

# Hypercortisolism Is More Common Than You Think—Here’s How to Find It

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## KEY TAKEAWAYS

- Hypercortisolism as a diagnosis is often delayed or missed, leading to detrimental consequences for patients, including unnecessary morbidity and mortality.
- Current data 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 clinically inapparent to classically overt.
- Hypercortisolism occurs along a continuum associated with cardiometabolic risks that increase with disease severity and duration.
- Screening for hypercortisolism in primary care requires appropriate patient selection with a high pretest probability, use of a sensitive screening test, and interpretation of results within the clinical context of the patient’s medical history and presentation.

- A successful referral to endocrinology requires communicating the patient’s relevant medical history and clinical findings, reasons for suspecting hypercortisolism, and results of screening tests.

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## DISCLOSURES

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## UNDERSTANDING HYPERCORTISOLISM: SUMMARY FOR PRIMARY CARE

Endogenous hypercortisolism, also known as Cushing syndrome, is a multisystemic endocrine disorder characterized by prolonged excessive cortisol activity.<sup>1</sup> This condition often goes undiagnosed or is misdiagnosed, resulting in unnecessary progression of morbidity and increased cardiovascular-related mortality.<sup>2-5</sup> Here we discuss the prevalence, variable presentation, and detrimental clinical consequences of hypercortisolism, emphasizing the importance of early detection and appropriate referral.

## CLASSIFICATION OF HYPERCORTISOLISM

Hypercortisolism can be classified into 2 main categories<sup>1</sup>:

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

Cushing disease with a pituitary source is traditionally viewed as the most common etiology of hypercortisolism. However, as routine abdominal imaging becomes increasingly common in medical practice, the recognition and understanding of adrenal hypercortisolism have grown substantially. Advances in imaging technologies, such as computed tomography and magnetic resonance imaging, have led to the detection of more incidental adrenal tumors, up to 50% of which are associated with autonomous cortisol secretion.<sup>6</sup> These findings enhance the understanding of the disease and its prevalence, which is higher than previously thought.<sup>7</sup>

## A MULTISYSTEMIC, HETEROGENEOUS DISEASE

The understanding of the disease’s presentation has also evolved, recognizing hypercortisolism as a multisystemic and heterogeneous condition. The “index case” of Cushing disease, described by Harvey Cushing in 1912, exhibited a full range of overt features, such as a round face, central obesity, purple striae, and proximal muscle wasting.<sup>1,8</sup> However, contemporary understanding recognizes that

hypercortisolism presents with a broad spectrum of symptoms and comorbidities.<sup>9</sup> These include nonspecific features that overlap with disorders common in the general population, such as weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders.<sup>2,3,5</sup> Thus, it is crucial to adopt a personalized approach to diagnosis that considers the patient's comprehensive clinical picture.

### A CONTINUUM WITH DETRIMENTAL CONSEQUENCES AND DELAYED DIAGNOSIS

The wide spectrum of clinical signs and symptoms that may vary among patients can complicate diagnosis, leading to significant diagnostic delays of up to 10 years.<sup>10,11</sup> The consequences of delayed diagnosis can be detrimental, as prolonged exposure to elevated cortisol leads to an increased risk of cardiometabolic abnormalities (diabetes, hypertension, and cardiovascular disease), osteoporosis, and psychiatric disorders.<sup>2-5</sup> Mortality rates 2 to 5 times higher than the general population are reported in untreated hypercortisolism.<sup>12-14</sup> The detrimental impact of delayed diagnosis underscores the need for a heightened awareness and timely intervention in primary care settings.

Importantly, hypercortisolism should be viewed as a continuum, with increased cardiometabolic comorbidities and mortality across the spectrum.<sup>15</sup> Even cases less clinically apparent and lacking the classically described overt features are linked to increased cardiometabolic comorbidities and mortality.<sup>15</sup> Early detection and management are crucial to mitigate these risks.

