

Perspectives on Hypercortisolism Diagnosis and Management in Community and Academic Centers

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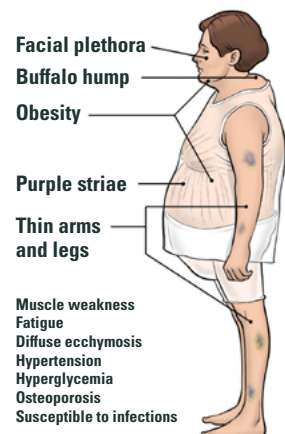
Summary

- The understanding of hypercortisolism has evolved significantly over the past decades to extend beyond classic physical manifestations (e.g., central obesity, facial plethora, buffalo hump, purple striae)
- Early identification of patients with mild autonomous cortisol secretion is important as hypercortisolism can lead to age-inappropriate and treatment-resistant metabolic syndrome
- Patient identification and management approaches for hypercortisolism can differ between academic and community settings due to differences in available resources and multidisciplinary management teams
- Educating primary care providers and community endocrinologists about the consequences of hypercortisolism and compiling a list of centers with expertise in hypercortisolism management to help patient referrals can be beneficial in bridging the gap between academic and community settings

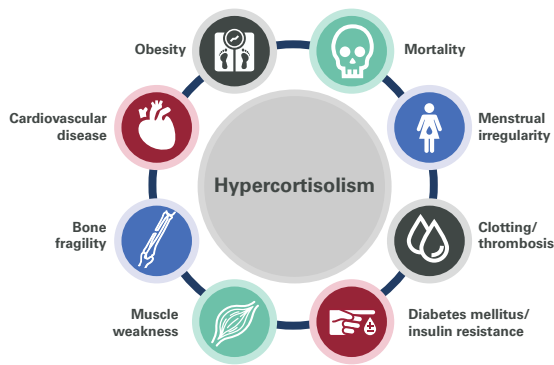
Evolution of Hypercortisolism

Lewis Blevins, MD: Our understanding of hypercortisolism has evolved drastically in the last century. Traditionally, patients with classic Cushing's Syndrome (CS) were thought to have a certain phenotype that included central obesity, facial plethora, buffalo hump, purple striae, and thin arms and legs.^{1,2} However, we now know that, depending on disease etiology, patients with hypercortisolism can present with a range of non-specific symptoms, such as obesity, cardiovascular disease, diabetes mellitus, bone fragility, and muscle weakness, with or without those traditional phenotypic features.³ **Thinking back to when you first learned about this disorder, how has your understanding of it changed over time? What does a typical patient with hypercortisolism look like in your clinic?** Being in an academic pituitary center, most of my patients present with overt CS, so they get a workup for hypercortisolism, and approximately 30% have a confirmed diagnosis for CS.

Classic CS^{1,2}



Hypercortisolism^{1,3}



Hypercortisolism Can Manifest as a Constellation of Symptoms, Making Diagnosis Difficult

Amir Hamrahian, MD: In my practice, hypercortisolism can come with a variety of different presentations, from very subtle to very severe. Some of my patients are worked up by a local endocrinologist before seeing me, whereas others are referred to me by a primary care provider following an adrenal incidentaloma in an abdominal computed tomography (CT). We have seen patients with extreme cyclic hypercortisolism, where they might have a low-normal urinary free cortisol one day and 20 times above the normal range the following week. So, I always listen to my patients and closely monitor them even if their cortisol level appears normal on the first workup.

Smita Kargutkar, MD: I am in a community practice and the majority of my patients present with hidden hypercortisolism, meaning they do not present with symptoms of classic CS, such as facial plethora, buffalo hump, and purple striae, and instead present with non-specific symptoms. I start to suspect hypercortisolism when a patient is struggling with obesity, uncontrolled diabetes, and hypertension despite lifestyle modifications, and they do not respond to medications. I have started working up these patients for hypercortisolism over the last few years.

