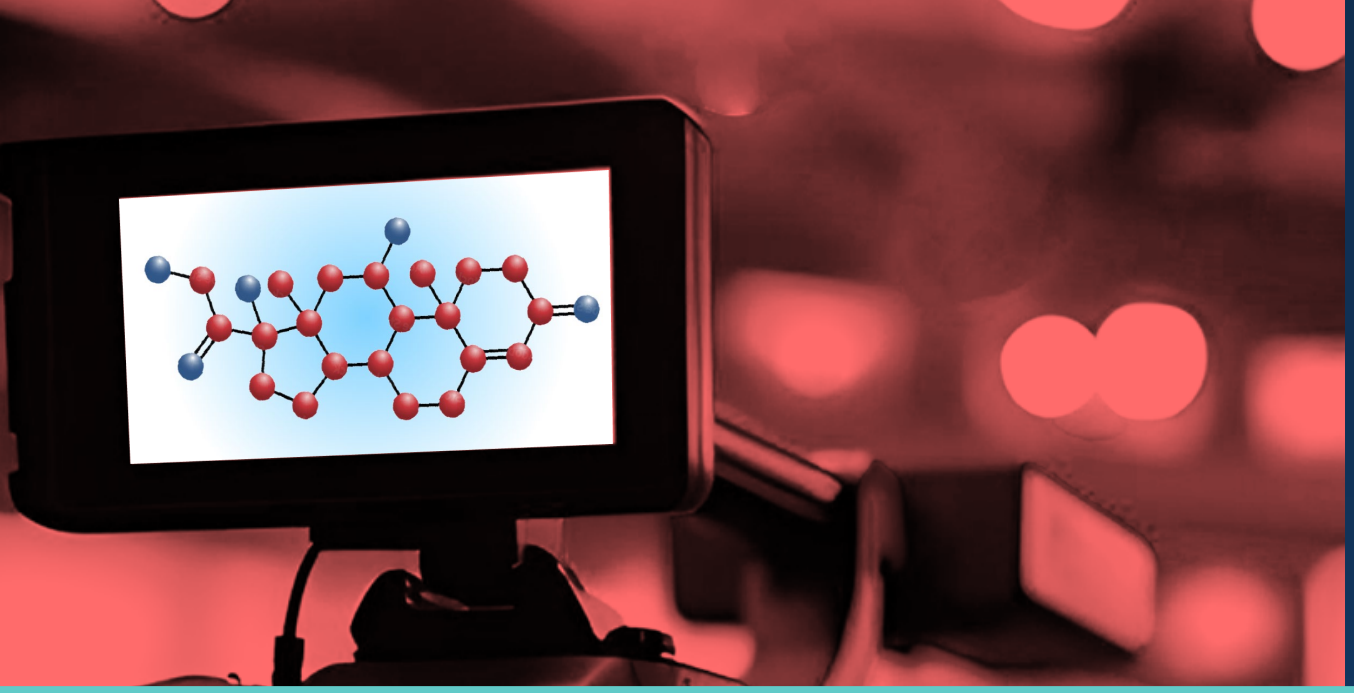

The Cortisol Reports

Episode 4 - The Cortisol Clue: Diagnosing Hypercortisolism in People with Difficult-to-Control Cardiometabolic Conditions

What is Hypercortisolism?

Also referred to as subclinical 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]

1. Reincke M, et al. *JAMA*. 2023; 2. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008; 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022; 4. Limumpornpetch P, et al. *J Clin Endocrinol Metab*. 2022.

Presentation Considerations

Clinicians may think:
Oh my gosh, that's a lot of my patients in clinical practice!

But it’s important to identify patients with those conditions that aren't responding to standards of care and conventional therapy

Could there be something at the center that is fueling this difficult disease state?

