The Hypothalamic−Pituitary−Adrenal Axis

A Complex Set of Feedback Influences*

- Hypothalamus releases CRH, which stimulates the pituitary gland
- Release of CRH is influenced by
  - Significant stressor
  - Physical activity
  - Sleep/wake cycle
  - Cortisol levels

*Graphical representation. 
The Hypothalamic–Pituitary–Adrenal Axis

A Complex Set of Feedback Influences*

- Pituitary gland subsequently secretes ACTH, resulting in the activation of the adrenal glands
- Adrenal glands respond by releasing cortisol into the bloodstream

*Graphical representation.


The Hypothalamic–Pituitary–Adrenal Axis

A Complex Set of Feedback Influences*

- When there is an adequate amount of cortisol, the hypothalamus and pituitary reduce the amount of CRH and ACTH, respectively (negative feedback)

*Graphical representation.


The Hypothalamic–Pituitary–Adrenal Axis

A Complex Set of Feedback Influences*

- Controls reactions to physical or psychosocial stress
- Regulates many processes, including
  - Carbohydrate metabolism
  - Immune response
  - Blood pressure

*Graphical representation.


Cortisol Secretion

Diurnal Variation

- In healthy, day-working people, cortisol is at its highest level between 6:00 AM and 8:00 AM, tapering off during the day, and reaching its trough toward midnight.\(^1\)

Healthy patients have a cyclic cortisol trough at night.\(^2\)

High

Normal

Low

Hormone Levels

CRH

ACTH

Cortisol

Serum Cortisol Levels

Normal diurnal rhythm

12am

12pm

8am

8pm

4am

4pm

Clinical Impact of Excess Cortisol

Excess Cortisol Causes Multisystemic Dysfunction

Insomnia/Concentration difficulties/Psychiatric/mood disturbances\(^1,2\)

Recurrent infection\(^2\)

Hypertension/Dyslipidemia\(^1\)

Obesity\(^1\)

Muscle weakness/strophi\(^1\)

Osteoporosis/Vertebral fracture\(^1,2\)

Dermatologic manifestations\(^2\)

Gonadal dysfunction/Menstrual irregularity\(^2\)

Clotting/Thrombosis\(^3\)

No single sign or symptom is pathognomonic of hypercortisolism.\(^1\)

Physiologic Impact of Excess Cortisol

**Blood Glucose and Insulin Resistance**

<table>
<thead>
<tr>
<th>Target Organ(s)</th>
<th>Clinical Consequence(s) of Excess Cortisol Secretion</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas, liver, adipose tissue, muscle</td>
<td>Diabetes</td>
<td>Increased glucose production</td>
</tr>
<tr>
<td></td>
<td>Glucose intolerance</td>
<td>Muscle: ( \Delta ) glucose uptake and storage (glycogen)</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
<td>Adipose tissue: ( \Delta ) lipolysis/fat redistribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreas: ( \Delta ) beta-cell function, leading to a decrease in insulin production</td>
</tr>
</tbody>
</table>

Excess cortisol promotes insulin resistance

Disrupts insulin receptor signaling

**Hypertension**

<table>
<thead>
<tr>
<th>Target Organ(s)</th>
<th>Clinical Consequence(s) of Excess Cortisol Secretion</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessels</td>
<td>Hypertension</td>
<td>Increases plasma volume, peripheral vascular resistance, and cardiac output</td>
</tr>
<tr>
<td></td>
<td>CV disease</td>
<td>Promotes endothelial dysfunction</td>
</tr>
</tbody>
</table>

Excess cortisol promotes resistant hypertension

**Osteoporosis**

<table>
<thead>
<tr>
<th>Target Organ(s)</th>
<th>Clinical Consequence(s) of Excess Cortisol Secretion</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Osteoporosis, fractures</td>
<td>Impacts bone formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases bone resorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits calcium absorption from the gut</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alters other factors impacting bone growth (e.g., gonadotropins, growth hormones, cytokines, growth factors)</td>
</tr>
</tbody>
</table>

Excess cortisol promotes bone loss

- Impacts BMD
- Impacts bone architecture and remodeling, which affects bone strength
Impact of Excess Cortisol