### WHO TO SCREEN FOR HYPERCORTISOLISM

Although the incidence of hypercortisolism in the general population is low, recent data suggest that the prevalence is higher in the at-risk population with certain risk factors. The 2008 Endocrine Society Clinical Practice Guideline recommends screening patients who have multiple risk factors for hypercortisolism to increase the pretest probability of hypercortisolism and the positive predictive value of the screening.<sup>16</sup> If the pretest probability for hypercortisolism is high, further evaluation is recommended even in patients with normal test results.

The guideline recommends screening for hypercortisolism in the at-risk population, including patients with the following features<sup>16</sup>:

1. Patients with unusual features for their age, such as osteoporosis/fragility fracture, type 2 diabetes (T2D), or hypertension in young individuals
2. Patients with multiple and unexplained/progressive features, like worsening T2D outside

of the normal progression or unexplained recent weight gain

3. All patients with adrenal mass

Applying these screening criteria in a prospective hypercortisolism registry, up to a 50% prevalence of hypercortisolism was identified in the at-risk patient populations.<sup>2</sup> Additionally, the ongoing CATALYST study (NCT05772169) has shown that patients with difficult-to-control diabetes represent an at-risk population with a high pretest probability of hypercortisolism. CATALYST is the first prospective, multicenter, US-based, large study including >1000 patients with difficult-to-control T2D (glycated hemoglobin [HbA1c] 7.5%–11.5% despite receiving multiple therapies); the prevalence of hypercortisolism is 24% in this study.<sup>17,18</sup>

These findings confirm a higher-than-expected prevalence of hypercortisolism, especially in patients with specific risk factors (**TABLE**).<sup>6, 17, 19-26</sup> These patients constitute an at-risk population, in which screening for hypercortisolism is warranted.

### HOW TO SCREEN FOR HYPERCORTISOLISM

Three tests are commonly used to screen for evidence of hypercortisolism: the 1-mg overnight dexamethasone suppression test (DST), late-night salivary cortisol (LNSC), and 24-hour urine-free cortisol (UFC).<sup>16,27</sup> Each test has strengths and limitations.<sup>16</sup> However, the 1-mg overnight DST, using a post-DST serum cortisol cutoff of >1.8 µg/dL, is recommended as the most sensitive first-line screening method due to its high sensitivity (up to 95%).<sup>16</sup> Well-known causes of false-positive DST results should be excluded before diagnosing hypercortisolism. Specific medications and conditions to watch for are shown in **FIGURE 1**.<sup>8</sup> It is also important to ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST.<sup>16</sup> The 24-hour UFC and LNSC tests are less sensitive in patients with milder presentations, but an abnormally high result strongly supports a hypercortisolism diagnosis.<sup>8</sup>

When interpreting biochemical test results, clinicians must account for the clinical index of suspicion, especially in the context of patients' medical history and comorbidities. **FIGURE 1** illustrates how to perform the tests and interpret the results, with testing considerations for primary care.

### SUMMARY OF SCREENING IN PRIMARY CARE

Effective screening for hypercortisolism in primary care involves the following:

- **Appropriate patient selection:** Identifying patients with signs and symptoms suggestive of

**TABLE. At-risk patient population to screen for hypercortisolism**

Population	Prevalence of hypercortisolism	Examples of clinical presentation
Patients with adrenal incidentaloma	Up to 50% <sup>6</sup>	Patients with unsuspected tumors discovered in one or both of their adrenal glands
Patients with poorly controlled T2D	Up to 24% <sup>17, 19, 23-26</sup>	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% <sup>20</sup>	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% <sup>21,22</sup>	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.

hypercortisolism and selecting patients with a high pretest probability of hypercortisolism<sup>16</sup>

- **Sensitive screening tests:** Using a sensitive screening test such as the 1-mg overnight DST can help identify patients who need further investigation<sup>8,16</sup>
- **Clinical context:** Interpreting test results within the context of the patient's medical history and presentation is necessary<sup>8</sup>

### SUCCESSFUL REFERRAL TO ENDOCRINOLOGY

A successful referral to endocrinology hinges on clear communication with the endocrinologist. Primary care clinicians (PCCs) should include the following in the referral letter (**FIGURE 2**):