Hypercortisolism: Multisystemic, Heterogeneous Presentation

- Overt symptoms of hypercortisolism include those clearly identifiable in the “index case” of Cushing's syndrome described by Dr. Cushing 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]
- Hypercortisolism contributes to difficult-to-control cardiometabolic disease[4]

Overt Symptoms of Hypercortisolism	Nonspecific Features of Hypercortisolism
Central obesity	Osteoporosis
Wasting of extremities	Hard to Control Diabetes Non GLP-1 responders
Easy bruising	Hypertension multiple
Purple striae	Obstructive Sleep Apnea
Rounded “moon” face	Dyslipidemia
	Excessive Weight Gain
	Kidney stones
	Depression and Anxiety

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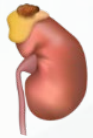
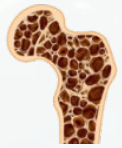
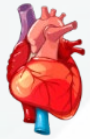
1. Reincke M, et al. *JAMA*. 2023; 2. Scoffings K, et al. *Br J Gen Pract*. 2022; 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022; 4. Ortiz R, et al. *Trends Endocr Metab*. 2022.

Hypercortisolism Prevalence in Selected Populations

Select Population	Prevalence of Hypercortisolism[a]
 Adrenal incidentaloma[1]	19% to 42.5%
 Bone fragility[2]	1.9% to 17.6%
 Hypertension[3-5]	Up to 8%
 Diabetes mellitus[6]	3.4%
 Obesity[7]	**0.9%** (pooled from 22 studies)

[a]Includes a range of disease severity and etiology.

1. Paschou SA, et al. *Endocrine*. 2016; 2. Chiodini I, et al. *Eur J Endocrinol*. 2016; 3. Anderson GH Jr, et al. *J Hypertens*. 1994; 4. Omura M, et al. *Hypertens Res*. 2004; 5. Martins LC, et al. *J Hypertens*. 2012; 6. Steffensen C, et al. *Eur J Endocrinol*. 2016; 7. van Hulsteijn LT, et al. *Eur J Endocrinol*. 2020; 8. Steffensen C, et al. *Horm Metab Res*. 2019.

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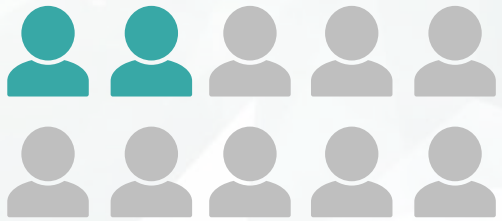
High Prevalence of Hypercortisolism in CATALYST Population

Hypercortisolism was defined as post-DST cortisol >1.8 µg/dL with Dex ≥140 ng/dL
(Those with known causes of false-positive test results were excluded from the study)

Patients with difficult-to-control T2D

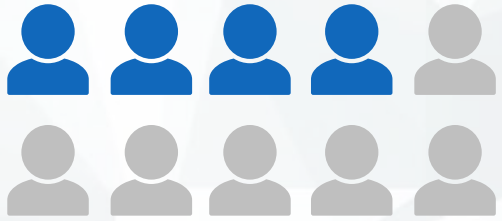


23.8% of patients had **hypercortisolism**

(n=252/1057)

Mean (range) **post-DST cortisol**: **3.5** (1.81-24.80) **µg/dL**
Mean **post-DST dexamethasone**: **412.5 ng/dL**

Patients with difficult-to-control T2D taking ≥3 BP medications



36.6% of patients had **hypercortisolism**

(n=86/235)

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Buse JB, et al. *Diabetes Care*. 2025.

New AACE Guidelines on Diabetes (Other Types of Diabetes)

- DM can develop secondary to Cushing syndrome and acromegaly.
- The diagnosis and management of both endocrine conditions are complex, and suspicion should prompt referral to an endocrinologist for appropriate testing and interpretation.
- Management approaches include treatment of the primary disease (surgical removal of the culprit neoplasm and/or treatment with medical therapy), as this can result in DM remission in some cases.
- Aside from overt Cushing syndrome, in individuals with **milder forms of hypercortisolism**, such as with autonomous cortisol secretion from an adrenal nodule, the classical Cushingoid signs may not be present, while **metabolic issues predominate**.
  - Results from the CATALYST trial demonstrated that, in adults meeting the study definition of difficult-to-control T2D, there is a **high prevalence of hypercortisolism (23.8%),** as determined by a non-suppressed morning cortisol (>1.8 mg/dL [50 nmol/L]) after 1 mg dexamethasone overnight, and this **prevalence was even higher in participants on multiple BP-lowering medications (36.6%)**.
  - Adrenal imaging abnormalities were found in 34.7% of those with an abnormal suppression test, of which 65.8% were unilateral adrenal nodules.
  - This finding is intriguing and a follow-up report showed that **treatment (24 weeks) with the glucocorticoid receptor antagonist**, mifepristone, **improved weight, waist circumference, and A1C (-1.5% or -16 mmol/mol), intimating that cortisol may be a culprit rather than a bystander.**

Samson SL, et al. *Endocr Pract*. 2026.

