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

Dr. Kushner is a paid consultant and a member of the advisory board and speakers bureau to Corcept Therapeutics. Dr. Brown serves as a consultant to Corcept Therapeutics and as a member of its advisory board and speakers bureau. Dr. Busch is a research consultant to Corcept Therapeutics and on the speakers bureau for Amgen, Astra Zeneca, Lilly, Novo Nordisk, and Sanofi. Austin Ulrich, PharmD, BCACP, has no disclosures to report.

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UNDERSTANDING HYPERCORTISOLISM: SUMMARY FOR PRIMARY CARE

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

CLASSIFICATION OF HYPERCORTISOLISM

Hypercortisolism can be classified into 2 main categories[1]:

- **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 1 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 associated with up to 50% of autonomous cortisol secretion.[6] These findings contribute to an understanding of the disease and its prevalence, which is higher than previously thought.[7]

A MULTISYSTEMIC, HETEROGENEOUS DISEASE

The understanding of the presentation of the disease has

evolved into the recognition of 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.[1,8] However, contemporary understanding recognizes that hypercortisolism presents with a broad spectrum of symptoms and comorbidities.[9] 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.[2,3,5] 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.[10,11] 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.[2–5] Mortality rates 2 to 5 times higher than the general population are reported in untreated hypercortisolism.[12–14] The detrimental impact of delayed diagnosis underscores the need for a heightened awareness and timely intervention in primary care settings.

Importantly, hypercortisolism should be considered a continuum, with increased cardiometabolic comorbidities and mortality across the spectrum.[15] Even cases less clinically apparent and lacking the classically described overt features are linked to increased cardiometabolic comorbidities and mortality.[15] 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 recognition of the pretest probability of hypercortisolism and the positive predictive value of the screen.[16] 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 (but not limited to)[16]:

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, the at-risk patient populations were identified with up to a 50% prevalence of hypercortisolism.[2] Additionally, the ongoing CATALYST study 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 antihyperglycemic medications); the prevalence of hypercortisolism is 24% in this study.[17,18]

These findings confirm a higher-than-expected prevalence of hypercortisolism, especially in patients with specific risk factors (**TABLE**).[6,19–26] 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).[16,27] Each test has strengths and limitations.[16] 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%).[16] 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**.[8] 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.[16] 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.[8]

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.

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 1 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, CVD, and PCOS
		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 treatmen
		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; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

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 hypercortisolism and selecting patients with a high pretest probability of hypercortisolism[16]
- ***Sensitive screening tests*:** Using a sensitive screening test such as the 1-mg overnight DST can help identify patients who need further investigation[8,16]
- ***Clinical context*:** Interpreting test results within the context of the patient's medical history and presentation is necessary to avoid false positives and negatives[8]

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.

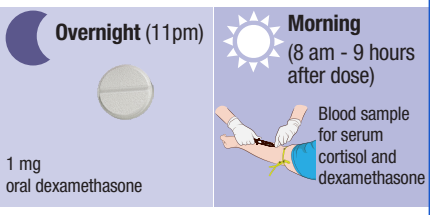
CONCLUSION

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

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.

