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Clinical Case Study

Low Cortisol in a Cushingoid Patient

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Case Description

A 52-year-old woman with a history of obesity and hypothyroidism saw her primary care provider (PCP), complaining of fatigue and a 30 pound (14 kg) weight gain over 3 months. Her body mass index was 45 kg/m^2 and she had recently become hypertensive (blood pressure 136/83 mmHg). The PCP checked her early morning serum cortisol level and, surprisingly, it was low at 0.5 µg/dL (13.8 nmol/L) (reference interval [RI]: 4 to 225 µg/dL, 110 to 6208 nmol/L) (Table 1). Her hypothyroidism was well controlled on a stable dose of levothyroxine 50 µg daily. In light of the low morning cortisol level, she was referred to a community endocrinologist who noted her rounded facial appearance and redness on her cheeks. The patient reported facial hair growth, easy bruising, and striae on her legs. On repeated questioning, she denied any use of steroids. Repeat early morning serum cortisol on several occasions was 0.5 µg/dL (13.8 nmol/L) with suppressed plasma adrenocorticotropic hormone (ACTH) levels of <5 pg/mL (<1.1 pmol/L) (RI, 6 to 50 pg/mL, 1.32 to 11 pmol/L). Other serum pituitary hormone levels, as well as estradiol, dehydroepiandrosterone (DHEA) sulfate, and a comprehensive metabolic panel were all within the RIs.

Because of the low cortisol values, adrenal insufficiency was initially suspected and she was prescribed hydrocortisone 20 mg in the morning and 10 mg in the early afternoon. However, this caused increased anxiety, nervousness, and emotional lability. As reducing the hydrocortisone dose by 50% produced little improvement in these symptoms, the patient ultimately self-discontinued. Due to the discrepancy between her laboratory values and clinical presentation, she was referred to our medical center for further evaluation and management of her apparent adrenal insufficiency.

QUESTIONS TO CONSIDER

1. What are the clinical features of Cushing syndrome and laboratory tests used to make the diagnosis?
2. What are the causes of a decreased serum cortisol concentration?
3. How does dexamethasone affect the hypothalamic–pituitary–adrenal axis?
4. Can substances not mentioned in the product label be found in dietary supplements?

Approximately 3 months after stopping hydrocortisone, the patient's repeat serum cortisol and plasma ACTH levels by immunoassay remained low at 0.8 µg/dL (22 nmol/L) (RI, 8 to 25 µg/dL, 221 to 690 nmol/L) and 2 pg/mL (RI, 4 to 48), respectively. Given that the patient had a phenotype more consistent with hypercortisolism, these laboratory values were most unexpected. To exclude the possibility of interference with the serum cortisol immunoassay, liquid chromatography–tandem mass spectrometry (LC-MS/MS) was used to measure urine and salivary cortisol; her 24-h urine cortisol was <1.49 µg/g creatinine (<0.46 µmol/mol) (RI, < 24 µg/g, < 7.4 µmol/mol) and salivary cortisol was 0.015 µg/dL (0.41 nmol/L) (RI, 0.149 to 0.739 µg/dL, 4.11 to 20.39 nmol/L), confirming the low concentrations previously obtained using immunoassay. A comprehensive serum steroid panel by LC-MS/MS showed broad suppression of endogenous steroid synthesis with low 11-deoxycortisol, 17-hydroxyprogesterone, 17-hydroxypregnenolone, 18-hydroxycorticosterone, cortisol, cortisone, corticosterone, androstenedione, unconjugated DHEA, deoxycorticosterone, pregnenolone, progesterone, and testosterone levels.

