richard J. Auchus, Timothy Bailey, Irina Bancos, Robert S. Busch, John B. Buse, Elena A. Christofides, Bradley Eileman, James W. Findling, Yehuda Handelsman, Steven E. Kahn, Harold J. Miller, Jonathan G. Ownby, John C. Parker, Athena Philis-Tsimikas, Richard Pratley, Julio Rosenstock, Michael H. Shanik, Lance A. Sloan, Guillermo Umpierrez, Samir Shambharkar, Iulia Cristina Tudor, Tina K. Schlafly, and Daniel Einhorn, for the CATALYST Investigators

Diabetes Care 2025;00(00):1–9 | *https://doi.org/10.2337/dc25-1055*

CATALYST
Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

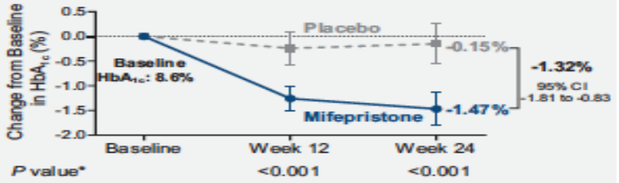
Inadequately Controlled Type 2 Diabetes and Hypercortisolism: Improved Glycemia With Mifepristone Treatment

CATALYST Treatment Phase: A Randomized, Placebo-Controlled Study



NCT05772169; randomized 2:1, stratified by adrenal imaging abnormality (yes/no)

Primary End Point Met: Mifepristone Improved HbA_{1c}



- Similar effect on HbA_{1c} seen in participants with and without adrenal imaging abnormality

Key Takeaway: In individuals with inadequately controlled T2D and hypercortisolism, treatment with mifepristone may reduce HbA_{1c}.

Other Key Findings

Improvements in glycemic control with mifepristone were accompanied by reductions in:

- **glucose-lowering medications** (e.g., insulin, sulfonylureas)
- **Body weight** (-4.4 kg; 95% CI -6.28 to -2.53)
- **BMI and waist circumference** (-1.5 kg/m² and -5.2 cm; 95% CIs -2.10 to -0.84 and 7.25 to -3.21, respectively)

Safety:

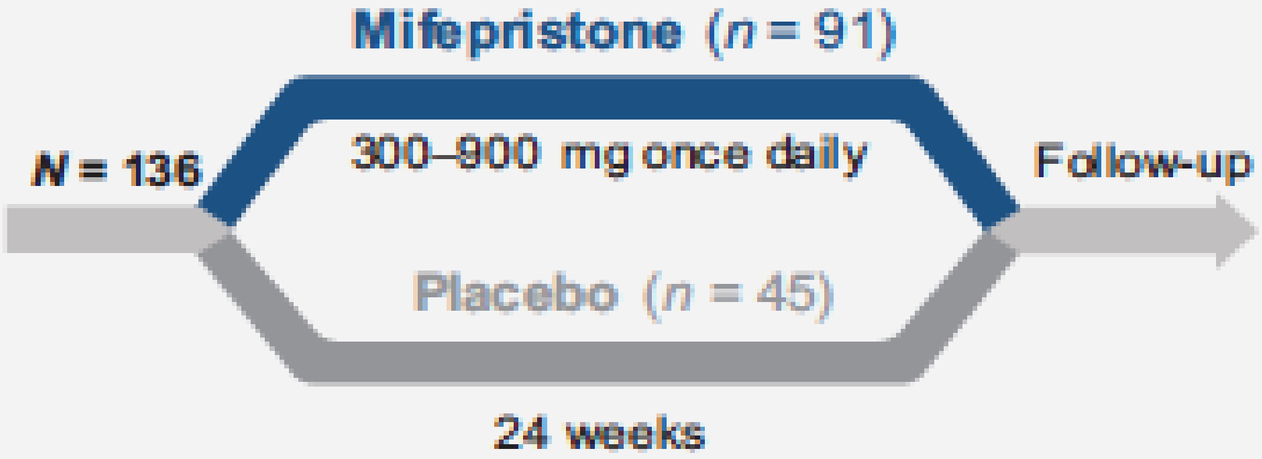
- Adverse events were manageable and consistent with mifepristone's known safety profile
- Adverse events occurring in >10% of participants treated with mifepristone: hypokalemia, fatigue, nausea, vomiting, headache, peripheral edema, diarrhea, and dizziness
- Increases in blood pressure also occurred

"Inadequately controlled T2D" defined as: type 2 diabetes with HbA_{1c} 7.5%–11.5% and at least 1 of the following: a) taking ≥3 glucose-lowering drugs, b) taking insulin and other glucose-lowering drugs, c) taking ≥2 glucose-lowering drugs and ≥1 microvascular or macrovascular complications, taking ≥2 glucose-lowering and ≥2 blood pressure–lowering drugs. "Hypercortisolism" defined as cortisol >1.8 µg/dL after dexamethasone suppression test (DST) with dexamethasone ≥140 ng/dL. *Graphic shows least squares mean (LSM) change from baseline and 95% CI; *P* value for least squares mean difference from placebo.