- The patient's relevant medical history and clinical findings
- Reasons for suspecting hypercortisolism, emphasizing the key factors contributing to high clinical suspicion

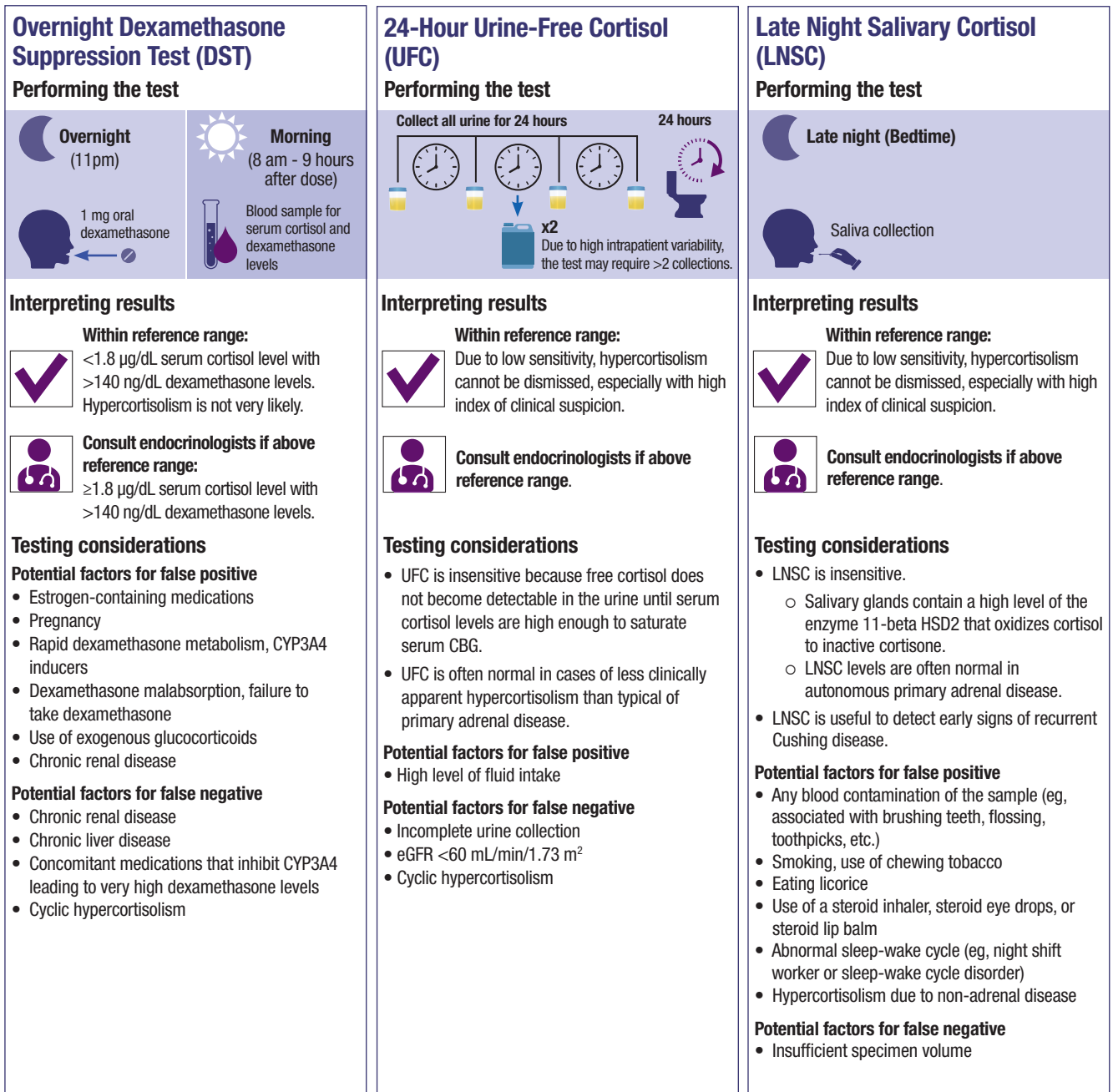
- Descriptions of the testing procedures and results of initial screening tests (including dexamethasone serum level for patients with 1-mg overnight DST)

By providing comprehensive and detailed referrals, PCCs can facilitate timely and effective specialist care, ultimately improving patient outcomes. **FIGURE 2** summarizes the process and considerations for screening, workup, and referral in primary care.