**Summary**

- Excess cortisol causes multisystemic dysfunction\(^1\)\(^3\)
- No single clinical sign or symptom defines hypercortisolism\(^1\)
- Notably, excess cortisol has profound impacts on
  - Glucose metabolism\(^4\)\(^5\)
  - CV disease\(^5\)\(^7\)
  - Structural tissue catabolism\(^8\)\(^9\)

**Evolution of Hypercortisolism**

**Introduction**

- HC is associated with high morbidity and mortality\(^1\)\(^2\)
- HC manifests as a spectrum of signs and symptoms (from mild to severe)\(^3\)
- Even mild HC has consequences\(^4\)\(^5\)
Mortality Associated With Hypercortisolism

**Cushing Syndrome**
- Historically, untreated Cushing syndrome is associated with ~50% mortality at 5 years

![Survival Graph](image)
- Survival rates: 53% for remission (R), 47% for no remission (NR)

**Cushing Disease**
- Patients in remission experienced reduced mortality compared to those with no remission

![Survival Graph](image)
- Survival rates: lower for NR compared to R

**Increased All-Cause Mortality in Patients With Mild Hypercortisolism**

*15-year, retrospective, single-center study; 198 consecutive patients with adrenal adenoma.

![Survival Rates](image)
- Survival rates for all-cause mortality:
  - Nonsecreting adrenal nodule: 100%
  - Mild hypercortisolism: 75%
  - Plasma cortisol level after 1-mg DST:
    - <1.8 μg/dL: 87.0%
    - 1.8 μg/dL-5.0 μg/dL or >5.0 μg/dL: 91.2%

Even when clinical signs of overt hypercortisolism are not present, patients with adrenal adenomas and mild hypercortisolism have an increased risk of CV events and mortality

**Studies Demonstrate Increased CV Disease Risk in Patients With Hypercortisolism**

*Retrospective, multicenter study; 206 patients with adrenal adenoma and no overt signs of hypercortisolism.
†Increase in ≥2 parameters: body weight, BP, glycemia, and/or low-density lipoprotein cholesterol.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent CV event</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident CV event</td>
<td>2.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Worsening metabolic profile†</td>
<td>3.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

In patients with an adrenal adenoma ≥2.4 cm, clinical and biochemical follow-up is required due to the potential development of mild hypercortisolism and its related consequences
Increased CV Mortality Associated With Disrupted Diurnal Rhythm


Hazard Ratios for All-Cause and CV-Related Mortality

<table>
<thead>
<tr>
<th>All-Cause Mortality</th>
<th>CV Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope across the day</td>
<td>1.30 (1.09-1.55)</td>
</tr>
<tr>
<td>Bedtime cortisol</td>
<td>1.33 (1.11-1.59)</td>
</tr>
</tbody>
</table>

*Prospective cohort study (N=907) subjects collected salivary cortisol samples daily at waking, 20 minutes to 2.5 hours after waking, and at bedtime.

Increased CV mortality associated with disrupted diurnal rhythm:
- Higher nighttime cortisol levels
- Less-steep cortisol decline during the day

Increased Risk for Composite Diabetes in Patients With Mild Hypercortisolism


- Patients with NFATs had significantly higher risk for incident composite diabetes than those without adrenal tumors (adjusted risk ratio was 1.87)

This suggests that even "nonfunctional" tumors are associated with hormonal dysregulation

Mild Hypercortisolism Is Common

Chiodini I. J Clin Endocrinol Metab. 2011;96(5):1223-1236.

0.2%-2.0% Estimated Prevalence of Mild Autonomous Cortisol Secretion in the Adult Population

- Percentage of imaged adults found to have an incidental adrenal nodule
- Percentage of incidental adrenal nodules estimated to be cortisol-secreting
Evolution of Hypercortisolism

**Summary**

- CS is associated with significant morbidity and mortality.\(^1\)\(^2\)
- Even when clinical signs of overt hypercortisolism are not present, patients with adrenal adenomas and mild hypercortisolism have an increased risk of CV events and mortality.\(^3\)
- Even “nonfunctional” adrenal tumors are associated with hormonal dysregulation.\(^4\)
- The degree of hypercortisolism by itself does not seem to be a sufficiently exhaustive parameter to assess the severity of active CS.\(^5\)
- Mild hypercortisolism is common.\(^6\)