Methods

CATALYST Treatment Phase: A Randomized, Placebo-Controlled Study

Adults with inadequately controlled T2D & hypercortisolism (based on a DST)



Primary Endpoint:
Change in HbA_{1c} from baseline to week 24

NCT05772169; randomized 2:1, stratified by adrenal imaging abnormality (yes/no)

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Key Inclusion & Exclusion Criteria

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 m^2
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; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal.

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Presented at the 85th American Diabetes Association Scientific Sessions in Chicago, IL.
https://corcept.com/publications/treatment-of-hypercortisolism-in-people-with-difficult-to-control-type-2-diabetes-final-results-of-the-catalyst-trial/

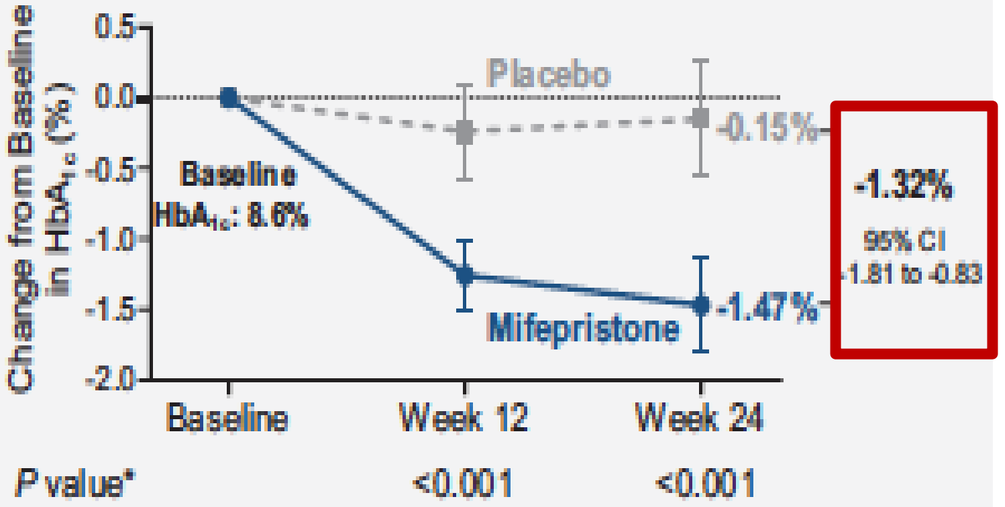
Results

Table 1—Demographics and baseline characteristics of participants enrolled in the treatment phase (intent-to-treat population)

	Mifepristone (*n* = 91)	Placebo (*n* = 45)	Total (*n* = 136)
Age, years	62.9 (8.9)	63.8 (11.5)	63.2 (9.8)
Male, *n* (%)	54 (59.3)	29 (64.4)	83 (61.0)
Race, *n* (%)			
White	71 (78.0)	39 (86.7)	110 (80.9)
Black or African American	16 (17.6)	5 (11.1)	21 (15.4)
Other*	4 (4.4)	1 (2.2)	5 (3.7)
Ethnicity, *n* (%)			
Hispanic or Latino	5 (5.5)	4 (8.9)	9 (6.6)
Not Hispanic or Latino	85 (93.4)	41 (91.1)	126 (92.6)
Missing	1 (1.1)	0	1 (0.7)
Body weight, kg	99.7 (23.21)	97.4 (23.43)	99.0 (23.22)
Waist circumference, cm	114.0 (17.45)	115.3 (18.24)	114.4 (17.66)
BMI, kg/m^2	33.1 (7.31)	33.7 (8.21)	33.3 (7.59)
HbA_{1c}, %†	8.62 (1.27)	8.41 (1.08)	8.55 (1.21)
Abnormal adrenal CT scan, *n* (%)	25 (27.5)	13 (28.9)	38 (27.9)
Post-DST cortisol, µg/dL‡	3.8 (3.1)	3.3 (2.1)	3.6 (2.8)
Post-DST dexamethasone, ng/dL§	415.5 (290.5)	436.2 (199.2)	422.3 (263.2)
ACTH, pg/mL¶	19.5 (12.0)	18.8 (11.2)	19.3 (11.7)
DHEAS, µg/dL‖	85.8 (71.05)	87.7 (86.87)	86.4 (76.33)