David Brown, MD, PhD: Thinking back over the decades, when I was in medical school, it was a requirement to have the classic Cushingoid presentation to be able to diagnose a patient with hypercortisolism. It is fascinating to see how far we have come in recognizing the diverse presentation of this disease and the fact that a physical exam is not sufficient to diagnose hypercortisolism. Rather, the diagnosis is based on a constellation of symptoms, findings across multiple tissues and organs, and suspicious biochemistry. In my experience, since biochemical diagnosis tools are lagging in this field, many endocrinologists still rely heavily on the physical exam to diagnose a patient with hypercortisolism. Therefore, if the classic physical features are absent, the diagnosis is missed. As an outpatient solo practice endocrinologist, my approach is similar to Dr. Kargutkar's – I am always on the lookout for patients who are falling outside the normal expectations, such as patients who are too young to have severe, resistant hypertension, patients who are not responding to their diabetes treatment, and patients who are too young to have severe osteoporosis, especially vertebral osteoporosis – so I look for the outliers in the spectrum of pathologies that we know are associated with hypercortisolism.

Richard Auchus, MD, PhD: Being in an academic center, I see a wide variety of patients with hypercortisolism. Beyond

patients who have age-inappropriate treatment-resistant metabolic disorders, I pay close attention to patients with an adrenal incidentaloma over 2.5 cm – I tend to do biochemical follow-up for these patients before ruling out hypercortisolism.

Blevins: The difference in patient etiologies between academic and community centers is interesting. Only about 40% of my patients present with hidden hypercortisolism, whereas it sounds like most of the patients diagnosed in community practices present with hidden hypercortisolism.

It is also interesting that if you were to look at a patient

with an incidental pituitary adenoma and a patient with an incidental adrenal adenoma, the patient with adrenal adenoma is more likely to have hypercortisolism. **When you think about patients with pituitary vs adrenal origins for hypercortisolism, how does the patient presentation differ?**

Auchus: Patients with pituitary hypercortisolism tend to present with classic features, such as supraclavicular fat pads, skin thinning, easy bruising, as well as depression or sleep disturbance. On the other hand, patients with adrenal hypercortisolism tend to lack these classic features and instead have metabolic consequences, such as difficult-to-control hypertension/diabetes, age-inappropriate bone disorders, and inability to lose weight despite trying.

Brown: While I agree with Dr. Auchus, I think how long the patient has had the disease and the progression of their disease also play a role in how the patient presents. I once spot-diagnosed a patient as having hypercortisolism because he had all the classic phenotypical features. I assumed that he had a pituitary origin for his disease, but instead, he had an untreated adrenal adenoma for 3 to 4 decades. The truly remarkable thing about hypercortisolism is the variability of presentation from patient to patient.

Kargutkar: My patients do not follow a clear presentation depending on pituitary or adrenal origin for their disease. I have had patients with pituitary microadenoma and hypercortisolism who only have metabolic presentation and no classic features for CS, and I have also had patients with adrenal adenomas who have all the classic features of CS. I have also seen patients who present with morbid obesity and a classic phenotypic CS profile who do not have elevated cortisol levels. Perhaps being in a community practice, I am catching these patients early on, unlike in academic centers.

Blevins: Your varying experiences are noteworthy and they emphasize the need to screen more patients for hypercortisolism. When we look at emerging data on autonomous cortisol secretion in patients with adrenal incidentalomas, multiple studies in recent years have shown that 18% to 44% of patients with adrenal incidentalomas have post-dexamethasone suppression test (DST) levels between 1.8-5 µg/dL.⁴⁻⁹ Additionally, studies have shown that despite this high prevalence, less than 30% of patients with adrenal incidentalomas get a biochemical workup.¹⁰⁻¹² **What are your impressions of these emerging data? Have you changed your practice in any way as a result of these data?**

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– Dr. Blevins

Auchus: With less than 30% of patients with adrenal incidentalomas getting a biochemical workup, I think there is a certain level of lack of awareness in the field when it comes to screening patients for hypercortisolism in both community and academic centers. Until the physician has a firsthand experience with a patient who has had an adrenalectomy and has seen improvement in their metabolic disorder, most endocrinologists tend to dismiss these emerging data because screening these patients is quite complex in practice. There are no clear tests with black-and-white cutoff that indicates whether a patient has hypercortisolism or not.

“ ...there is a certain level of lack of awareness in the field when it comes to screening patients for hypercortisolism in both community and academic centers. ”
– Dr. Auchus

Brown: While I agree with this general trend, our practice has definitely evolved based on these data. Previously, patients with hypercortisolism were just observed, but after the trio of research came out in 2014 from Debono et al, Di Dalmazi et al, and Morelli et al, we realized that there is a significant cardiovascular risk associated with this disease,⁷⁻⁹ so wait and watch is no longer a valid approach – early intervention is crucial.