New Patient Consult: Poorly Controlled T2DM

- 55-year-old Caucasian female
- Duration Diabetes 15 years
- BMI 45.58 BP 130/67
- A1c 8.9% (previous A1c 10.4%)
- Medications
  - Insulin Glargine U300 180 units SQ daily
  - Insulin Aspart U100 30 units 3-4 times per day
  - Semaglutide 2mg daily (recently initiated 4 mos prior)
  - Rosuvastatin 20mg
  - Spironolactone 25mg
  - Propranolol 120mg
  - Irbesartan 150mg
  - CGM (recently restarted) with current AGP in chart TIR 21% Hypo 0%

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

Diving Into Her History…

- PMHX- 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- Type 2 DM (father) Coronary Artery Disease (father), mother in good health with HTN and normal BMI
- Mentioned her challenging diabetes control and lack of significant improvement with recent max dose GLP-1 RA
  - Asked if she had a dexamethasone suppression test- she couldn't remember (no mention of adrenal mass)

Overnight Dexamethasone Suppression Test (DST)

Performing the test

1 mg oral dexamethasone at 11-12 pm

Blood sample at 8-9 am (~9 hours after dose) for serum cortisol and dexamethasone levels

Interpreting results

<1.8 mcg/dL serum cortisol with >140 ng/dL dexamethasone level: hypercortisolism not likely

≥1.8 mcg/dL serum cortisol with >140 ng/dL dexamethasone level: consult endocrinologist or specialist

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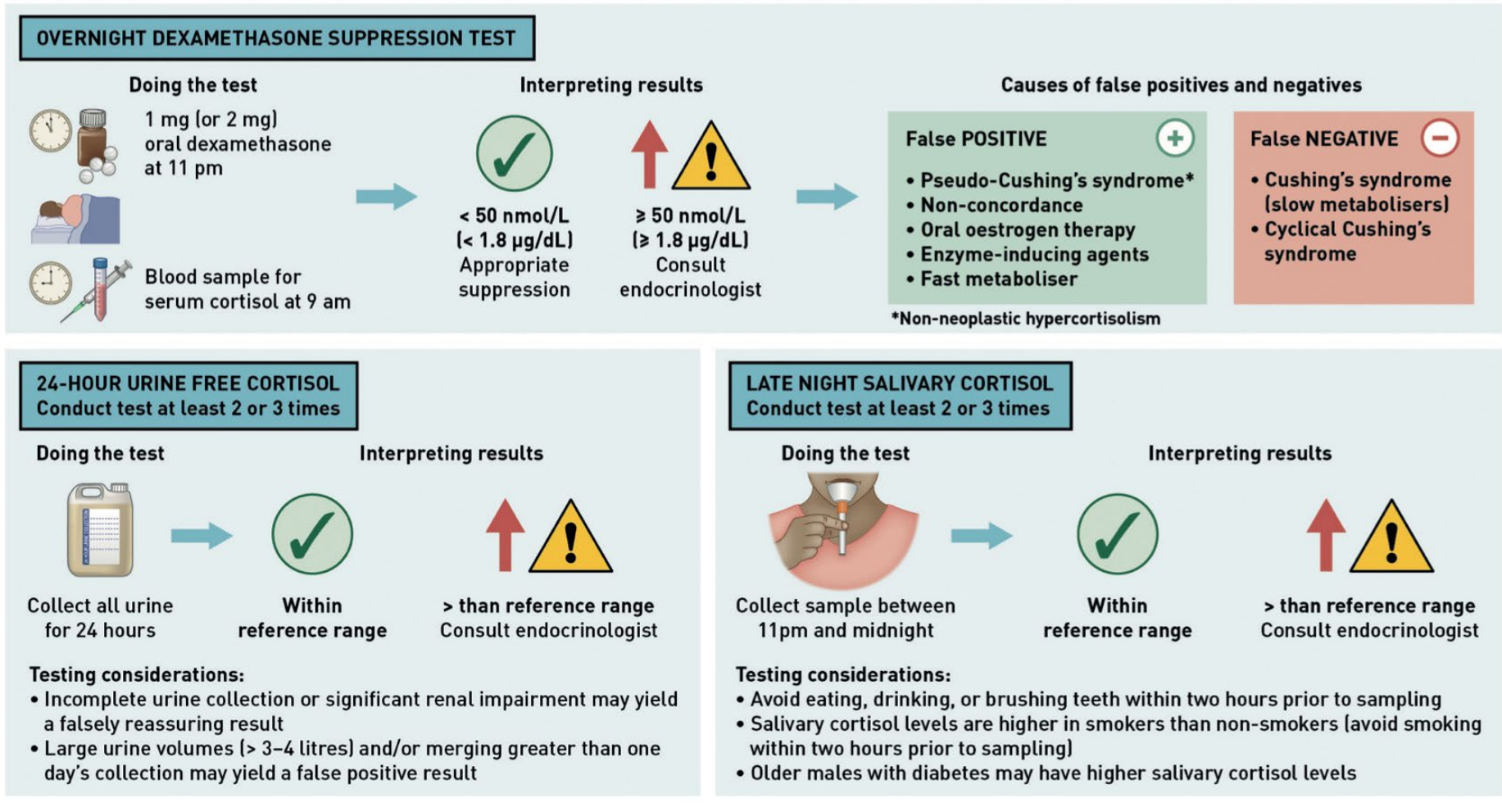
Scoffings K, et al. *Br J Gen Pract*. 2022.