Data are means (SD) unless otherwise indicated. CT, computed tomography. *"Other" category includes "multiple" and "other." †To convert HbA_{1c} value to millimoles per mole, use the equation HbA_{1c} (mmol/mol) = (HbA_{1c} (%) × 10.93) − 23.5. ‡To convert cortisol value to nanomoles per liter, multiply by 27.59. §To convert dexamethasone value to picomoles per liter, multiply by 25.48. ¶To convert adrenocorticotropic hormone (ACTH) value to picomoles per liter, multiply by 0.22. ‖To convert dehydroepiandrosterone sulfate (DHEAS) value to micromoles per liter, multiply by 2.71.

Primary End Point Met: Mifepristone Improved HbA_{1c}



- Similar effect on HbA_{1c} seen in participants with and without adrenal imaging abnormality

Key Takeaway: In individuals with inadequately controlled T2D and hypercortisolism, treatment with mifepristone may reduce HbA_{1c}.

Other Key Findings

Improvements in glycemic control with mifepristone were accompanied by reductions in:

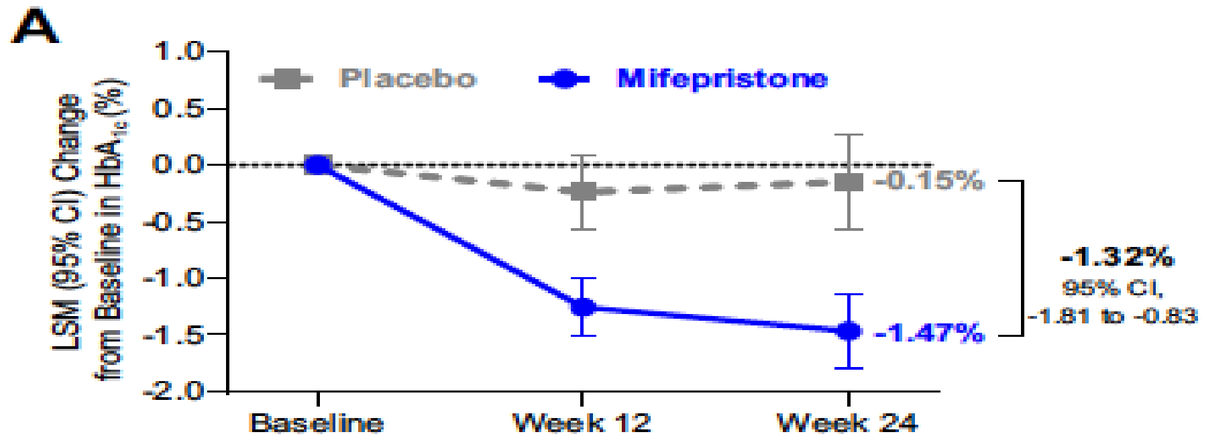
glucose-lowering medications (e.g., insulin, sulfonylureas)

Body weight (-4.4 kg; 95% CI -6.28 to -2.53)

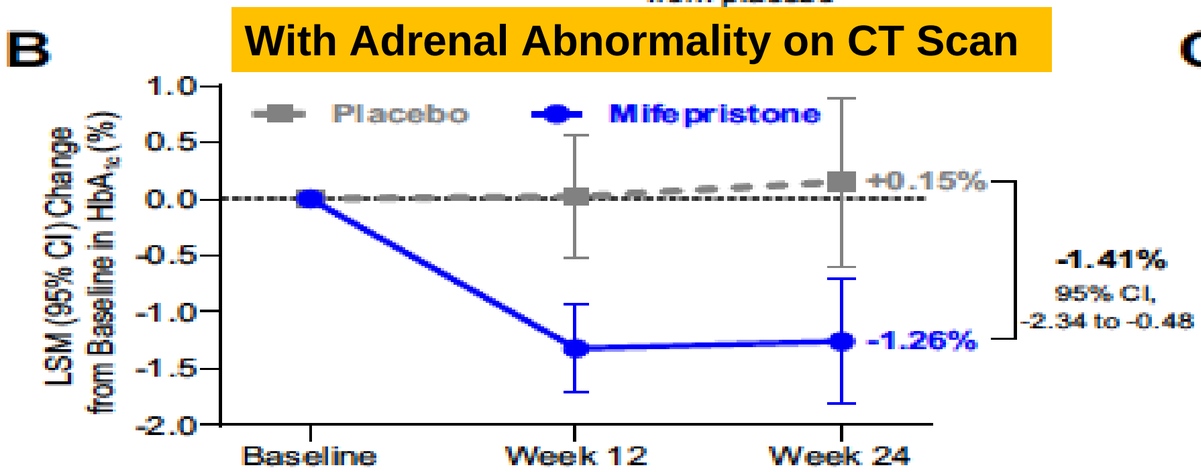
BMI and waist circumference (-1.5 kg/m^2 and -5.2 cm; 95% CIs -2.10 to -0.84 and 7.25 to -3.21, respectively)