---

**Epidemiology, Screening, and Diagnostic Tests**

**How Common Is Endogenous Cushing Syndrome?**

- Overt CS affects an estimated 10-15 people per million each year.\(^1\)
  - \(\approx\)20,000 patients in the United States.\(^2\)
  - Affects women more commonly than men (3:1 ratio).\(^3\)
  - Peaks in 3rd or 4th decade of life.\(^4\)
- Mild hypercortisolism is more common than overt hypercortisolism.\(^5\)
  - Estimated prevalence of about 0.8 per 1000 people in the general population.\(^6\)

- This prevalence is probably underreported because of the lack of symptoms or signs in these patients.\(^6\)
- Mild CS may be present in a large proportion of cases of adrenal adenomas.\(^6\)
Etiology of “Classic” Cushing Syndrome

- Pituitary source (Cushing disease)
- Ectopic source
- Adrenal source

Not Every Patient With Hypercortisolism Presents With the Classic Features of Cushing Syndrome

<table>
<thead>
<tr>
<th>More Specific Signs</th>
<th>Common Signs</th>
<th>Specific Symptoms</th>
<th>Common Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen c/ht et al.</td>
<td>- Acne</td>
<td>- None</td>
<td>- Depression</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>- Peripheral edema</td>
<td>- Fatigue</td>
<td></td>
</tr>
<tr>
<td>Proximal myopathy</td>
<td>- Muscle weakness</td>
<td>- Weight gain</td>
<td></td>
</tr>
<tr>
<td>Easy bruising</td>
<td>- Truncal obesity</td>
<td>- Back pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Supraclavicular fullness</td>
<td>- Irritability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dorsocervical &quot;buffalo&quot; hump</td>
<td>- Decreased libido</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- None</td>
<td>- Menstrual abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Spectrum of Hypercortisolism

Screening Considerations for Hypercortisolism

- Mild hypercortisolism prevalence in patients with diabetes, hypertension, obesity, and osteoporosis may reach 10.8%¹

Patient Populations to Be Screened for Hypercortisolism*

**Recommended**
- Patients with multiple signs and symptoms compatible with classic CS¹
- All patients with adrenal adenoma¹/²
- Patients with pituitary adenoma in the presence of other features suggesting hypercortisolism³

**Suggested**
- Patients with diabetes <50 years of age (poorly controlled)⁴
- Patients with hypertension <50 years of age (poorly controlled)⁴
- Patients with low BMD vs matched controls, BMD that rapidly declines, or fragility fractures⁵
- Patients with suspected polycystic ovary syndrome⁷

*Use clinical judgment based on overall clinical presentation.

Screening Model for Cushing Syndrome in At-Risk Populations

- Observational, prospective, multicenter study
- Develop/validate scoring system to predict CS based on clinical signs and LNSC
- Cutoff score of 4
  - 83% subjects without CS correctly identified
  - Only 1 case of CS missed


Total Number of Subjects and Prevalence of CS Per Score Category Using the Scoring System Obtained From the Combined Clinical and LNSC Model

<table>
<thead>
<tr>
<th>Score</th>
<th>CS</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>199</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>68</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>327</td>
<td>26</td>
<td>353</td>
</tr>
</tbody>
</table>

Independent Diagnostic Indicators and Risk Score for CS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>4</td>
</tr>
<tr>
<td>Dorsocervical fat pad</td>
<td>2</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>3</td>
</tr>
<tr>
<td>LNSC</td>
<td></td>
</tr>
<tr>
<td>- Medium, 9.17 nmol/L-13.93 nmol/L</td>
<td>4</td>
</tr>
<tr>
<td>- High, ≥13.93 nmol/L</td>
<td>5</td>
</tr>
</tbody>
</table>

Testing for Hypercortisolism

UFC

- Measures excretion of circulating unbound cortisol in the urine across 24 hours

This test measures the gross overproduction of cortisol across a period of time

<table>
<thead>
<tr>
<th>What is Collected</th>
<th>How</th>
<th>CS Diagnosis Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>At-home collection – 24 hr</td>
<td>Assay-dependent</td>
</tr>
</tbody>
</table>

*May need up to 3 collections due to variability of cortisol secretion and inaccurate collections. Urine needs to be refrigerated.

Discard first morning void to collect sample with empty bladder.


