Low DHEAS Level: A Surrogate Marker of Adrenal Cushing Syndrome with Grey Zone ACTH Levels

Sir,

Endogenous Cushing's syndrome (CS), characterised by excess cortisol secretion, can be adrenocorticotropic hormone (ACTH)-independent or ACTH-dependent depending on the plasma ACTH levels. However, 30% of the patients with CS may have ACTH levels in the 'grey zone' (10–20 pg/mL), thereby necessitating repeat ACTH testing.[1] Diagnosing adrenocortical carcinoma (ACC) is often straightforward in the presence of worrisome radiological phenotype, suppressed ACTH and elevated Dehydroepiandrosterone sulphate (DHEAS).[1] However, owing to the slow evolution of the disease and incomplete ACTH suppression, repeated ACTH testing may often prove to be futile in cases of adrenal adenoma, which happens to be the most common form of adrenal CS. While the unavailability of corticotrophin-releasing hormone in many countries mandates pituitary or adrenal imaging to explore the underlying condition in this scenario, the presence of pituitary incidentalomas poses a risk of wrong localisation.[2] Considering the potential role of DHEAS in reflecting plasma ACTH levels over a longer period, the present study aimed to explore the performance of DHEAS to distinguish adrenal adenomas with 'grey zone' ACTH levels from ACTH-dependent CS.

A retrospective chart review was performed from 2018 to 2022 to identify adults (≥18 years) admitted to our tertiary care centre with a diagnosis of CS confirmed through clinical examination overnight, 1 mg-dexamethasone suppression test (ONDST) and midnight serum cortisol, or 24-hour urinary free cortisol tests as per standard guidelines. The causes of CS were explored by ACTH levels and adrenal/pituitary imaging as appropriate. In selected cases, inferior petrosal sinus sampling was also conducted. Finally, the diagnosis was confirmed through surgery and biopsy. Cortisol, ACTH, and DHEAS were measured by chemiluminescence immunoassay analyser in IMMULITE-1000 platform. The intra-assay coefficient of variability of DHEAS and ACTH were 1.3% and 6.3%, respectively. Age and gender-specific normal ranges for DHEAS were taken as mentioned in laboratory kits [Table 1].

Out of 32 patients with clinical CS, the identified causes were adrenal adenoma (n = 12), ACC (n = 3), Cushing's disease (n = 11), ectopic CS (n = 5), and non-localised CS (n = 1). In individuals with adrenal adenoma (n = 12), only two patients reported suppressed ACTH, the majority (n = 8) had intermediate ACTH levels (10–20 pg/mL) despite repeat testing, and two individuals even had an ACTH level above 20 pg/mL. Out of these 12 patients with diagnosed adrenal adenoma, one patient with intermediate ACTH level had pituitary incidentaloma (3 × 2.3 mm). Notably, low DHEAS (as per age and sex-appropriate cut-offs) were found in all eight patients with adrenal adenoma and intermediate ACTH levels and in two other subjects with ACTH >20 pg/mL. Two patients with suppressed ACTH also had low DHEAS, while subjects with ACTH-dependent CS had normal to high DHEAS [Table 1].

Adrenocorticotropic hormone levels measured using immunoassays in patients with adrenal CS due to adenomas may often overlap with ACTH levels as seen in healthy individuals, reflecting its pulsatile secretion and incomplete ACTH suppression due to slow evolution of disease.[1] IMMULITE-1000 platform, primarily used in this study, is also known to have a positive bias when compared to ROCHE cobas E411 platform.[3,4] Thus, ACTH levels of 10–20 pg/ml may actually be diagnostic of adrenal CS in the IMMULITE platform unlike the ROCHE platform or Liquid chromatography with tandem mass spectrometry (LC-MS/MS) assays.[3,4] Notably, only one patient with ACTH-dependent CS had ACTH in 10–30 pg/ml range, whereas one patient with adrenal adenoma had ACTH in the 20–30 pg/mL range. Hence, increasing the ACTH cut-off to 30 pg/mL could reliably distinguish adrenal adenomas from ACTH-dependent CS except one case in each in present cohort. However, this approach should also be exercised with caution considering pre-analytical errors with ACTH testing that may lead to falsely low ACTH values.