Safety:

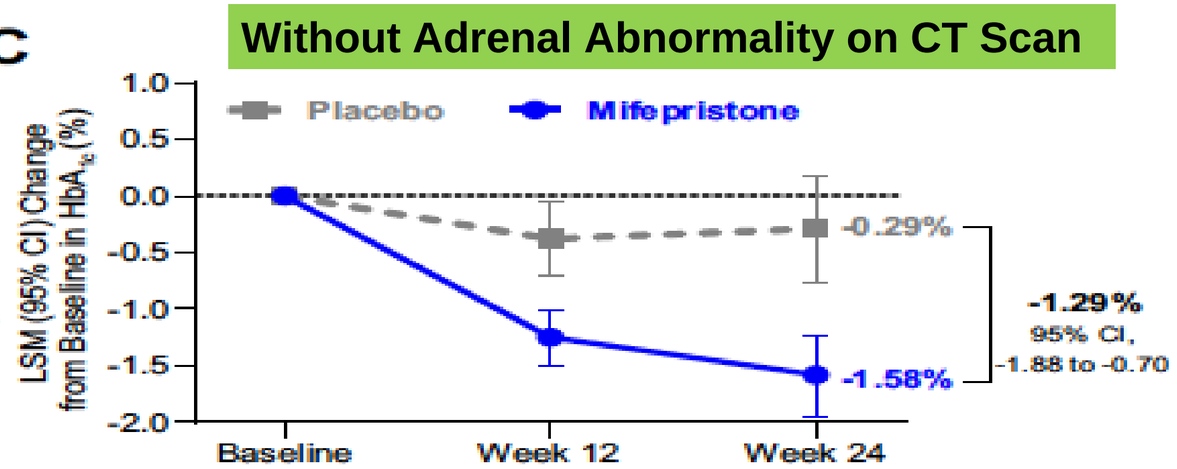
- Adverse events were manageable and consistent with mifepristone's known safety profile
- Adverse events occurring in >10% of participants treated with mifepristone: hypokalemia, fatigue, nausea, vomiting, headache, peripheral edema, diarrhea, and dizziness
- Increases in blood pressure also occurred



Number of participants			
Mifepristone	86	74	62
Placebo	44	40	38
P value for LSM difference from placebo		<0.001	<0.001



Number of participants			
Mifepristone	25	22	19
Placebo	13	11	11



Number of participants			
Mifepristone	61	52	43
Placebo	31	29	27

Figure 1—LSM change from baseline in HbA_{1c} in all participants (*A*), participants with adrenal abnormality on computed tomography (CT) scan (*B*), and participants without adrenal abnormality on computed tomography scan (*C*). Note that the widths of CIs in *B* and *C* have not been adjusted for multiplicity and cannot be used to infer treatment effect.

Table 2—Secondary efficacy end points (intent-to-treat population)