Frequent False-Positive Results May Occur

- Patients with cyclical hypercortisolism (if collected when disease is inactive)
- Patients with poor control of diabetes, severe obesity, psychiatric disorders, polycystic ovary syndrome, alcoholism, or pregnancy

Frequent False-Negative Results May Occur

- Patients with extreemest ACTH elevation
- Patients with glucocorticoids
UFC Test Is Insensitive

The degree of hypercortisolism by itself does not seem to be a sufficiently exhaustive parameter to assess the severity of active CS

- Retrospective analysis (2000-2013)
- 192 patients with confirmed CS distributed into 3 groups based on mean UFC levels
  - Mild hypercortisolism (UFC ≤2x ULN): 19.2%
  - Moderate hypercortisolism (2x ULN < UFC <5x ULN): 59.8%
  - Severe hypercortisolism (UFC ≥5x ULN): 20.8%
- No significant correlations were found between the degree of hypercortisolism (as measured by UFC) and the severity of comorbidities and/or biochemical parameters

ULN, upper limit of normal.

Testing for Hypercortisolism

LNSC

- Measures the free cortisol in the saliva at a time point when cortisol should be at its lowest level

This test detects the loss of diurnal rhythm

<table>
<thead>
<tr>
<th>What is Collected</th>
<th>How</th>
<th>CS Diagnostic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>At-home collection 11:00 PM – midnight Assay-dependent</td>
<td></td>
</tr>
</tbody>
</table>

LNSC, late-night salivary cortisol.


Testing for Hypercortisolism (cont’d)

False-Negative Results May Occur

- Patients with cyclical hypercortisolism (if collected when disease is inactive)

False-Positive Results May Occur

- Patients experiencing stress during time of the test collection
- Sample contaminated with blood (eg, flossing teeth before test)
- If patients smoke, chew tobacco, or eat licorice the day of the test
- If patients use steroid inhaler or topical steroids
- If patients have blunted circadian rhythm*

“LNSC seems to be the best early predictor of [Cushing disease] recurrence…”
—AACE/ACE Disease State Clinical Review

*eg, shift workers or critically ill.
AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology.
Testing for Hypercortisolism

Overnight DST

This test detects autonomous cortisol secretion

- Dynamic test that assesses the HPA axis responsiveness to glucocorticoids
- False-positive results can be seen after administration of dexamethasone in patients
  - Taking medications that induce CYP3A4
  - On oral contraceptives
- False-negatives can be seen in critically ill or nephrotic patients

What Is Collected

<table>
<thead>
<tr>
<th>Time</th>
<th>Test Description</th>
<th>Diagnosis Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>At home:</td>
<td>1 mg dexamethasone between 11:00 PM and midnight</td>
<td>&gt;1.8 μg/dL</td>
</tr>
<tr>
<td>Blood</td>
<td>Next day healthcare practitioner blood draw between 8:00 AM and 9:00 AM</td>
<td></td>
</tr>
</tbody>
</table>

Overnight DST* (cont’d)

*Graphical representation.

Testing for Hypercortisolism

Overnight DST Is Considered the Most Valuable Test to Screen for Mild Cushing Syndrome

“We suggest use of the 1-mg DST or LNSC test, rather than UFC, in patients suspected of having mild Cushing syndrome.”
—Endocrine Society

“Patients are screened for [mild Cushing syndrome] with a 1-mg overnight DST.”
—AACE/AAES

“Given our objective of using tests with high sensitivity…we recommend use of the more stringent cutoff of 1.8 μg/dL.”
—Endocrine Society

Testing for Hypercortisolism

Overnight DST

Normal Response
- Decrease in cortisol levels
- Decrease in ACTH levels

CS
- Adrenal:
  - No decrease in cortisol levels
  - Low ACTH levels
- Ectopic tumor:
  - No decrease in cortisol levels
  - High ACTH levels
- Cushing disease:
  - No decrease in blood cortisol levels
  - High ACTH levels


Testing for Hypercortisolism

Summary

• UFC measures the gross overproduction of cortisol across a period of time, and is not an ideal test to detect mild hypercortisolism.

• LNSC measures the free cortisol in the saliva at a time point when cortisol should be at its lowest level, detecting the loss of diurnal rhythm.
  – LNSC seems to be the best early predictor of Cushing disease recurrence.

• The overnight DST is a dynamic test that assesses the HPA axis responsiveness to glucocorticoids, detecting autonomous cortisol secretion.
  – Recommended for patients with mild hypercortisolism.