Identifying Patients With Hypercortisolism

Blevins: Catching these patients early and intervening in a timely manner is indeed crucial. **What are some of the clinical presentations that make you suspect hypercortisolism?** In my practice, for pituitary disease, I look for patients who are generally of normal weight, but gain a large amount of weight within a short period of time. I also look for the constellation of metabolic and other features that may be unified by a single diagnosis.

Brown: I look for patients who have advanced metabolic disease characteristics (e.g., hypertension, diabetes, bone disease) for their age that are treatment resistant. If a patient presents with even one of these significant comorbidities, I work them up.

Hamrahian: In my practice, any patient with adrenal incidentaloma gets a workup. During my exam, I pay special attention to the presence of skin manifestations, such as facial plethora, pathological striae, and skin bruising, in the absence of blood thinners. I request old pictures to look for any changes.

Kargutkar: I screen all patients who present with phenotypic features of hypercortisolism, patients with depression and anxiety, and patients with treatment-resistant metabolic syndrome (e.g., hypertension, diabetes, hypercholesterolemia).

Auchus: I think it is important to take a holistic approach when screening patients for hypercortisolism. If a patient has supraclavicular fat pads, but if they are proportionate to the fat on their belly, arms, and legs, that does not raise my suspicion; but when the obesity is disproportionate in the head and neck with thin arms and legs, I will screen them for hypercortisolism. So, you have to see how the symptoms fit together – if something does not fit, then you have to screen them for hypercortisolism.

Blevins: **Given the multisystemic presentation of this disease, how do you work with other specialties to identify these patients early on to prevent long-term comorbidities?**

Is there a difference between how community and academic centers evaluate these patients?

Hamrahian: Radiologists tend to focus on the features that may suggest underlying malignancy in their report without much reference to the importance of ruling out a functional tumor. Accordingly, we have been working with our radiology colleagues to include specific language in their reports to recommend a biochemical workup for patients with adrenal incidentalomas.

Blevins: Probably the biggest difference between community and academic practices is the existence of tumor boards in academia. A monthly meeting to go over films provides a nice opportunity for endocrinologists and radiologists to work together – something to consider for community practices. When thinking about the diagnosis of hypercortisolism, we know that it is often delayed in these patients, requiring them to see multiple physicians before being diagnosed. Part of the problem is relying on diagnostic tests that are not 100% specific or sensitive. **How do you use the DST, 24-hour urinary free cortisol (UFC), and late-night salivary cortisol (LNSC), in your practice?**

Brown: 24-hour UFC is a highly specific test for severe hypercortisolism, but its sensitivity is very poor for less severe hypercortisolism, so one must use it appropriately. DST is the most sensitive test for less severe hypercortisolism, so I often start the evaluation with the DST. But I am not confident about the traditional use of the 1.8 µg/dL cutoff for DST because that cutoff was largely validated in pituitary disease and not less severe forms of hypercortisolism.* So, if the patient has a DST cortisol of 1.5 or 1.6 µg/dL, hypercortisolism is not necessarily ruled out. Having said that, although sensitive, the DST is not very specific. Therefore, a clinical evaluation is essential for refining both the sensitivity and the specificity of the analysis. This is where the art of medicine comes into play, and we need to assess the patient holistically to confirm their diagnosis.

“ ...there is a significant cardiovascular risk associated with [hypercortisolism], so wait and watch is no longer a valid approach – early intervention is crucial. ”
– Dr. Brown

Auchus: For someone who is just starting to screen patients for hypercortisolism, I would advise them to start with a physical exam to gauge their index of suspicion. If the patient is referred for evaluation of an adrenal mass, I would follow with a DST. If the post-dexamethasone cortisol is >5 µg/dL, that confirms hypercortisolism; if the value is 2-5 µg/dL, I would suggest a follow-up with an endocrinologist; and if the value is <2 µg/dL, it's unlikely that they have hypercortisolism, but does not rule it out completely.* The next step would be to determine whether the hypercortisolism is ACTH-dependent or ACTH-independent. Inferior petrosal sinus sampling (IPSS) is the cornerstone test to determine whether ACTH-dependent hypercortisolism is of pituitary or ectopic origin.

Hamrahian: Among the screening tests for hypercortisolism, my least favorite test is the LNSC. It is easy to collect, and one may obtain multiple samples; however, the significant fluctuations in the levels can be confusing. I almost never send my patients for surgery based on elevated LNSC alone, unless I have additional abnormal DST or 24-hour UFC.

