

The Overnight Low-Dose Dexamethasone Suppression Test Can Be Used to Evaluate Patients With Chronic Kidney Disease

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Abbreviations: ACTH, adrenocorticotropic hormone; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LNSC, late-night salivary cortisol; oDST, overnight 1-mg dexamethasone suppression test.

The diagnosis of neoplastic hypercortisolism (endogenous Cushing syndrome) is very challenging. Since validating the use of late-night (bedtime) salivary cortisol (LNSC) for its diagnosis in the 1990s [1], I am often asked whether LNSC can be used to establish or rule out neoplastic hypercortisolism in patients with chronic kidney disease (CKD) and end-stage renal failure [2]. Although it is known that patients with renal failure may appear “Cushingoid” and have increased serum cortisol, it was assumed that this was due to the systemic effects of uremia and to changes in cortisol metabolic clearance rather than a centrally driven “stress state.” Although cortisol metabolism is altered in renal failure, cortisol negative feedback control of the hypothalamic-pituitary-adrenal axis and adrenocorticotropic hormone (ACTH) secretion should be intact, thereby limiting the degree of nonneoplastic hypercortisolism. However, if hypothalamic release of corticotropin-releasing hormone into the hypothalamic-pituitary portal veins is chronically increased due to stress inputs, ACTH-dependent hypercortisolism may persist.

My group previously demonstrated that patients with end-stage renal failure have ACTH-dependent (centrally driven) increases in cortisol, particularly when nearing or at the circadian nadir [3]. This nonneoplastic, stress-induced chronic increase in ACTH is not surprising, considering the heightened inflammatory state, poor quality of life, and chronic distress of patients with renal failure [3, 4]. Furthermore, hypercortisolism has been demonstrated even with more moderate degrees of CKD [5]. Thus, although a late-night salivary cortisol level within the reference range excludes the diagnosis of neoplastic hypercortisolism with ~90% to 95% certainty, just as it does in patients with normal renal function, an increased LNSC in patients with CKD does not establish the existence of an ACTH- or cortisol-secreting neoplasm, and the patient will need a further work-up by an experienced Endocrinologist with expertise in the diagnosis of Cushing syndrome.

The issue, then, is whether the 2 other established first-line tests for the diagnosis of neoplastic hypercortisolism—the overnight 1 mg dexamethasone suppression test (oDST) and 24-hour urine free cortisol (UFC)—can be useful if LNSC is elevated. It is obvious that UFC is problematic in patients with chronic decreases in estimated glomerular filtration rate (eGFR). Could the post-oDST serum/plasma cortisol cut-offs be modified to be useful in patients with CKD [6]?

The timely study by Garg et al not only addresses this important problem but provides very preliminary reference intervals for the concentrations of post-oDST serum dexamethasone that will need to be validated with more subjects [7]. In patients with suspected neoplastic hypercortisolism with normal renal function, the measurement of post-oDST serum dexamethasone concentration improves the performance of the oDST by ensuring that the patient actually took the dexamethasone at the proper time and that it was adequately absorbed into the bloodstream [8]. However, what is needed is (a) interlaboratory harmonization of dexamethasone assays (preferably using liquid chromatography–tandem mass spectrometry [LC-MS/MS]) and (b) reliable laboratory-established reference intervals of post-oDST serum dexamethasone concentrations.

Garg et al clearly demonstrated that post-oDST serum cortisol and plasma ACTH concentrations were inversely correlated with eGFR in patients without neoplastic hypercortisolism [7]. In patients with eGFR > 90 mL/min/1.73 m², the 95th percentile upper cutoff for post-oDST serum cortisol was 1.2 µg/dL. This is lower than the accepted cutoff of 1.8 µg/dL for the diagnosis of neoplastic hypercortisolism [2, 8]. This could be, in part, because the subjects in [7] were very lean (body mass index 20–26 kg/m²), from India, and/or few in number. At an eGFR of 60 to 89 mL/min/1.73 m², the 95th percentile upper post-oDST cortisol cutoff was more than doubled (3.0 µg/dL). In patients with severe CKD on

dialysis (eGFR <15 mL/min/1.73 m²), the post-oDST cortisol cutoff was ~6 times higher (7.1 µg/dL) than controls with normal renal function. These cutoffs were derived from only 30 patients in each eGFR group, and more subjects of diverse background will be needed for a thorough validation. The study demonstrated that the oDST can be used in patients with CKD if the cutoff for the post-oDST serum cortisol is increased appropriately.

Another contribution of this study is providing preliminary post-oDST serum dexamethasone ranges measured by LC-MS/MS in an exploratory group (~15 subjects per eGFR group). There was a suggestion that these values increased with decreasing eGFR although the magnitude of the effect was not statistically significant. For an eGFR of >90 mL/min/1.73 m², the serum dexamethasone interquartile range was 2.4 to 8.1 ng/mL and for an eGFR of <15 mL/min/1.73 m², it was 3.8 to 9.4 ng/mL. Beware that laboratories often report serum dexamethasone levels in units different from [7] (eg, in ng/dL or nmol/L) and that the assay results may not be commutable from laboratory to laboratory. Also beware that a much larger group of diverse subjects will be needed to validate actual reference ranges. That said, the concept of measuring serum dexamethasone to prove that an adequate concentration was reached is the optimal approach in patients with or without abnormal renal function when using the oDST to make the diagnosis of neoplastic hypercortisolism [7, 8].

As an aside, the post-oDST cortisol ranges in the exploratory groups with low eGFR were higher by immunoassay compared with by LC-MS/MS, suggesting that immunoreactive steroids may have accumulated in the patients with CKD. Any new post-oDST reference ranges in patients with CKD must take the assay method into account.

Many clinical endocrinologists are starting to measure post-oDST plasma ACTH concentrations as an adjunct to post-oDST serum cortisol. Garg et al also provided useful albeit very preliminary post-oDST plasma ACTH ranges in the exploratory group. In subjects with a normal eGFR, the post-oDST plasma ACTH range was 2.3 to 8.4 pg/mL, whereas in severe CKD, the range was 4.6 to 15.9 pg/mL.

These are exciting times for research into the challenging diagnosis and treatment of neoplastic hypercortisolism. Not only is our diagnostic approach using LNSC and oDST achieving optimal performance and accuracy, but more

medical options to treat milder and milder forms of neoplastic hypercortisolism are available or in development. Considering the personal and societal burden of CKD, a new approach to improve outcomes and quality of life by attenuating the catabolic and neurological effects of concurrent hypercortisolism may be just around the corner.

Affirmation of Originality and Authorship

Author affirms that the Work submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration.

Disclosures

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