Recognizing/Diagnosing CS in Primary Care: Challenging BUT NOT IMPOSSIBLE



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Scoffings K, et al. *Br J Gen Pract*. 2022.

Overnight Dexamethasone Suppression Test (DST): Testing Considerations

Potential Factors for False Positive
Estrogen-containing medications-BCP
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

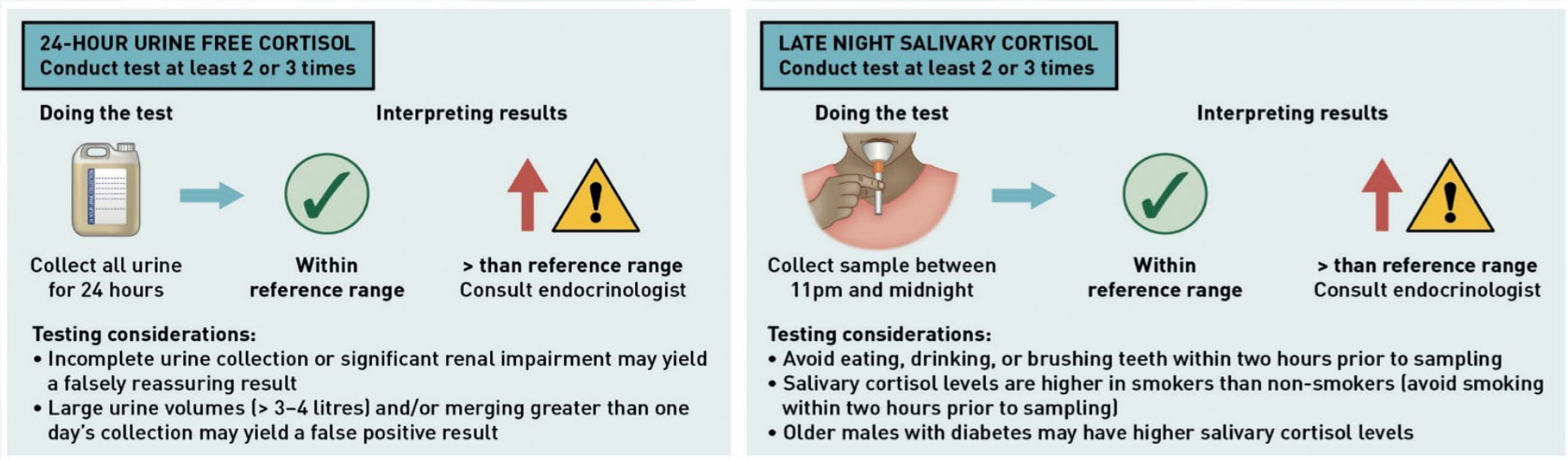
Potential Factors for False Negative
Chronic renal disease
Chronic liver disease
Concomitant medications that inhibit CYP3A4 leading to very high dexamethasone levels
Cyclic hypercortisolism

CYP3A4, cytochrome P450 isoform 3A4.