*Endocrine Society Clinical Practice Guidelines: serum cortisol >1.8 µg/dl after 1-mg DST is suggestive of CS.¹³

Patient Management in Community and Academic Settings

Blevins: The disease etiology, the patient's disease journey, and whether they have a new diagnosis or have had residual or recurrent disease after treatment all determine the management approach for patients with hypercortisolism. **What are some of the factors you consider when initiating a treatment for your patients with hypercortisolism?**

Hamrahian: If a patient has an adrenal etiology with an isolated tumor and multiple comorbidities, I prefer the surgical option. However, if the patient prefers not to undergo surgery, is not a good surgical candidate, or the surgery must be delayed due to other circumstances like the early months of the COVID-19 pandemic, I prefer medical management. In patients with bilateral disease, I may go after the larger tumor and then reassess or pursue medical therapy. For patients with less severe comorbidities, I generally do active surveillance or offer them a trial of medical treatment.

Auchus: Any time a patient is a good surgical candidate, we prefer to take out the adenoma. For ACTH-dependent tumors, if a patient is a poor surgical candidate from the consequences of hypercortisolism, we might treat medically pre-operatively for a short term to lower their surgical risk. Patients with ectopic tumors are tricky because they often present with very severe disease, and they also may have anything from an occult tumor to widely metastatic disease. So, I often try to temporize with medical management until I can find the tumor and/or get them ready for surgery. If I am not able to cure their tumor, I often have their adrenals taken out at some point because the medical therapy for hypercortisolism will often interfere with their chemotherapy regimens down the line anyway.

Brown: My approach depends on how big the adenoma is and the patient's age. This is because the prevalence of nonfunctional adenoma increases with age. If I have a 40-year-old patient with a 3-cm adenoma, I would recommend surgical removal; however, if I have a 65-year-old patient with a 1.5- to 2-cm adenoma, I cannot be sure that removing the tumor will resolve the hypercortisolism, so I consider adrenal vein sampling (AVS) to determine whether they have unilateral or bilateral hypercortisolism before I can make a recommendation for therapy. Unfortunately, AVS is not yet well standardized or widely available for the evaluation of hypercortisolism. Also, it is an invasive procedure that is declined by many patients. For these reasons, medical therapy is an attractive option for treating an older patient with a small adenoma.

Blevins: Managing patients with hypercortisolism can be challenging as they present with multisystemic comorbidities.

Being in an academic center, I have the privilege to work with other endocrinologists, radiologists, cardiologists, and other specialists to manage different aspects of the patient's disease. **How does multidisciplinary management look like for you?**

Auchus: We have a tumor board that allows us to work closely with radiologists to identify patients that need further workup. I previously started a pituitary conference where community doctors can present their cases, which allows us to determine which patients may need a surgery in collaboration with our neurosurgeon. These types of activities that bring academic and community doctors together can be beneficial for patient identification and management.

Kargutkar: Being in a community setting, I manage everything myself – diabetes, blood pressure, cholesterol, osteoporosis, hyperthyroidism. I mainly work with cardiologists to get the surgical clearance, neurosurgeons for pituitary microadenoma, and endocrine surgeons for adrenal adenoma.

Bridging the Gap Between Community and Academic Centers

Blevins: There are some striking differences in patient management between academic and community settings. **What can we do to bridge the gap between academic and community practices?** I think educational opportunities are bound to help bridge the gap. Academicians could be invited to give Grand Rounds at regional medical centers. Speakers in academic institutions can rarely speak at dinner programs, which is unfortunate as this used to be one of the best venues for academia and private practices to mingle.

Kargutkar: Creating more awareness about hypercortisolism among primary care providers and community endocrinologists through webinars or CME lectures can be helpful. Also, creating a list of tertiary centers to which doctors can refer patients with suspected hypercortisolism can help more patients get the care they need.

Brown: I agree with Dr. Kargutkar. Compiling a list of centers with expertise in managing hypercortisolism, including IPSS, transsphenoidal surgery, selective AVS, laparoscopic adrenalectomy, and medical therapy, can be helpful. This list can then be made available on a website and publicized through multiple journals and national meetings.

Blevins: Thank you all for sharing your valuable insights on identifying and managing patients with hypercortisolism, and how patient management differs between academic and community settings. There is still much to do to ensure that these patients get the appropriate and timely care they deserve, but today's discussion is a step in the right direction.

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