	Mifepristone	Placebo	LSM difference from placebo at week 24 (95% CI)
Body weight, kg			
Baseline, mean (SD) [*n*]	99.7 (23.21) [91]	97.4 (23.43) [91]	—
LSM change from baseline to week 24 (95% CI) [*n*]	−4.40 (−6.275 to −2.525) [65]	0.72 (−1.838 to 3.272) [38]	−5.12 (−8.203 to −2.031)
BMI, kg/m^2			
Baseline, mean (SD) [*n*]	33.1 (7.31) [91]	33.7 (8.21) [45]	—
LSM change from baseline to week 24 (95% CI) [*n*]	−1.47 (−2.096 to −0.841) [65]	0.28 (−0.577 to 1.131) [38]	−1.75 (−2.779 to −0.713)
Waist circumference, cm			
Baseline, mean (SD) [*n*]	114.0 (17.45) [91]	115.3 (18.24) [45]	—
LSM change from baseline to week 24 (95% CI) [*n*]	−5.2 (−7.25 to −3.21) [65]	−0.1 (−2.74 to 2.51) [38]	−5.1 (−8.23 to −1.99)
Fasting plasma glucose, mg/dL*			
Baseline, mean (SD) [*n*]	177.8 (66.45) [89]	161.8 (65.36) [45]	—
LSM change from baseline to week 24 (95% CI) [*n*]	−30.7 (−45.13 to −16.28) [57]	−10.7 (−28.32 to 6.96) [38]	−20.0 (−41.34 to 1.30)
Systolic blood pressure, mmHg			
Baseline, mean (SD) [*n*]	125.0 (15.98) [91]	125.4 (14.78) [45]	—
LSM change from baseline to week 24 (95% CI) [*n*]	8.0 (3.82 to 12.18) [65]	−2.1 (−7.47 to 3.27) [39]	10.1 (3.62 to 16.59)
Diastolic blood pressure, mmHg			
Baseline, mean (SD) [*n*]	74.1 (9.12) [91]	73.3 (9.44) [45]	—
LSM change from baseline to week 24 (95% CI) [*n*]	2.4 (−0.12 to 4.98) [65]	−1.3 (−4.57 to 2.00) [39]	3.7 (−0.29 to 7.72)
Cholesterol, mg/dL			
Baseline, mean (SD) [*n*]	146.8 (48.50) [85]	135.0 (36.62) [44]	
LSM change from baseline to week 24 (95% CI) [*n*]	−17.1 (−27.24 to −7.03) [61]	0.0 (−12.76 to 12.83) [38]	−17.2 (−32.36 to −1.98)
HDL cholesterol, mg/dL			
Baseline, mean (SD) [*n*]	45.3 (18.67) [85]	42.8 (12.61) [44]	
LSM change from baseline to week 24 (95% CI) [*n*]	−3.8 (−6.66 to −0.97) [61]	1.1 (−2.45 to 4.72) [38]	−4.9 (−9.13 to −0.77)
LDL cholesterol, mg/dL			
Baseline, mean (SD) [*n*]	63.7 (32.83) [80]	63.2 (32.06) [42]	
LSM change from baseline to week 24 (95% CI) [*n*]	−6.8 (−14.75 to 1.18) [55]	2.0 (−7.95 to 11.98) [36]	−8.8 (−20.77 to 3.17)
VLDL cholesterol, mg/dL			
Baseline, mean (SD) [*n*]	31.8 (17.23) [80]	28.5 (13.68) [43]	
LSM change from baseline to week 24 (95% CI) [*n*]	−5.4 (−8.07 to −2.68) [55]	0.9 (−2.41 to 4.26) [37]	−6.3 (−10.22 to −2.38)
Triglycerides, mg/dL			
Baseline, mean (SD) [*n*]	229.4 (528.47) [85]	150.1 (83.90) [44]	
LSM change from baseline to week 24 (95% CI) [*n*]	−64.0 (−85.54 to −42.44) [61]	−45.3 (−72.84 to −17.78)	−18.7 (−50.37 to 13.01)

Note that the widths of CIs have not been adjusted for multiplicity and cannot be used to infer treatment effect. *To convert fasting plasma glucose value to millimoles per liter, divide by 18.

