# Understanding the spectrum of hypercortisolism

## Cortisol: An important hormone for homeostatic well-being[1,2]

Cortisol is the most abundant endogenous glucocorticoid in the human body. The widespread impact of cortisol is mediated by the glucocorticoid receptor, a modular protein in which cortisol and other glucocorticoids bind. Cortisol regulates numerous physiologic processes including metabolism, immune response, blood sugar levels, and cardiovascular (CV) function.[1-3] Over time, hypercortisolism—also referred to as Cushing syndrome—can lead to multisystemic dysfunction.[4]

## Exogenous vs endogenous: The hidden clues to a complex disease

Hypercortisolism can develop after taking glucocorticoid medicines (eg, steroids). This is called exogenous hypercortisolism, meaning it results from an **outside** source. Conversely, endogenous hypercortisolism results from something **inside** the body, usually an adenoma.[5,6] However, regardless of its source, patients often have a constellation of signs and symptoms caused by hypercortisolism, but those symptoms (eg, hypertension, glucose intolerance, obesity) may also be caused by other disease processes that are common in the general population. As a result, hypercortisolism may be challenging to diagnose.[5,7]

## Clinical consequences of hypercortisolism

Excess cortisol activity can lead to serious health consequences, increasing the risk of type 2 diabetes, hypertension, obesity, and cardiovascular disease.[4,7-9] When left untreated, classically described overt Cushing syndrome is associated with 50% mortality in as few as 5 years.[10]

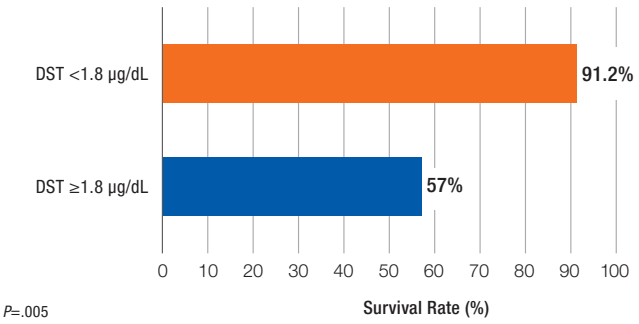
## Risk of CV and mortality associated with autonomous cortisol-secreting adenomas

A 15-year retrospective, multicenter study analyzed the correlation between long-term excess cortisol secretion, CV events, and mortality. The 198 participants were diagnosed with at least 1 adrenal adenoma before the study. They were grouped based on their cortisol levels, determined using the overnight dexamethasone suppression test (DST) at baseline and study end. The ranges of cortisol levels that defined each of the 3 groups were <1.8 µg/dL, 1.8-5.0 µg/dL, and >5.0 µg/dL. Patients with classically described overt Cushing syndrome were excluded.[9]

Individuals were assessed every 18 to 30 months for the first 5 years, with a mean follow-up period of 7.5 years (range: 26 months to 15 years). New CV events were defined as nonfatal acute myocardial infarction, percutaneous transluminal coronary angioplasty, and surgical bypass for ischemic heart disease, or ischemic stroke, which occurred during the study. The study compared the rates of CV events and mortality for patients with different DST thresholds. CV events and mortality were also assessed based on unchanged and worsened cortisol secretion levels.[9]

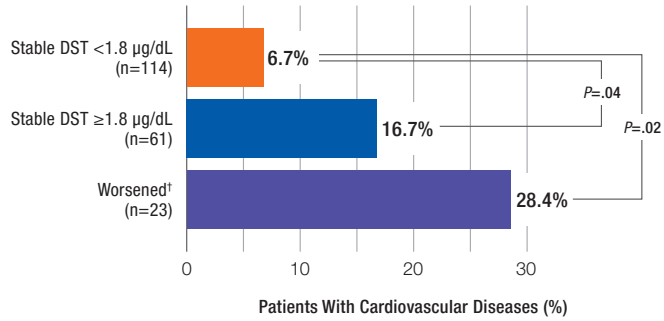
At the end of the study, patients with cortisol-secreting adrenal adenomas (≥1.8 µg/dL) had a survival rate for all-cause mortality of 57%, compared with 91.2% of those with nonsecreting adrenal masses (<1.8 µg/dL; Figure 1).[9]

Figure 1
**Survival Rates for All-Cause Mortality at End of Follow-Up[9]**




Additionally, patients whose post-DST cortisol levels increased between baseline and follow-up were 4 times more likely to have a CV event than patients with stable DST cortisol levels <1.8 µg/dL (28.4% vs 6.7%, *P*=.02; Figure 2).[9]

Figure 2
**Incidence of New Cardiovascular Events at End of Follow-Up[9]***




*New cardiovascular events were defined as nonfatal acute myocardial infarction, percutaneous transluminal coronary angioplasty, and surgical bypass for ischemic heart disease, or ischemic stroke, which occurred during the study.

†Worsened=moved up at least 1 category.

Even when clinical signs of classically described overt Cushing syndrome are not present, patients with adrenal adenomas and less severe hypercortisolism showed an increased risk of CV events and CV-specific mortality.[9]

## The importance of early diagnosis

Hypercortisolism tends to progress over time. Since severe hypercortisolism is associated with a worse outcome, early recognition and treatment of less severe disease would likely reduce the risk of residual morbidity.[5] Excess cortisol can greatly diminish a patient's quality of life by aggravating several physical and psychological conditions.[11]

>80% of patients experience weight gain[11]

≥70% experience depression, psychosis, and cognitive dysfunction[7]

~66% fulfill at least 3 criteria for metabolic syndrome[12]

38%-50% experience osteoporosis[13]

## Who should be screened for hypercortisolism?

The Endocrine Society guidelines state that healthcare professionals should screen any patient with[5]:

- Unusual features for his or her age (eg, osteoporosis, hypertension)
- Multiple and progressive features, especially those more predictive of Cushing syndrome
- Decreasing height percentile and increasing weight (in children)
- One or more adrenal incidentalomas

It is also important to evaluate adrenal adenomas for secretory function. Of adults who underwent magnetic resonance imaging, 4% to 7% were found to have an incidental adrenal adenoma. From that group, it was estimated that 5% to 30% of the adrenal adenomas were of the autonomous cortisol-secreting type.[13]

## Testing for hypercortisolism

**The Endocrine Society recommends these 3 tests when screening patients for hypercortisolism[5,15,16]:**

### 1-mg overnight DST

The DST assesses the responsiveness of hypothalamic–pituitary–adrenal axis to glucocorticoids

Detects autonomous cortisol secretion

**ABNORMAL RANGE:** >1.8 µg/dL

### Late-night salivary cortisol (LNSC)

The LNSC test measures free cortisol in the saliva when cortisol should be at its lowest level

Detects the loss of diurnal rhythm

**ABNORMAL RANGE:** Exceeds the upper limit of normal for the assay*

### Urinary-free cortisol (UFC)

The UFC test measures excretion of circulating unbound cortisol in the urine over a 24-hour period

Detects the gross overproduction of cortisol over a period of time

**ABNORMAL RANGE:** Exceeds the upper limit of normal for the assay

*Abnormal range: >0.145 µg/dL (based on enzyme-linked immunosorbent assay and liquid chromatography with tandem mass spectrometry assay validation).[5]

## Bring hypercortisolism to light

**Learn more about the signs and symptoms of hypercortisolism, its clinical consequences, and the importance of early detection**

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