Adrenal Adenomas

Cushing Syndrome: Adrenal Source

Secretion Patterns

• Patients with adrenal CS do not get a cortisol break at night.
  – May not have high peak cortisol levels.
  – Mild overexposure may be more harmful than previously thought.
Cushing Syndrome: Adrenal Source

Hormone Alterations*
- Cortisol is secreted independently of ACTH stimulation; therefore, production is outside of the control of normal HPA axis function
  - Bilateral adrenocortical hyperplasia
  - Adrenocortical tumors
- Secretion of cortisol will lower concentration of ACTH

*Graphical representation.

Test for Hypercortisolism
Overnight DST* (cont’d)

Normal Response
- Decrease in cortisol levels
- Decrease in ACTH levels

CS
- No decrease in cortisol levels
- Low ACTH levels

Ectopic tumor
- No decrease in cortisol levels
- High ACTH levels

Cushing disease
- No decrease in blood cortisol levels
- High ACTH levels


Cushing Syndrome: Adrenal Source

General Approach to Adrenal Adenoma

Rule out malignancy

Characterize biochemically

Assess for autonomous cortisol secretion

Other tests

Useful in rounding out the clinical picture

- ACTH: may be subnormal
- DHEA-S: may be subnormal
- Concurrent metabolic and cardiorenal derangements
  - 1 mg overnight DST: >1.8 μg/dL (50 nmol/L)
- Concurrent medical conditions
- 1 level of suspicion

*Graphical representation.
Asymptomatic Patients With Adrenal Adenomas May Be at Risk for Mild Cushing Syndrome

- Mild CS may appear after 5 years of follow-up in some patients\(^1,2\)
- Annual screening for ≥5 years is recommended for
  - Patients with adrenal adenoma ≥2.4 cm\(^1\)
  - Patients with adrenal adenomas treated conservatively with possible mild CS\(^2\)
- Patients should be reevaluated if there is any change in their medical status\(^1\)

Use the overnight DST\(^1\)
If DST is ≥1.8 μg/dL, reassess LNSC and ACTH levels\(^1\)

Cushing Syndrome: Adrenal Source

**Treatment Options**

**Adrenalectomy**
- Evidence best established in moderate-to-severe CS\(^1\)
- Long-term prospective data vs medical therapy unavailable in mild CS\(^1\)

**Medical Therapies**
- Noninvasive
  - Can be stopped if not tolerated or no improvement seen
  - May reduce threshold for initiating treatment

**Active Surveillance**
- No significant metabolic changes\(^3\)
  - At least annual monitoring recommended\(^1\)

---

**Cushing Syndrome: Adrenal Source**

**Adrenalectomy Considerations**

**Benefits**
- Immediate resolution of hypercortisolism\(^1\)
- Improvement in many manifestations of disease in ~67% of patients\(^1,2\)
  - Metabolic (BP, weight, diabetes control)
  - Physical signs

**Concerns**
- Lifelong hormone replacement therapy may be needed
- Irreversible
- Significant lifestyle changes
- Potential long-term complications

---

Pituitary Adenoma

Cushing disease

Cushing Syndrome: Pituitary Source

**Secretion Patterns**

- Patients with Cushing disease generally have high cortisol and ACTH levels, and loss of diurnal rhythm\(^1\)

**Serum Cortisol Levels**

- Normal diurnal rhythm\(^2\)
- Cushing disease\(^1\)


**Hormone Alterations\(^*\)**

- Known as Cushing disease
- Secretion of ACTH by a pituitary tumor stimulates the adrenal glands to constantly secrete excess cortisol
- Tumor does not require CRH to stimulate ACTH secretion, and is not responsive to negative feedback
- This leads to unchecked ACTH secretion

Testing for Hypercortisolism

Overnight DST (cont’d)

Dexamethasone

Hypothalamus

Pituitary Gland

Adrenal Gland

Kidney

- Decrease in cortisol levels
- Decrease in ACTH levels

CS

Adrenal:
- No decrease in cortisol levels
- Low ACTH levels

Ectopic tumor:
- No decrease in cortisol levels
- High ACTH levels

Cushing disease:
- No decrease in blood cortisol levels
- High ACTH levels


Cushing Syndrome: Pituitary Source

Treatment Options: Surgery

- First-line treatment for those eligible for surgery¹
- Surgery may not be successful, nor its impact sustained²,³

TSS, transsphenoidal surgery.