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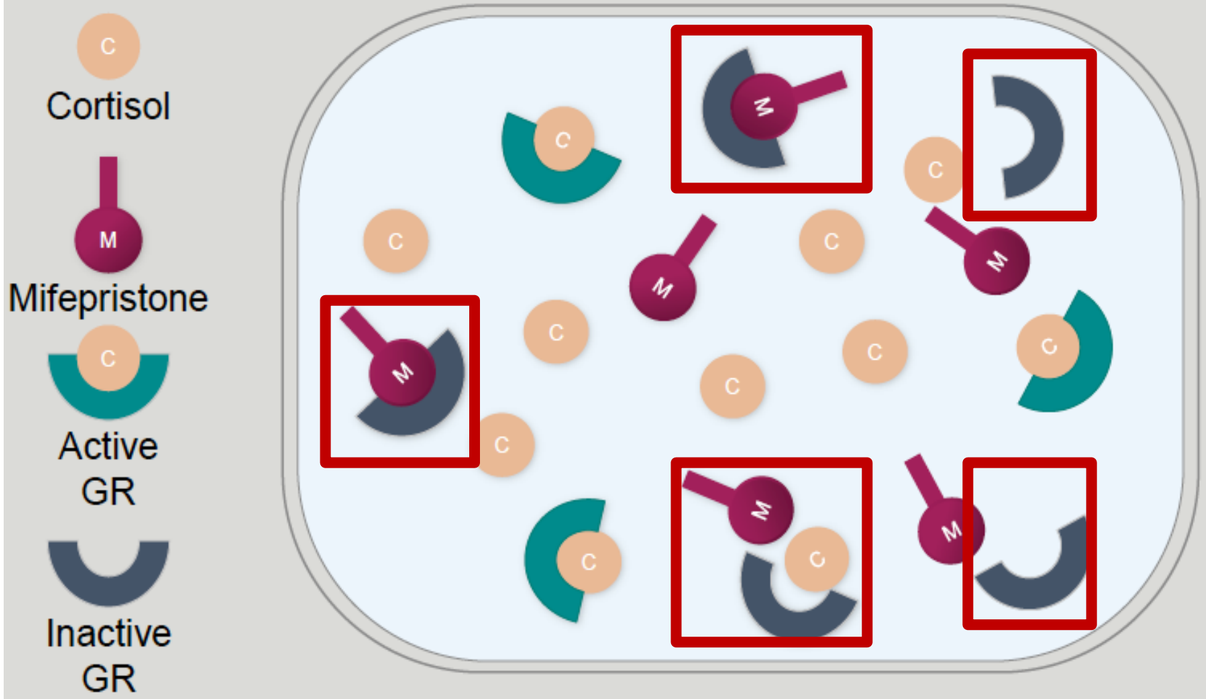
mifepristone

How Does Mifepristone 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.

Presented at the 85th American Diabetes Association Scientific Sessions in Chicago, IL.
https://corcept.com/publications/treatment-of-hypercortisolism-in-people-with-difficult-to-control-type-2-diabetes-final-results-of-the-catalyst-trial/

Mifepristone 300 mg

- Classification: Cortisol Receptor Blocker
  - Competitive glucocorticoid receptor (GR) antagonist (not a complete antagonist)
- Mechanism of Action:
  - Competes with cortisol for binding to GR → Modulates (not eliminates) the effects of excess cortisol in the body
    - Reduces the negative effects of hypercortisolism without directly lowering cortisol levels
- Indication:
  - Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery
- Key Safety Consideration:
  - ***Hypokalemia***: should be corrected prior to treatment and monitored for during treatment (might need to start *spironolactone*)
  - ***Glucocorticoid withdrawal syndrome***: profound fatigue, sleep disturbance, mood changes, etc.

Korlym® (mifepristone) 300 mg Tablets Prescribing Information. Corcept Therapeutics, Inc. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202107s008lbl.pdf

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

** Due to ***overstimulation*** of the mineralocorticoid receptor by cortisol. **

Table 3—Overview of treatment-emergent adverse events and summary of treatment-emergent adverse events occurring in ≥5% of participants (safety population)

	Mifepristone (*n* = 91)	Placebo (*n* = 43)
Participants with at least one		
Treatment-emergent adverse event	86 (94.5)	36 (83.7)
Treatment-related adverse event	56 (61.5)	14 (32.6)
Treatment-emergent adverse event leading to study medication discontinuation	26 (28.6)	1 (2.3)
Treatment-emergent adverse event leading to dose interruption	24 (26.4)	5 (11.6)
Treatment-emergent adverse event leading to dose reduction	12 (13.2)	1 (2.3)
Serious treatment-emergent adverse event	29 (31.9)	2 (4.7)
Serious treatment-emergent adverse event related to study medication*	2 (2.2)	0
Most common treatment-emergent adverse events		
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)
Headache	11 (12.1)	5 (11.6)
Peripheral edema	14 (15.4)	1 (2.3)
Diarrhea	10 (11.0)	3 (7.0)
Dizziness	10 (11.0)	3 (7.0)
Hypoglycemia	9 (9.9)	3 (7.0)
Increased blood thyroid-stimulating hormone	9 (9.9)	2 (4.7)
Constipation	9 (9.9)	1 (2.3)
Hypothyroidism	7 (7.7)	0
Hypertension	6 (6.6)	1 (2.3)
Arthralgia	5 (5.5)	2 (4.7)
Back pain	5 (5.5)	2 (4.7)
Decreased appetite	5 (5.5)	2 (4.7)

Data are *n* (%). *Both serious treatment-related adverse events were cases of hypokalemia. Hypokalemia was defined as potassium <3.6 mmol/L.

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

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ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Approximately one-quarter of people with type 2 diabetes who do not meet glycemic targets despite treatment with multiple medications may have endogenous hypercortisolism. We wanted to understand whether mifepristone treatment may lower HbA_{1c} in these individuals.