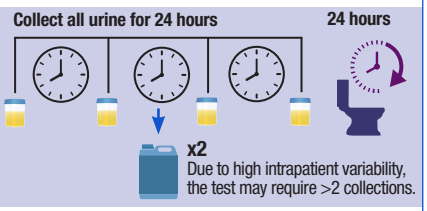
Testing Considerations

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

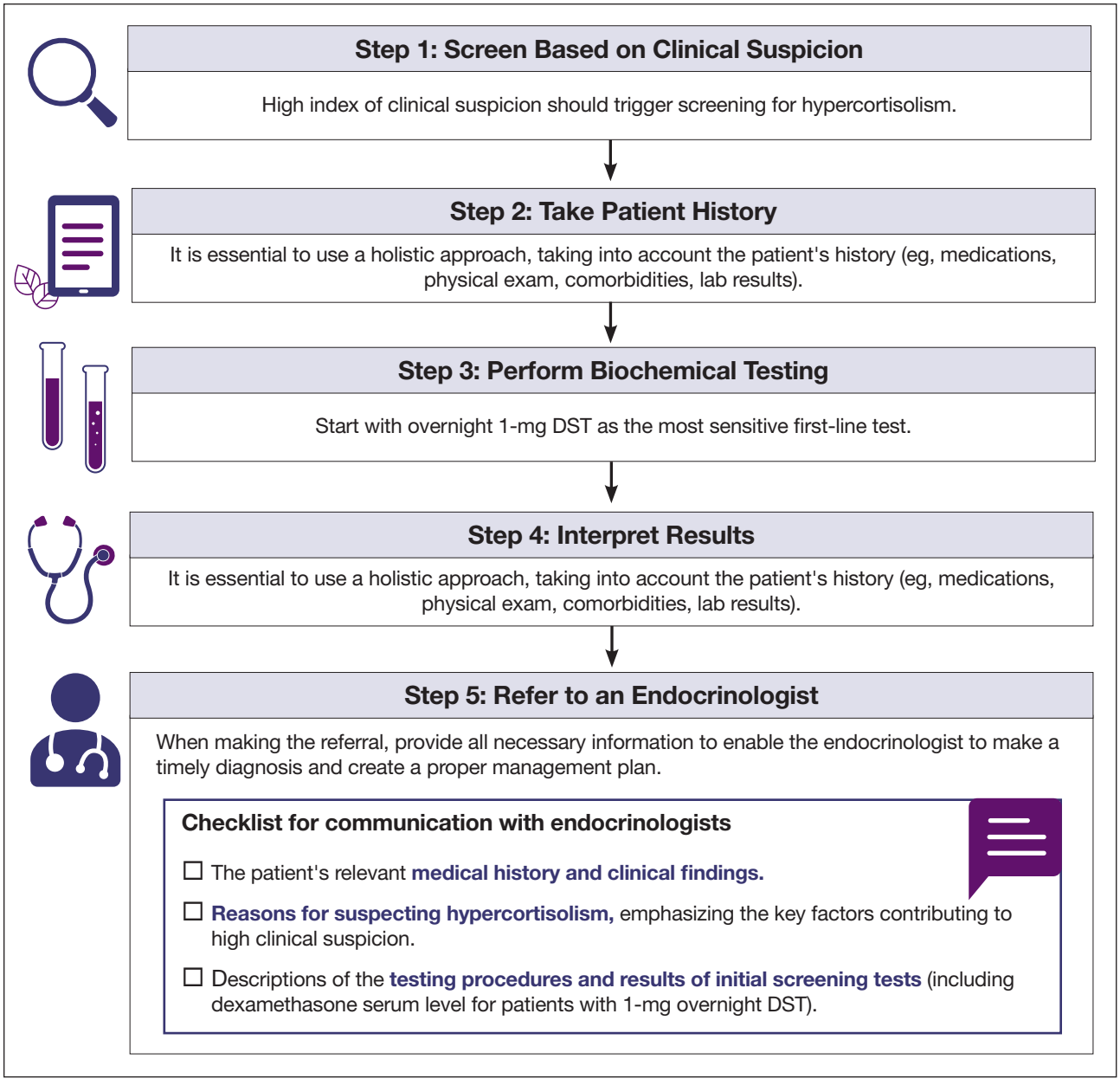
Abbreviations: CBG, cortisol-binding globulin; CYP3A4, cytochrome P450 isoform 3A4; eGFR, estimated glomerular filtration rate; HSD2, hydroxysteroid dehydrogenase type 2.

Source: Adapted from Scoffings K et al. Recognising and diagnosing Cushing's syndrome in primary care: challenging but not impossible. *Br J Gen Pract*. 2022;72(721):399-401.

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 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!"

FIGURE 2. Process and considerations for screening, workup, and referral for hypercortisolism in Primary Care



Abbreviation: DST, dexamethasone suppression test.

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)[28]
- Post–1-mg DST serum cortisol: 3.5 µg/dL (normal range <1.8 µg/dL)[16]
- Post–1-mg DST serum dexamethasone: 412.7 ng/dL (expected range >140 ng/dL for adequate serum cortisol suppression)[29]
- 24-hour UFC: 38 µg/24 hr (normal range varies depending on specific test; example normal range <11–53 µg/24 hr)[30]

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 pounds.

