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Original research

Serum dehydroepiandrosterone sulfate in assessing the integrity of the hypothalamic-pituitary-adrenal axis

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ABSTRACT

Objective: To evaluate the relationship between age- and gender-adjusted dehydroepiandrosterone sulfate (DHEA-S) levels and low-dose adrenocorticotropic hormone (ACTH) stimulation in assessing the integrity of the hypothalamic-pituitary-adrenal (HPA) axis, in patients who were at risk of HPA insufficiency, including those currently being treated with glucocorticoids.

Methods: Forty-six participants with a suspicion of secondary adrenal insufficiency were recruited from the Diabetes and Endocrinology Clinic at Ramathibodi Hospital, Mahidol University, Bangkok. Low-dose (1 μg) ACTH stimulation was performed in every participants, and serum DHEA-S was measured at baseline before ACTH injection.

Results: Individuals with normal age- and gender-specific DHEA-S levels had baseline serum cortisol and peak cortisol levels higher than those with reduced DHEA-S. Normal age- and gender-specific DHEA-S levels predicted intact HPA function with a sensitivity of 87.1%, a specificity of 86.7%, a positive predictive value of 93.1%, and a negative predictive value of 76.5%. To account for the age and gender dependency of DHEA-S, the DHEA-S ratio was calculated by measured DHEA-S divided by the lower limit of the respective reference range for all participants. A DHEA-S ratio of more than 1.78 had 100% sensitivity regarding intact HPA function. Area under the receiver operating characteristic [ROC] curve was 0.920. (95% CI, 0.844–0.997).

Conclusion: Normal age- and gender-specific DHEA-S level or a DHEA-S ratio of more than 1.78 are valuable markers of HPA integrity. Serum DHEA-S may be a candidate for a less costly approach where ACTH stimulation is unavailable.

Introduction

The hypothalamic-pituitary-adrenal axis (HPA) is a complex process of influences and feedback interactions among three endocrine glands – the hypothalamus, the pituitary gland and the adrenal glands – which is important in maintaining many vital organ functions. The impairment of HPA function as a result of decreased corticotropin-releasing hormone (CRH) and/or adrenocorticotropic hormone (ACTH) secretion from the hypothalamus and pituitary gland, respectively, is called secondary adrenal insufficiency. Nowadays, establishing a diagnosis of secondary adrenal insufficiency remains challenging. Dynamic testing with low-dose (1 μg) ACTH stimulation is the most commonly used method to define HPA integrity [1–3]. The exact diagnostic serum cortisol cut-offs of low-dose ACTH stimulation are still debated, and depend on assay-specific local reference ranges. In clinical practice, they are set at 18–20 μg/dL, with very low false negative results [4,5]. However, low-dose ACTH stimulation is usually troublesome for many internists and patients, especially in primary care setting, because of its time-consuming protocol and the unavailability of synthetic ACTH.

Dehydroepiandrosterone sulfate (DHEA-S) is the most abundant steroid hormone in the circulation; almost all is secreted by the zona reticularis of the adrenal cortex. DHEA-S secretion is mediated by the trophic effect of ACTH. Only minimal concentrations of DHEA-S are contributed by the testes [6,7]. DHEA-S measurement is quite convenient, with a widely available assay. Blood sampling can be performed at any time of the day because of the long half-life of DHEA-S and the lack of circulating diurnal variations

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[8–11]. Recent evidence has suggested that DHEA-S level is a good predictive marker of HPA impairment [12,13]. When DHEA-S level is normal, the diagnosis of HPA impairment is extremely unlikely. However, this finding was based on patients with a large pituitary tumor. A relationship between serum DHEA-S level and low-dose ACTH stimulation in real-world populations – including patients currently being treated with glucocorticoids, with or without a pituitary lesion – is still questionable.

Materials and methods

Study design

We conducted a cross-sectional study in adult participants, 18–59 years of age, with a suspicion of HPA insufficiency or secondary adrenal insufficiency (e.g. known pituitary or hypothalamic tumors, other central nervous system tumors which structurally involve the pituitary gland and/or hypothalamus, and previous history of consecutive glucocorticoid intake or injections more than 3 months). All participants were sent for HPA axis evaluation using low-dose ACTH stimulation test. The testing was performed at least 3 months after the onset of HPA axis insult to ensure that adrenal atrophy had occured. Participants were recruited from the Diabetes and Endocrinology Clinic at Ramathibodi Hospital, Mahidol University, Bangkok. Written informed consent was obtained from all participants. The study was approved by the Mahidol University Institutional Review Board.