- **What is the specific question(s) we wanted to answer?**
  Does treatment with mifepristone improve glucose control in individuals with inadequately controlled diabetes and hypercortisolism?

- **What did we find?**
  Mifepristone lowered HbA_{1c} by ~1.5% and improved weight. While side effects were generally manageable, serious side effects and early study discontinuations were more common with mifepristone.

- **What are the implications of our findings?**
  Individuals with inadequately controlled type 2 diabetes should be considered for hypercortisolism screening. In those with hypercortisolism, cortisol-directed therapy may lower HbA_{1c}, weight, and waist circumference.

DeFronzo RA, Fonseca V, Aroda VR, et al. Inadequately controlled type 2 diabetes and hypercortisolism: Improved glycemia with mifepristone treatment. Diabetes Care. Published online June 23, 2025. doi:10.2337/dc25-1055

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E. Case Discussion & Conclusion

Clinical Case Vignette: Jayden

- 74-year-old Indian man
- Medical History: type 2 diabetes, chronic kidney disease, hypertension, hyperlipidemia, asthma, osteoarthritis, atrial fibrillation, GERD, erectile dysfunction, BPH
- A1c Trend:
  - 7.6% (9/10/2025)
  - 7.5% (6/10/2025)
  - 7.3% (3/27/2025)

- eGFR: 51 (9/10/2025)
- FIB-4 Score: 1.46 (1/24/2025)
- 10-Year ASCVD Risk: 33%
- CGM Data
  Data from 9/24/25 - 10/7/25
  Overall mean glucose: 193
  TAR: 60%
  TIR: 40%
  TBR <70: 0%
  TBR <54: 0%
  GMI: 7.9%

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Clinical Case Vignette: Jayden

Type 2 Diabetes

- Tirzepatide 7.5 mg SQ once weekly on Fridays
- Insulin Glargine-yfgn 25 units SQ once daily at bedtime
- Empagliflozin 25 mg 1 tablet PO daily QAM

HTN

- Amlodipine 10 mg 1 tablet PO daily QAM
- Losartan 100 mg 1 tablet PO daily QAM
- Carvedilol 25 mg 1 tablet PO 2 times daily with a meal
- Triamterene-HCTZ 37.5 mg/25 mg 1 tablet PO daily

HLD

- Atorvastatin 40 mg 1 tablet PO daily
- Omega-3-FA 1,000 mg 2 capsules PO daily

- Before tirzepatide…
  - Rybelsus 14 mg (8/1/24 – 11/19/24)
  - Ozempic 2 mg (1/28/25 – 8/28/25)

- A1c Trend:
  - 7.6% (9/10/2025)
  - 7.5% (6/10/2025)
  - 7.3% (3/27/2025)

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What Would You Do?