In our centre, all patients with adrenal adenomas having initial ACTH levels in 'grey zone' or above 20 pg/mL on initial testing had low DHEAS levels, which proved to be an important surrogate marker of adrenal CS and could help to avoid false localisation owing to pituitary incidentaloma in one case. In contrast to ACTH, DHEAS can have relatively stable serum levels throughout the day with a long half-life (10–16 hours), making it a more suitable marker to detect chronically suppressed ACTH in overt or subclinical CS in adrenal adenomas.[5] The importance of DHEAS has indeed been established in the diagnosis of adrenal subclinical CS.[6] A single basal measurement of DHEAS showed comparable sensitivity and greater specificity to the gold-standard ONDST for detecting subclinical CS in adrenal incidentalomas.[5] In the presence of intermediate laboratory findings, low DHEAS was the strongest predictor of subclinical CS.[7] Nonetheless, considering the age-related decline in DHEAS, the role of DHEAS may be limited in elderly population in such a scenario.

In conclusion, in the presence of 'grey zone' ACTH levels on immunoassays, low DHEAS levels along with adrenal

Table 1: Demographic and biochemical profile in patients with Cushing syndrome

Serial No.	Gender (M/F)	Age (Years)	Diagnosis	Basal Cortisol (mcg/dl)	ONDST Cortisol (mcg/dl)	ACTH (pg/ml)	DHEAS (mcg/dl)
1	F	18	CD	50	44.7	143	154
2	F	17	CD	29.8	24.3	145	171
3	F	39	ECS	75	18.6	241	304
4	F	18	ECS	43	16.2	207	312
5	F	38	AA	18	22.4	24	28.6
6	F	22	CD	31.2	19.3	145	195
7	M	31	CD	21.8	26.4	204	204
8	M	30	AA	22.7	23.3	16.9	55.4
9	F	23	ECS	33.8	12.6	270	197
10	F	49	CD	65	9	31.3	156
11	F	36	CD	22.2	36.8	85.7	199
12	F	22	CD	32.5	22.3	128	244
13	M	18	ECS	39.9	17.2	213	292
14	F	23	AA	23	14.5	12.4	30.2
15	F	23	AA	25.7	20.6	12.1	16.7
16	F	18	AA	37.6	22.3	36.8	32.1
17	F	30	AA	28.3	24.1	17.2	15
18	M	42	ECS	40.8	31.5	313	169
19	M	29	CD	44.4	11.5	18.8	134
20	F	26	AA	39.5	15.6	18	24.7
21	F	34	AA	20.9	12.8	1.32	42.2
22*	F	23	AA	23.75	43	1*	48.9
23	F	30	NL	9.83	4.67	44.2	133.4
24	F	30	CD	25.4	24.1	113	156.7
25	F	23	AA	29.1	8.9	16.7	46.3
26	M	12	CD	29.5	11.2	59.1	167.1
27	F	18	CD	18.8	6.5	52.87	134.9
28	F	26	ACC	46.7	20.1	16.3	478
29	F	36	AA	16.09	12.5	10.2	15
30	M	19	AA	16.6	19.3	17.8	23.1
31	F	32	ACC	7.65	8.1	4.64	656
32	F	41	ACC	4.5	4.55	1.43	>1000

* On repeat testing

Cut-offs to define low DHEAS as per the ranges in our laboratory kits: age 18–29 years, <65 µg/dl (females), <280 µg/dl (males); age 30–39 years, <45 µg/dl (females), <120 µg/dl (males); age 40–49 years, <32 µg/dl (females), <95 µg/dl (males); age 50–59 years, <26 µg/dl (females), <70 µg/dl (males)

ONDST, overnight dexamethasone suppression test; DHEAS, Dehydroepiandrosterone sulfate; ACTH, adrenocorticotropic hormone; AA, Adrenal Adenoma; CD, Cushing Disease; ECS, Ectopic Cushing syndrome; NL, Not localised; ACC, Adrenocortical Carcinoma

imaging, can reliably distinguish adrenal CS due to adenomas from ACTH-dependent CS.

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Conflicts of interest

There are no conflicts of interest.

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