Recent Advances on Subclinical Hypercortisolism

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KEYWORDS

• Subclinical • Mild • Cushing • Hypercortisolism • Adrenal

KEY POINTS

- The most recent guidelines suggest the use of 1-mg dexamethasone suppression test in all patients with adrenal incidentalomas.
- Mass spectrometry–based steroid profiling is useful in evaluation of subclinical hypercortisolism.
- Adrenal protocol computed tomography scan provides morphologic information that may be predictive of cortisol hypersecretion.
- Subclinical hypercortisolism is associated with increased incidence of cardiovascular diseases and increased mortality from cardiovascular events and infections.
- Adrenalectomy in patients with subclinical hypercortisolism and unilateral adenomas has some beneficial effects on associated comorbidities, as shown by retrospective studies.

INTRODUCTION

The term "adrenal incidentaloma" refers to an adrenal mass discovered during imaging performed for reasons unrelated to adrenal disorders. Even though most adrenal incidentalomas do not show biochemical evidence of hormonal excess, up to 30% of those tumors are associated with subclinical hypercortisolism (SH).[1] SH is a pathologic condition defined as biochemical evidence of hypercortisolism in patients without typical signs or symptoms of Cushing syndrome.[1] In recent years, this condition has been evaluated in several studies that increased the understanding regarding its natural history and the outcomes of available therapeutic options. The refined radiological techniques and the introduction of metabolomic profiling by mass spectrometry have improved the performance of current diagnostic criteria and provided new insights regarding the pathogenesis of subtle cortisol excess. The purpose of this review is to present the most recent advances in SH.

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BIOCHEMICAL DIAGNOSIS OF SUBCLINICAL HYPERCORTISOLISM

Considering that SH occurs in patients without overt signs of cortisol excess, laboratory tests plays a pivotal role in the diagnosis of this condition (**Box 1**). Cortisol suppression to 1-mg dexamethasone suppression test (DST) has been traditionally considered the most reliable parameter to screen for endogenous Cushing syndrome. The cortisol value that defines SH has been a topic of controversy.[2] The sensitivity and the specificity of the different cutoffs for cortisol vary across different studies.[3] The European Society of Endocrinology (ESE) clinical guidelines on the management of adrenocortical tumors published in 2016 introduced some important points.[1] First, the 1-mg DST is recommended in all patients with adrenal incidentalomas, with a cutoff for serum cortisol of greater than 5 μg/dL defining SH, whereas suppression to 1.8 to 5 μg/dL indicates possible SH. The usefulness of the 1-mg DST has been proven in several studies investigating the natural history of SH. Patients with cortisol levels greater than 1.8 μg/dL are at increased risk for cardiovascular diseases.[4,5] Moreover, patients with SH had a lower survival rate than those with nonsecreting adrenal tumors, because of cardiovascular events and infectious complications.[4,6] Second, the ESE experts' panel recommended that cortisol levels after DST should be considered a continuous rather than a categorical variable, supporting the concept of a continuum of progression of hypercortisolism over time. Finally, even though several additional tests can help with the diagnosis of SH in patients with cortisol suppression between 1.8 and 5 μg/dL, the presence of comorbidities related to hypercortisolism should be carefully considered when making therapeutic recommendations. These recommendations include diabetes mellitus, hypertension, and cardiovascular disease.[7]

Additional tests for patients with abnormal DST include basal adrenocorticotropic hormone (ACTH) levels (helpful in diagnosing ACTH-independent hypercortisolism when suppressed <10 pg/mL). However, ACTH is inhibited in a variable proportion of patients with adrenal incidentalomas and is sometimes detectable in patients with ACTH-independent Cushing syndrome.[8] Moreover, ACTH immunoassays are vulnerable to interference of endogenous antibodies.[9] Unlike overt Cushing syndrome, SH patients do not benefit much from urinary free cortisol (UFC) measurement,[8] mainly because of the low sensitivity in detecting mild cortisol excess. However, a recent study showed that high UFC levels measured by mass spectrometry might be a biomarker of cardiovascular risk in patients with SH.[10] Dehydroepiandrosterone-sulfate (DHEAS) levels are frequently reduced in patients with hypercortisolism for 2 reasons: reduced activity of the 17,20-lyase in hyperfunctioning tumors[11] and reduced stimulation of adrenal cortex adjacent/contralateral to the tumor by the low levels of pituitary ACTH. A large retrospective study showed that DHEAS levels less than 40 μg/dL had a specificity of 75% and a sensitivity of 68% in identifying SH.[12] Moreover, DHEAS offered comparable sensitivity and greater specificity to the 1-mg DST for the detection of SH.[13]

Box 1
Diagnostic testing for subclinical hypercortisolism

- All patients with adrenal incidentalomas should undergo a 1-mg DST.
- Cortisol suppression less than 1.8 μg/dL indicates a normal response, whereas values greater than 5 μg/dL define subclinical hypercortisolism.
- For cortisol suppression between 1.8 and 5 μg/dL, additional tests include late-night salivary cortisol and DHEAS, whereas ACTH and UFC levels seem less helpful.
- Reduced levels of adrenal androgens measured by mass spectrometry may be used as markers of SH.