TSS Failures in Patients With Cushing Disease¹

Recurrence Rates Increase Across Time²

<table>
<thead>
<tr>
<th>Postsurgical Failures</th>
<th>5 Years</th>
<th>5-13 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSS Failure Rates (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26%</td>
<td>46%</td>
<td></td>
</tr>
</tbody>
</table>

Cushing Syndrome: Pituitary Source

Additional Treatment Options

Radiotherapy

- Effective in controlling excess cortisol in up to 86% of patients⁴
- Prevents tumor regrowth in approximately 90%-100% of patients⁴
- Concerns:
  - Takes a long time to work¹
  - External beam radiation takes significantly longer to work than stereotactic radiotherapy, and frequently leads to loss of normal pituitary function across 5-10 years⁴
  - Neurologic complications (optic neuropathy, other cranial neuropathies) and secondary neoplasia have been reported rarely with both types of radiotherapy²,⁵

Medical Therapy²

- Pituitary-directed
- Adrenal-directed
- Competitive glucocorticoid receptor antagonist

Patients with an ectopic source of ACTH have very high cortisol levels.

**Hormone Alterations**
- Secretion of ACTH from an ectopic tumor stimulates the adrenal glands to secrete cortisol.
- These tumors exist completely outside of the HPA axis, do not require stimulation by CRH, and are not sensitive to negative feedback.
- This leads to unchecked ACTH secretion, very high cortisol levels, and loss of diurnal rhythm.
Testing for Hypercortisolism

Overnight DST (cont'd)

Normal Response
- Decrease in cortisol levels
- Decrease in ACTH levels

CS Adrenal
- No decrease in cortisol levels
- Low ACTH levels

Ectopic tumor:
- No decrease in cortisol levels
- High ACTH levels

Cushing disease:
- No decrease in blood cortisol levels
- High ACTH levels

Overnight DST* (cont'd)

ACTH
Cortisol
Dexamethasone
Hypothalamus
Pituitary
Gland
Adrenal
Gland
Kidney
Kidney
Dexamethasone
Tumor

Normal Response
- Decrease in cortisol levels
- Decrease in ACTH levels

CS Adrenal
- No decrease in cortisol levels
- Low ACTH levels

Ectopic tumor:
- No decrease in cortisol levels
- High ACTH levels

Cushing disease:
- No decrease in blood cortisol levels
- High ACTH levels

*Graphical representation.

Cushing Syndrome: Ectopic Source

Treatment
- When possible, the treatment of choice for ectopic ACTH-secreting tumors is resection of the primary tumor
  - The best results have been achieved when the tumor is found to be carcinoid in origin
  - In many cases, the primary tumor is found to be an inoperable carcinoma of the bronchus
    - In these cases, the prognosis is so poor that surgery often is not indicated
  - In cases where the primary tumor cannot be localized, the treatment of choice is bilateral adrenalectomy

Treatment


Summary

- Cortisol production is under control of a complex set of feedback influences1
- Healthy, day-working people have a diurnal variation in cortisol levels, with the peak occurring just before waking and the trough near midnight2
- Excess cortisol causes multisystemic dysfunction1,3,4
- No single clinical sign or symptom defines hypercortisolism1
- Diagnostic testing should align with the suspected pathophysiology5
  - UFC measures the gross overproduction of cortisol across a period of time, and is not an ideal test to detect mild hypercortisolism5
  - LNSC measures the free cortisol in the saliva at a time point when cortisol should be at its lowest level, detecting the loss of diurnal rhythm6
  - LNSC seems to be the best early predictor of Cushing disease recurrence6
  - The overnight DST is a dynamic test that assesses the HPA axis responsiveness to glucocorticoids, detecting autonomous cortisol secretion5
- Recommended for patients with mild hypercortisolism5

Summary, cont’d

- Cushing syndrome is associated with significant morbidity and mortality\(^1,2\)
  - Even when clinical signs of overt hypercortisolism are not present, patients with adrenal adenomas and mild hypercortisolism have an increased risk of CV events and mortality\(^2\)
  - Even “nonfunctional” adrenal tumors are associated with hormonal dysregulation\(^4\)
- The degree of hypercortisolism by itself does not seem to be a sufficiently exhaustive parameter to assess the severity of active CS\(^5\)
- Mild hypercortisolism is common\(^6\)
- Treatment options include surgery, directed medical therapy, and/or active surveillance\(^7,8\)