Exclusion criteria included known primary adrenal insufficiency, known ACTH-producing tumor, or current use of medications known to have significant effects on cortisol and DHEA-S measurements, including oral contraceptive drugs, central nervous system agents that induce hepatic enzymes (e.g. carbamazepine, clomipramine, imipramine, phenytoin), dopaminergic drugs (e.g. levodopa/dopamine, bromocriptine), neuroleptic agents, danazol, and nicotine [14]. Patients with serum albumin of less than 25 g/L, which can cause falsely low cortisol levels, were also excluded.

Baseline data collected from all participants included gender, age, current height and weight, indication for HPA axis evaluation, and a detailed medical history including current medications. If patients were currently on glucocorticoid treatment, the regimen must be stopped for at least 24 h before testing. Any food or caloric intake was prohibited for at least 8 h before testing.

ACTH preparation

Synacthen is a brand name of tetracosactide (1–24 synthetic ACTH) used at Ramathibodi Hospital. It is available in the form of a vial containing 250 μg of tetracosactide per 1 mL. One mL of Synacthen was drawn from the vial and was reinjected into a 49 mL bag of normal saline. After mixing, Synacthen was refrigerated at 4 °C. The drug was discarded after being used by 10 participants, or more than 2 months after mixing.

Low-dose ACTH stimulation

Low-dose ACTH stimulation was performed in an ambulatory setting, in the early morning (mostly between 8.00 and 9.00 a.m.). Synacthen (0.2 mL, equivalent to 1 μg) was drawn from the already-mixed solution, diluted with normal saline to a volume of 1 mL, and injected intravenously into each participant. Serum cortisol, albumin and DHEA-S levels were measured at baseline before the injection. Serum cortisol was measured at 20, 30 and 40 min after the injection.

Laboratory methods

Serum DHEA-S was analyzed by a solid-phase, competitive chemiluminescent enzyme immunoassay on an IMMULITE® immunoassay system (Siemens Healthcare, Erlangen, Germany). The intra-assay coefficient of variation of serum DHEA-S level was 5.8%. Normal DHEA-S levels were defined as values greater than the 5th percentile of the manufacturer's reference data.

Serum cortisol was analyzed by IMMULITE 2000 immunoassay using a chemiluminescent technique (Siemens Healthcare). The lower limit of detectability was 0.2 μg/dL.

Statistical analysis

Data were analyzed using SPSS version 18 (SPSS, Chicago, IL). Data were summarized using mean ± SD if the data were normally distributed, or median (interquartile range) if the data were not normally distributed. Two-independent-sample *t*-test was used to analyze differences in continuous variables between study groups where the variables were normally distributed. Mann–Whitney *U* test was used to analyze differences in continuous variables between study groups where the variables were not normally distributed. Significance was determined according to $P < 0.05$. Diagnostic values, including sensitivity, specificity and predictive value, were assessed by confusion matrix calculations. Receiver operating characteristic (ROC) curves were plotted for DHEA-S ratios, which were derived by dividing the measured DHEA-S by the lower limit (5th percentile) of the respective reference range for all participants, using peak cortisol response after low-dose ACTH stimulation of more than 18 μg/dL as the definition of an intact HPA axis.

Results

A total of 46 patients were included in the study. Among them, 30 were female (65%) with a mean age of 46.5 years; 45.7% of the participants were 50–59 years of age. Most of the participants were sent for HPA axis evaluation due to the presence of pituitary macroadenoma (31 participants; 67.4%). The other indications included past history of prolonged glucocorticoid exposure (10 participants; 21.6%), and other CNS tumors, e.g. meningioma and lymphoma which structurally involve the pituitary gland (5 participants; 11%) (Table 1). For the patients with history of prolonged glucocorticoid exposure, all of them received prednisolone of more than 7.5 mg per day for more than 3 months prior to evaluation.

Of all participants, 31 (67.4%) were found to have intact HPA function, defined by peak cortisol response of more than 18 μg/dL after low-dose ACTH stimulation, whereas 15 were found to have less than 18 μg/dL of peak cortisol response, which was defined as abnormal HPA. Participants with abnormal HPA had mean baseline serum cortisol levels that were lower than those with intact HPA function (6.53 ± 3.54 μg/dL and 10.48 ± 3.46 μg/dL, respectively, p = 0.01). Median peak cortisol levels after ACTH stimulation in the abnormal and intact HPA groups were 15.3 μg/dL (IQR = 10.4–17.3) and 21.7 μg/dL (IQR = 19.7–24.1), respectively (p < 0.01) (Table 2).

Serum DHEA-S levels

Median serum DHEA-S levels in the abnormal HPA group (30.4 μg/dL, IQR = 10.5–55.7) were apparently lower than those with intact HPA function (87.6 μg/dL, IQR = 48.7–150), p < 0.01 (Table 2). Participants with normal age- and gender-specific DHEA-S levels had baseline serum cortisol levels and peak cortisol levels higher than those with reduced DHEA-S. Median peak corti-