Scoffings K, et al. *Br J Gen Pract*. 2022.

Additional Confirmatory Tests

- Secondary Laboratory to rule out pituitary dysfunction
  - ACTH
  - DHEA
- Imaging Non contrast Abdominal CT (adrenal CT challenge for approval)
  - Neoplastic (hyperplasia vs adenoma)
  - Non-neoplastic (negative imaging)



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Scoffings K, et al. *Br J Gen Pract*. 2022.

Hypercortisolism Work Up (Primary Care)

- UACR 65, eGFR >60 mL/min/1.73m^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 mcg/dL (<1.8 mcg/dL is the new normal range)
  - Dexamethasone level 315 ng/dL (range >140 ng/dL for adequate cortisol suppression)
  - DHEA 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 despite suppression of the dexamethasone
- I indicated she needed to get a CT of her adrenal gland to look for an adenoma

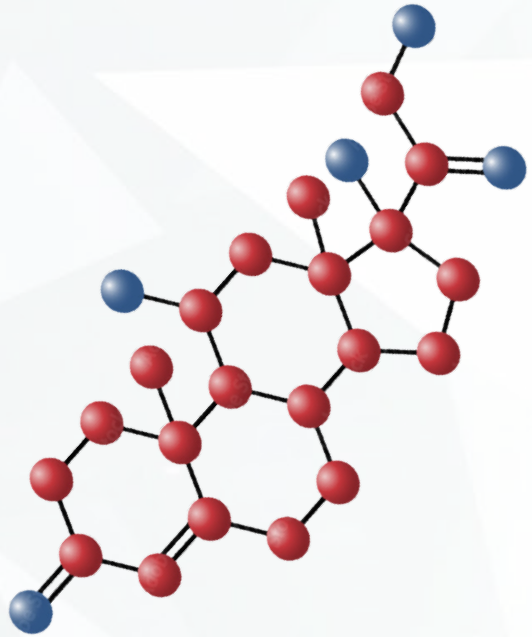
Oh, I have an adrenal mass, they found it 10 years ago

What!!!
Did they work it up?

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

ACTH and Hypercortisolism

- ACTH is usually undetectable in adrenal CS
- ACTH is usually (but not always) <15 mg/mL in MACS; DHEAS is usually low in both adrenal CS and MACS
- CT abdomen is the localization study of choice
  - If unilateral adrenal mass → unilateral adrenal hypercortisolism confirmed
  - If bilateral adrenal mass → usually bilateral adrenal hypercortisolism (though unilateral hypercortisolism is possible → adrenal vein sampling)
  - If no adrenal tumors → (very rare) → diagnosis is likely micronodular adrenal hyperplasia (always bilateral)



Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

Interprofessional Team Overview: What is the Role(s) of the Care Team?

Physicians: Endocrinologists work with primary care, internists, neurosurgeons, endocrine surgeons, radiologists, pathologists

- Screen, diagnose, determine and oversee treatment plans

Advanced Practice Providers: Nurse Practitioners, Physician Assistants

- Perform patient assessments, manage symptoms, provide follow-up care, and support treatment delivery in collaboration with physicians

Clinical Pharmacy Specialists:

- Optimize pharmacologic treatment plans, educate patients on medication use and side effects, and answer drug information questions

Nurses:

- Provide day-to-day care coordination, triage symptoms, administer treatments, and serve as key points of patient contact
- Educate patients and families about care plans and procedures

Social Workers:

- Address psychosocial needs, coordinate resources (transportation, financial support, counseling), and facilitate communication between patients, families, and the care team

Obtained Previous 10 Year 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)

Additional Work Up at Endocrinology Over 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
- Cortisol lowering therapy was initiated, labs monitored, HTN and Diabetes related medication reduction

Elevated Cortisol Intervention

- Discussed treatment with patient; effects and side effects
- Chose a start date that would work for patient
- Detailed review of current medication for any interactions
- Added spironolactone and 1-2 week standing order lab for potassium review
- Reviewed instructions for insulin reduction using CGM
- Filled out modified work duty if needed
- Scheduled 2 week follow up for review