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. ●

REFERENCES

1. Reincke M, Fleseriu M. Cushing syndrome: a review. *JAMA*. 2023;330(2):170. doi:10.1001/jama.2023.11305
2. Braun LT, Vogel F, Zopp S, et al. Whom should we screen for Cushing syndrome? The Endocrine Society Practice Guideline Recommendations 2008 revisited. *J Clin Endocrinol Metabol*. 2022;107(9):e3723-e3730. doi:10.1210/clinem/dgac379
3. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O. Screening for Cushing syndrome at the primary care level: what every general practitioner must know. *Int J Endocrinol*. 2017;2017:1-6. doi:10.1155/2017/1547358
4. Limumpornpetch P, Morgan AW, Tiganescu A, et al. The effect of endogenous Cushing syndrome on all-cause and cause-specific mortality. *J Clin Endocrinol Metabol*. 2022;107(8):2377-2388. doi:10.1210/clinem/dgac265
5. Fallo F, Di Dalmazi G, Beuschlein F, et al. Diagnosis and management of hypertension in patients with Cushing's syndrome: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens*. 2022;40(11):2085-2101. doi:10.1097/HJH.0000000000003252
6. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2023;189(1):G1-G42. doi:10.1093/ejendo/lvad066
7. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. *Endocr Rev*. 2004;25(2):309–340. doi:10.1210/er.2002-0031
8. Scoffings K, Morris D, Pullen A, Temple S, Trigell A, Gurnell M. Recognising and diagnosing Cushing's syndrome in primary care: challenging but not impossible. *Br J Gen Pract*. 2022;72(721):399-401. doi:10.3399/bjgp22X720449
9. Kelsall A, Newell-Price J. Cushing's disease—from Minnie G to key issues in the early 21st century. *Lancet Diabetes Endocrinol*. 2019;7(12):959–964. doi:10.1016/S2213-8587(19)30343-2
10. Valassi E, Chiodini I, Feelders RA, et al. Unmet needs in Cushing's syndrome: the patients' perspective. *Endocr Connect*. 2022;11(7):e220027. doi:10.1530/EC-22-0027
11. Page-Wilson G, Oak B, Silber A, et al. Evaluating the burden of endogenous Cushing's syndrome using a web-based questionnaire and validated patient-reported outcome measures. *Pituitary*. 2023;26(4):364-374. doi:10.1007/s11102-023-01314-7
12. Lindholm J, Juul S, Jørgensen JOL, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metabol*. 2001;86(1):117-123. doi:10.1210/jcem.86.1.7093
13. Dekkers OM, Horváth-Puhó E, Jørgensen JOL, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metabol*. 2013;98(6):2277-2284. doi:10.1210/jc.2012-3582
14. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metabol*. 2011;96(3):632–642. doi:10.1210/jc.2010-1942
15. Araujo-Castro M, Pascual-Corrales E, Lamas C. Possible, probable, and certain hypercortisolism: a continuum in the risk of comorbidity. *Ann Endocrinol*. 2023;84(2):272-284. doi:10.1016/j.ando.2023.01.005
16. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. doi:10.1210/jc.2008-0125
17. Auchus R, DeFronzo R, Philis-Tsimikas A, Fonseca V, Buse J. Prevalence of hypercortisolism in difficult-to-control Type 2 Diabetes P at the 84th American Diabetes Association (ADA) Scientific Sessions, June 21-24, 2024, Orlando, FL
18. DeFronzo RA, Auchus RJ, Bancos I, et al. Study protocol for a prospective, multicentre study of hypercortisolism in patients with difficult-to-control type 2 diabetes (CATALYST): prevalence and treatment with mifepristone. *BMJ Open*. 2024;14(7):e081121. doi:10.1136/bmjopen-2023-081121
19. Costa DS, Conceição 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(6):1032-1038. doi:10.1016/j.jdiacomp.2016.05.006
20. Chiodini I, Mascia ML, Muscarella S, et al. Subclinical hypercortisolism among outpatients referred for osteoporosis. *Ann Intern Med*. 2007;147(8):541. doi:10.7326/0003-4819-147-8-200710160-00006
21. Trifanescu R, Carsote M, Caragheorgheopol A, et al. Screening for secondary endocrine hypertension in young patients. *Maedica (Bucur)*. 2013;8(2):108-115.
22. Martins LC, Conceição FL, Muxfeldt ES, Salles GF. Prevalence and associated factors of subclinical hypercortisolism in patients with resistant hypertension. *J Hypertens*. 2012;30(5):967-973. doi:10.1097/HJH.0b013e3283521484
23. 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(6):837-844. doi:10.1530/eje.1.02045
24. León-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, et al. A probabilistic model for Cushing's syndrome screening in at-risk populations: a prospective multicenter study. *J Clin Endocrinol Metabol*. 2016;101(10):3747–3754. doi:10.1210/jc.2016-1673
25. Catargi B, Rigalleau V, Poussin A, et al. Occult Cushing's syndrome in type-2 diabetes. *J Clin Endocrinol Metab*. 2003;88(12):5808-5813. doi:10.1210/jc.2003-030254
26. Van Hulsteijn LT, Pasquali R, Casanueva F, et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. *Eur J Endocrinol*. 2020;182(1):11-21. doi:10.1530/EJE-19-0666
27. Galm BP, Qiao N, Klibanski A, Biller BMK, Tritos NA. Accuracy of laboratory tests for the diagnosis of Cushing syndrome. *J Clin Endocrinol Metabol*. 2020;105(6):2081-2094. doi:10.1210/clinem/dgaa105
28. Goder N, Gerstenhaber F, Gal Oz A, et al. Cortisol levels during first admission day are associated with clinical outcomes in surgical critically ill patients. *Crit Care Explor*. 2024;6(5):e1086. doi:10.1097/CCE.0000000000001086
29. Farinelli DG, Oliveira KC, Hayashi LF, Kater CE. Overnight 1-mg dexamethasone suppression test for screening Cushing syndrome and mild autonomous cortisol secretion (MACS): what happens when serum dexamethasone is below cutoff? How frequent is it? *Endocr Pract*. 2023;29(12):986-993. doi:10.1016/j.eprac.2023.09.007
30. Petersenn S, Newell-Price J, Findling JW, et al. High variability in baseline urinary free cortisol values in patients with Cushing's disease. *Clin Endocrinol*. 2014;80(2):261-269. doi:10.1111/cen.12259