### CONCLUSION

Awareness and understanding of hypercortisolism are essential for PCCs. Recognizing the signs and symptoms, selecting patients with a high pretest probability, utilizing appropriate screening methods, and making informed referrals can significantly impact patient health by reducing the delay in diagnosis and preventing the severe complications associated with this condition.

**FIGURE 1. Screening tests for hypercortisolism: Process and considerations<sup>8</sup>**



**Abbreviations:** CBG, cortisol-binding globulin; CYP3A4, cytochrome P450 isoform 3A4; eGFR, estimated glomerular filtration rate; HSD2, hydroxysteroid dehydrogenase type 2.

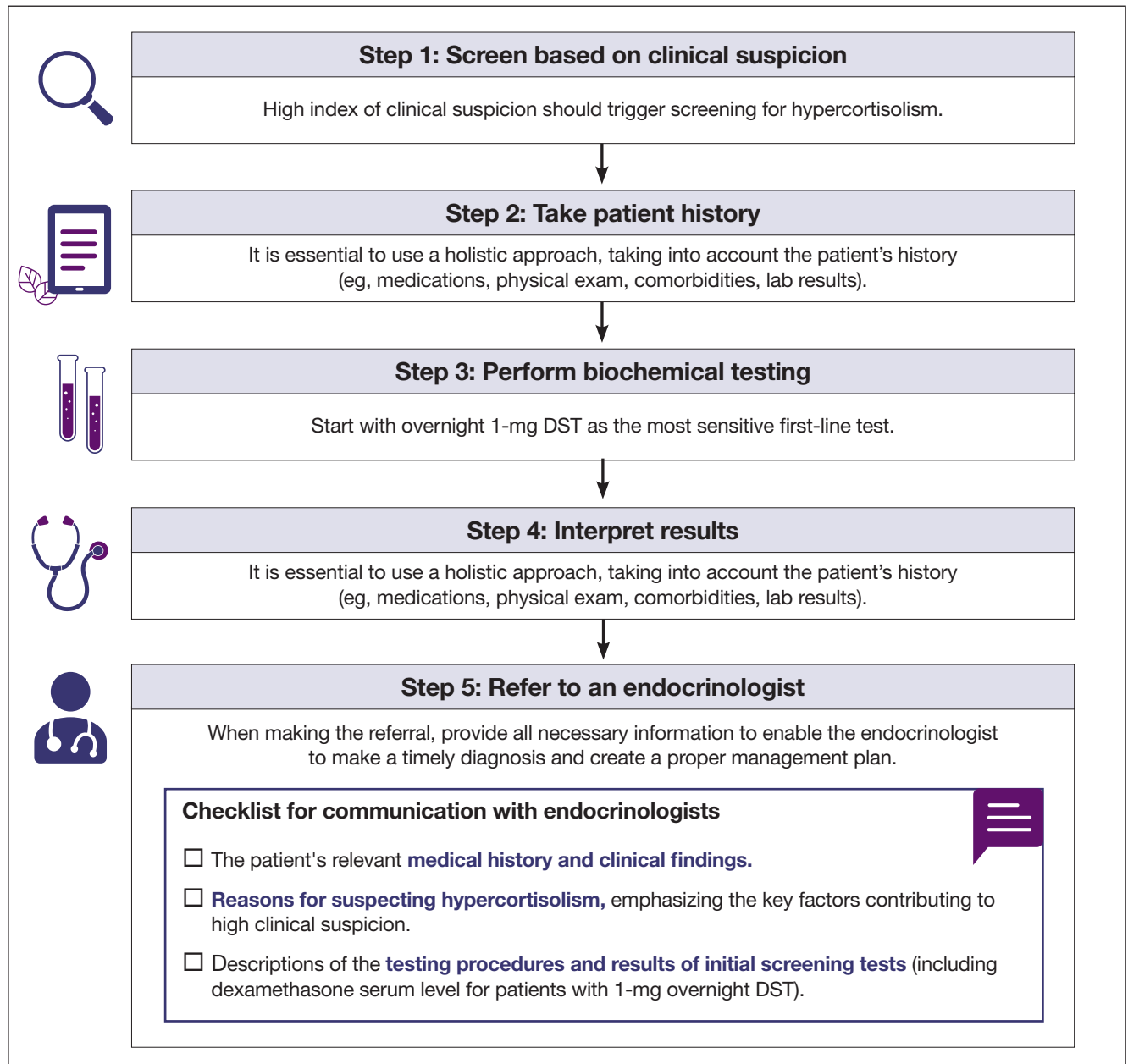
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**CASE STUDY**