Clinically, How It's Going

- 2 week follow up with lowest starting dose Mifepristone 300mg daily
  - No side effects with medication
  - Normal potassium
  - 10% reduction in Total Daily insulin 1% hypoglycemia on CGM
  - Increased Mifepristone to 600mg daily
- 1 month follow up
  - Side effects of muscle aching and swelling in one of her legs
    - Feeling aching and fatigued
  - Potassium at 3.2mmol/L replacement was started at 20 mEq and additional reduction in rapid acting insulin with meals but basal rate slightly increased to AM target less 100
- 3 month follow up
  - Doing well on 600mg Mifepristone, potassium normal, review of CGM and insulin dosing current GMI of 8.4% which is lowest A1c in 10 years
  - Increased Mifepristone to 900mg daily

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]

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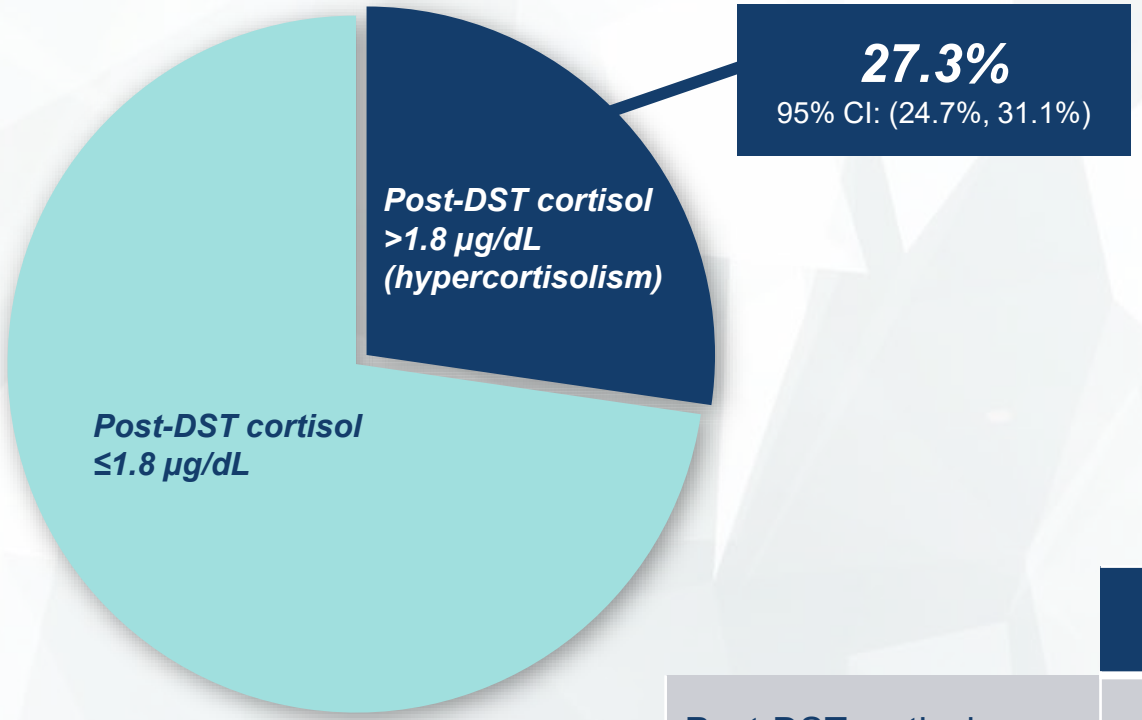
1. Valassi E, et al. *Endocr Connect*. 2022; 2. Page-Wilson G, et al. *Pituitary*. 2023; 3. Braun LT, et al. *J Clin Endocrinol Metab*. 2022; 4. Dekkers OM, et al. *J Clin Endocr Metab*. 2013; 5. Yorke E, et al. *Int J Endocrinol*. 2017.

New Data: Prevalence of Hypercortisolism in Resistant HTN



	Mean (SD)	Diagnostic Threshold for Hypercortisolism
Post-DST cortisol	4.2µg/dL (3.5 µg/dL)	≤1.8 µg/dL
Dexamethasone	484.2 ng/dL (336.8 ng/dL)	>140 ng/dL

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Bhatt DL, et al. *ACC*. 2026.