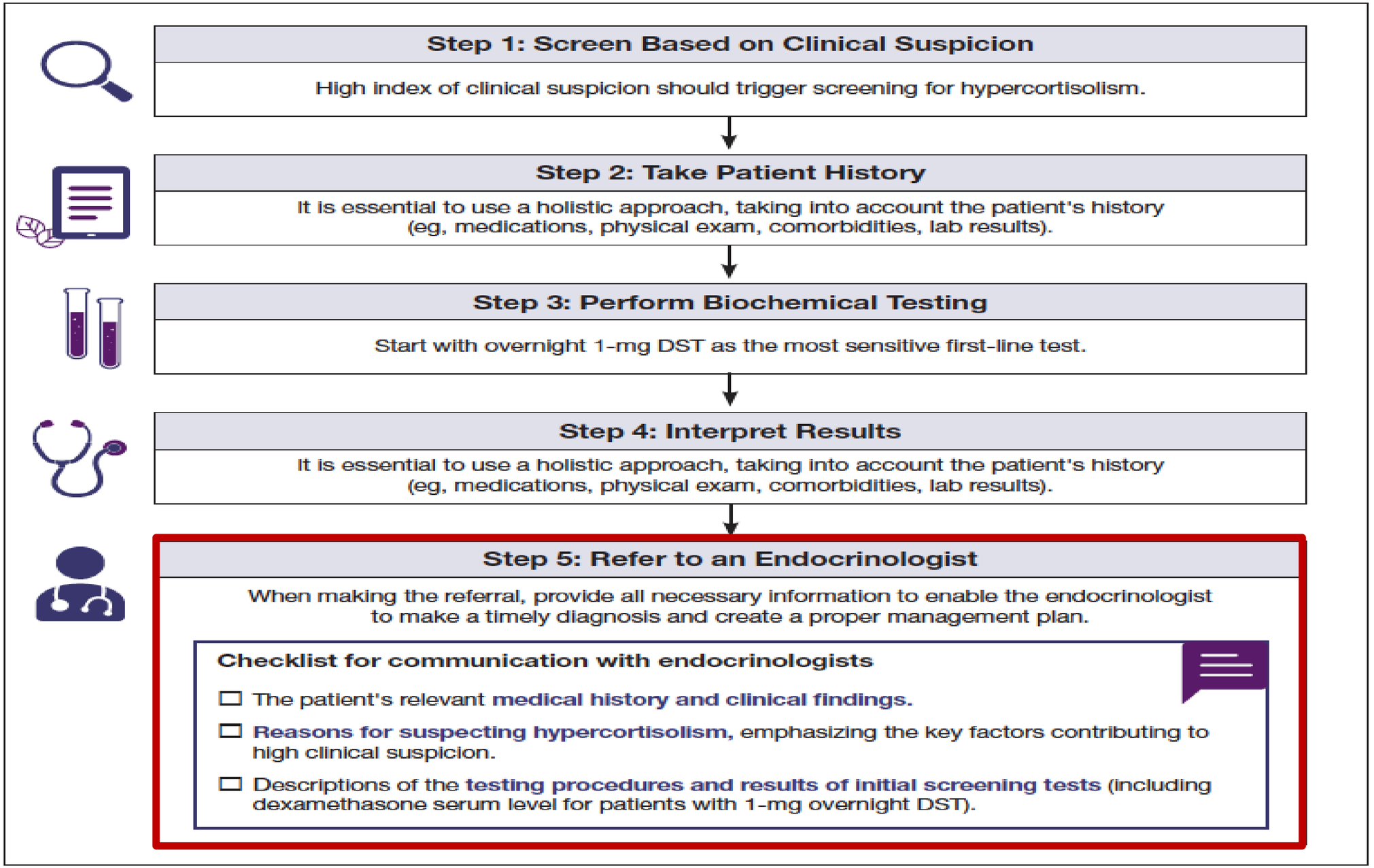
Hypercortisolism Screening – 9/18/2025

- 1 mg of dexamethasone (11 pm the night before the lab)
- Cortisol, A.M. = **3.0** mcg/L
- Level of dexamethasone: Lab Not Ordered

Hypercortisolism Screening – 11/13/2025

- 1 mg of dexamethasone (11 pm the night before the lab)
- Cortisol, A.M. = **3.2** mcg/L
- Level of dexamethasone: not yet available (as of 11.20.25)

FIGURE 2. Process and considerations for screening, workup, and referral for hypercortisolism in primary care



Abbreviation: DST, dexamethasone suppression test.

Kushner, P., Brown, D. R., & Busch, R. S. (2024). Hypercortisolism is more common than you think—Here's how to find it. *Federal Practitioner*, 41(Suppl 6), S23–S28.

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Key Points: Call to Action

- **Take a thorough history to look for clinical red flags** (and treatment resistance)
  - Keep hypercortisolism on the differential in any patient with difficult-to-control T2D despite adherence and guideline-directed therapy
- **Screen systematically using the first-line test**
  - **1 mg overnight dexamethasone suppression test (DST)**
- **Embed screening into the disease management workflow**
  - Add an EHR prompt for “T2D with persistent hyperglycemia/resistant HTN”
  - DST: Order set with 1 mg dexamethasone + cortisol (AM) and dexamethasone levels
  - Confirm positive (repeat DST) → ACTH + DHEAS + Cortisol (AM) Levels +/- CT scan
  - Refer to endocrinology

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Concluding Thoughts: A Public-Health-&-Clinical Message

- **Actionable Prevention**:

- Early identification & appropriate endocrine care
  → reduce morbidity
  → improve glycemic management
  → potentially curb downstream costs from complications

- **Public-Health-&-Clinical Takeaways**:

- For patients with T2D whose glucose levels “just won’t budge”
  → Think cortisol
  → Normalize screening wherever indicated
  → Educate teams and patients
  → Build referral pathways
- Small workflow changes can yield outsized clinical impact

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Podcasts

Additional Resources

- American Diabetes Association – Diabetes Core Update
  1. Special Edition: Hypercortisolism – May 2025 (23 minutes)
  2. Special Edition: Treatment of Hypercortisolism in Difficult to Manage Diabetes – July 2025 (27 minutes)
  3. Special Edition: Treatment of Hypercortisolism in Uncontrolled Diabetes, Part 3 – August 2025 (28 minutes)

Thank You!

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