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Summary of Screening and Treatment

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Diagnosing Cushing Syndrome

**Step 1: Is There an Index of Suspcion for CS?**

- Exclude exogenous CS\(^1\)
- Identify features of CS\(^2\)

**Endogenous CS\(^1\)**
- Due to pituitary, adrenal, or other tumors causing overproduction of cortisol

**Exogenous CS\(^1\)**
- Due to long-term use of high doses of glucocorticoids

**Pseudo-CS\(^1\)**
- Presence of partial clinical signs of hypercortisolism
  - Can be caused by
  - Alcoholism
  - Depression
  - Obesity

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Diagnosing Cushing Syndrome

Step 2: Identify Hypercortisolism

- Perform one of the following tests:
  - 24-hour UFC (≥2 tests)
  - Overnight 1-mg DST
  - LNSC (≥2 tests)

Determine ACTH-dependent vs ACTH-independent cause

Early-morning ACTH levels

- <10 pg/mL = ACTH-independent
- >10 pg/mL = ACTH-dependent

Diagnosing Cushing Syndrome

Step 3: Determine the Cause

An Algorithm for the Treatment of CS

ACTH-dependent CS vs ACTH-independent CS

Presumed EAS

Imaging: no tumor

Presumed EAS

Imaging: + tumor

Presumed CD based on IPSS or >6 mm mass

Tumor resection

Resection not possible

Remission

Monitor for recurrence

Failed surgery, no surgery, or recurrence

Control Hypercortisolism

If CD, consider:

- Repeat TSS
- Pituitary-directed medical treatment
- RT and steroidogenesis inhibitors

For all etiologies, consider:

- Medical therapy
- Bilateral adrenalectomy

ACTH-independent CS

Adrenal imaging

Unilateral or bilateral adenoma

Remission

Repeat localization studies

Treat metastatic disease if applicable

Tests to Find the Cause of Cushing Syndrome

- CRH stimulation test
  - Helps distinguish pituitary adenomas from ectopic ACTH syndrome or adrenal tumors
  - Pituitary adenomas = ↑ ACTH and ↑ cortisol because CRH acts directly on the pituitary
  - Ectopic or adrenal tumor = response rarely seen

- High-dose DST
  - Same as the low-dose DST, except that it uses higher doses of dexamethasone
  - Distinguishes excess production of ACTH due to pituitary adenomas from those with ectopic ACTH-producing tumors
  - High doses of dexamethasone usually suppress cortisol levels in people with pituitary adenomas, but not in those with ectopic ACTH-producing tumors

- Radiologic imaging: direct visualization of the endocrine glands
  - Imaging tests reveal the size and shape of the pituitary and adrenal glands and help to determine if a tumor is present
  - The most common imaging tests are the computed tomography scan and MRI

- Petrosal sinus sampling
  - Best way to distinguish pituitary from ectopic causes of CS

Cushing Syndrome: Pituitary Source

General Approach to Diagnosis

Inferior petrosal sinus sampling

• This test can be used to accurately distinguish pituitary and ectopic sources of ACTH-causing CS. The principle of the test is to sample the blood from the petrosal sinuses draining the pituitary gland, to compare the levels of ACTH with those found in the peripheral blood. A petrosal:peripheral ratio of >2, indicating excess ACTH from the pituitary, is necessary to diagnose Cushing disease with confidence. Accuracy can be improved using CRH stimulation to exaggerate the difference.

Pituitary MRI

• MRI is the best modality for imaging the pituitary. It has 77% sensitivity for the detection of pituitary microadenomas. Specificity is only 80%; therefore, images must be viewed in conjunction with other test results.
Patients Need Lifelong Follow-Up After TSS

- There is no expert consensus with regard to postoperative testing for surgical success
  - The timing of biochemical measurements differs among treatment centers, and can vary considerably within the same center
  - Intervals between surgery and biochemical measurement range from 1-2 days up to several weeks or months
  - Additional factors impact cortisol levels after surgery
    - Prophylactic medications (e.g., glucocorticoids, steroidogenesis inhibitors)
    - Early-morning serum cortisol measured between 8:00 AM and 10:00 AM is the most commonly used measure of immediate remission following surgery
      - Typically, early-morning serum cortisol levels of either <2 μg/dL (~50 nmol/L) or <5 μg/dl, within a few days after surgery are considered to be indicative of remission