A 68-year-old man presents with gradual abdominal weight gain over the past 4 years and finds it increasingly difficult to control his hypertension and T2D, especially postprandial blood glucose, despite adherence to multiple antihyperglycemic agents

and efforts to control his diet. He has a history of obesity (with recent, unexplained central weight gain), kidney stones, mixed hyperlipidemia, osteopenia (with a previous nontraumatic stress fracture), coronary artery disease, diabetic neuropathy, and peripheral polyneuropathy. He takes multiple blood pressure and

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



**Abbreviation:** DST, dexamethasone suppression test.

antihyperglycemic medications. The patient presents to his PCC, noting, "I am taking too many drugs—you are missing something. There has got to be a better way!"

#### Laboratory Evaluations

- Glycated hemoglobin (HbA1c): 7.8%
- Fasting glucose: 124 mg/dL
- 4-hour postprandial glucose: 240–295 mg/dL, despite dietary carbohydrate control
- Morning cortisol: 19 µg/dL (normal 10–25 µg/dL)<sup>28</sup>
- Post-1-mg DST serum cortisol: 3.5 µg/dL (normal range <1.8 µg/dL)<sup>16</sup>
- Post-1-mg DST serum dexamethasone: 412.7 ng/dL (expected range >140 ng/dL for adequate serum cortisol suppression)<sup>29</sup>
- 24-hour UFC: 38 µg/24 hr (normal range varies depending on specific test; example normal range <11–53 µg/24 hr)<sup>30</sup>

### Clinical assessment

The patient has several risk factors that increase the pretest probability of hypercortisolism and should trigger screening. These include difficult-to-control T2D with microvascular and macrovascular complications, postprandial hyperglycemia elevated out of proportion to fasting glucose and HbA1c levels, resistant hypertension, unexplained central weight gain, kidney stones, osteopenia, and fragility fracture. In the presence of these risk factors, the diagnosis of hypercortisolism, with careful exclusion of known causes leading to false-positive results, is confirmed with a 1-mg DST serum cortisol level >1.8 µg/dL and serum dexamethasone >140 ng/dL.

### Outcome

The patient was referred to an endocrinologist for further evaluation and confirmation of ACTH-independent autonomous adrenal hypercortisolism. Adrenal imaging confirmed a structural source of excess cortisol, and cortisol-directed therapy was provided. The patient experienced improvements in glucose control with an HbA1c reduction to 5.7%. In addition, this patient was able to discontinue 4 of his antihyperglycemic medications. Blood pressure control improved, even though 3 of 5 blood pressure medications were discontinued, and he lost 25 lbs.

### Clinical learning

This patient could have been considered a “typical” patient seen in the primary care setting. This case underscores the importance of a holistic approach, taking into account the patient’s medical history and comorbidities. This comprehensive assessment enabled effective screening and appropriate treatment, ultimately improving the patient’s outcomes. ●

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