

## Endocrine Surgery Reviews

### Low DHEAS:

#### A Sensitive and Specific Test for the Detection of Subclinical Hypercortisolism in Adrenal Incidentalomas

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### In Brief

Subclinical hypercortisolism (also called subclinical Cushing's syndrome) secondary to ACTH-independent cortisol hypersecretion is present in 5-30% of patients with adrenal incidentalomas. Subclinical hypercortisolism is associated with hypertension, diabetes, and vertebral fractures, in addition to adverse clinical outcomes, including cardiovascular morbidity and mortality [1, 2]. The 1mg overnight dexamethasone suppression test (ONDST) has 99% sensitivity for subclinical hypercortisolism, but has poor specificity (70 - 80%), leading to false positives and inefficient resource utilization for further testing. The adrenal androgen dehydroepiandrosterone sulfate (DHEAS) is regulated by pituitary ACTH, so sustained ACTH suppression is associated with decreased DHEAS levels. Therefore, the authors in this study set out to assess the utility of DHEAS (in the form of the ratio of DHEAS level divided by the lower limit of normal for the age- and sex-matched reference range) in the diagnosis of subclinical hypercortisolism [3].

To do this, the authors performed a retrospective review of 185 consecutive patients with adrenal incidentalomas who were referred for endocrinology evaluation between 2006 and 2013. 18 patients were excluded for overt Cushing's syndrome and other conditions that were anticipated to affect the hypothalamic-pituitary-adrenal axis. The diagnosis of subclinical hypercortisolism in patients with positive screening ONDST or urinary free cortisol (UFC) was confirmed based on inpatient testing by two endocrinologists blinded to DHEAS level. Receiver operating characteristic (ROC) curves, sensitivities, and specificities were then generated for DHEAS, ONDST, and UFC and compared.

Subclinical hypercortisolism was identified in 29 out of 167 patients. DHEAS ratio was found to have a sensitivity of 100% and specificity of 91.9% at a cutoff value of 1.12, with ROC analysis demonstrating good accuracy with an area under the curve (AUC) of 0.95. It also differentiated between ACTH-dependent and ACTH-independent hypercortisolemia. ONDST performed well as a screening test for subclinical hypercortisolism at the currently accepted cutoff of 1.9mcg/dL with a sensitivity of >99%, but performed poorly as a confirmatory test with a specificity of 82.9%. At its best performance, ONDST had a sensitivity of 92.5% and a specificity of 88.6% with a cutoff of 2.1mcg/dL (AUC 0.97). 24-hour UFC did not perform well as a screening or confirmatory test.

The authors concluded that a low DHEAS level in a patient with an adrenal incidentaloma is a sensitive and specific screening test and should be performed more widely and prompt further investigation for subclinical hypercortisolism.

### **Critique**

The authors present a straight-forward and well-designed study of the utility of DHEAS as a screening test for subclinical hypercortisolism, the results of which have practical application in the frequently performed work up of adrenal incidentalomas. With standardized and complete laboratory data on all 187 patients with adrenal incidentalomas who were referred for biochemical evaluation, the authors were able to produce reliable estimates of the sensitivity and specificity of our currently used screening tests and compare it to those for DHEAS, which is often used in clinical practice but has not previously been recommended as a screening test in guidelines [4-6]. By using ONDST, which has >99% sensitivity for identifying subclinical hypercortisolism in this and other studies[7], to identify patients for confirmatory testing, the authors avoid verification bias (the results of the test being studied affecting who receives confirmatory testing), which is commonly a challenge in the evaluation of diagnostic tests. In addition, the blinding of diagnosticians to DHEAS level in their identification of subclinical hypercortisolism ensures an unbiased assessment of its performance in this clinical setting.

The most notable limitation of this study is that all patients were from a single, tertiary-referral institution and, as such, the reported test performance may not be generalizable to a wider population. The authors provide the mean and standard deviations of age, sex, and BMI for patients with non-functioning adenomas and those with subclinical hypercortisolism, but further information on race and associated comorbidities were lacking and may be relevant in the application of this diagnostic test. In addition, the pretest probability of subclinical hypercortisolism will affect the clinical utility of DHEAS testing, so further information on the prevalence of subclinical hypercortisolism in different study populations would be relevant.

### **Future Directions**

This study suggests that a single DHEAS measurement may be sufficient and perform better as a screening test for subclinical hypercortisolism in patients with adrenal incidentalomas, eliminating the costly and labor-intensive use of 24-hr urine collections or timed studies with dexamethasone suppression. The next steps in assessing the performance of DHEAS would involve testing in a large, multi-institutional cohort to confirm that its diagnostic performance is consistent in unselected patient populations and DHEAS can be recommended as a first line screening test in the future. In addition, the use of the ratio of DHEAS level to age- and sex-matched controls should be validated through comparison of its performance to that of absolute DHEAS levels.

### **References:**

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**Additional High Yield Reading:**

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