Case Discussion

The hypothalamic–pituitary–adrenal (HPA) axis carefully regulates serum cortisol levels by integrating a series of complex humorally mediated positive and negative feedback loops. Hypothalamic-derived corticotropin-releasing

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Table 1. Laboratory results (all specimens are serum, unless indicated).[a]

Test	Result	Reference interval
Cortisol, AM	0.7 μg/dL	4-22
ACTH, plasma	<5 pg/mL	6-50
Estradiol	<15 pg/mL	≤31
Dehydroepiandrosterone (DHEA) sulfate	5 ng/mL	8-188
Testosterone, total	4 ng/dL	2-45
Follicle-stimulating hormone	47.8 mIU/mL	23-116.3
Luteinizing hormone	32.1 mIU/mL	10-54.7
Insulin-like growth factor 1 (IGF-1)	119 ng/mL	50-317
IGF-1, z-score	−0.3	−2.0 to +2.0
Prolactin	10.4 ng/mL	2-20
Thyroid-stimulating hormone	3.25 mIU/L	0.40-4.50
Thyroxine, free	1.3 ng/dL	0.8-1.8
Aspartate transaminase	51 U/L	10-35
Alanine transaminase	80 U/L	6-29
Alkaline phosphatase	138 U/L	37-153
Bilirubin	0.6 mg/dL	0.2-1.2
Blood urea nitrogen	11 mg/dL	7-25
Creatinine	0.69 mg/dL	0.5-1.05
Glucose	89 mg/dL	65-99
CO_2	30 mmol/L	20-32
Sodium	142 mmol/L	135-146
Potassium	4.0 mmol/L	3.5-5.3
Chloride	103 mmol/L	98-110
Albumin	4.1 g/dL	3.6-5.1
Total protein	7.0 g/dL	6.1-8.1

[a]SI conversion factors: cortisol nmol/L × 27.6; estradiol pmol/L × 3.67; DHEA sulfate nmol/L × 3.47; testosterone pmol/L × 34.7; bilirubin umol/L × 17.1; blood urea nitrogen mmol/L × 0.357; creatinine umol/L × 88.4 ; glucose mmol/L × 0.055.

hormone (CRH) stimulates the pituitary secretion of ACTH, which in turn stimulates adrenal glucocorticoid biosynthesis and secretion. Simultaneously, serum cortisol levels circulate back to the pituitary and hypothalamus to exert negative feedback control to suppress hypothalamic-derived CRH and pituitary-derived ACTH, respectively. In a similar manner, exogenous steroids can cause HPA axis suppression, after relatively short-term steroid use (1,2). Abnormally elevated cortisol levels over time, whether due to endogenous causes (such as Cushing syndrome) or prolonged exogenous steroid ingestion, can cause significant morbidity with central weight gain, facial rounding, prominence of the dorsal neck fat pad, easy bruising, proximal myopathy, and striae on the abdomen, breasts, hips, and/or under the arms. Women may also note increased hair on their face, neck, chest, abdomen, and thighs. Dexamethasone is a synthetic glucocorticoid that is 25-fold more potent than cortisol and sustained use can cause Cushing syndrome (3).

Screening tests for suspected cortisol excess include serial measurement of 24-h urinary free cortisol (UFC) levels (at least 2 to 3 collections), an overnight 1 mg or 48 h 2-mg/day (0.5 mg × 8 doses) dexamethasone suppression test (DST), and measurement of plasma or late-night salivary cortisol (LNSC) level. Elevated 24-h UFC or LNSC may indicate possible cortisol excess. As an exogenous steroid, dexamethasone suppresses ACTH and subsequently cortisol levels, the normal response being a morning cortisol concentration below 1.8 μg/dL (50 nmol/L). Failure to suppress cortisol following dexamethasone administration suggests cortisol excess. As with any screening test, false-positive or false-

negative results may be observed. For equivocal screening results, confirmatory testing using the low dose 2-day 2-mg DST or desmopressin (DDAVP) stimulation test can be used to definitively diagnose Cushing syndrome.

Our patient presented with many of the symptoms and signs consistent with a Cushingoid state; however, surprisingly, her serum cortisol levels were virtually undetectable. In addition, she had low salivary and 24-h UFC levels by LC-MS/MS methods from 2 different reference laboratories. Given her clinical symptoms were highly suspicious for exogenous steroid exposure (despite patient denial of any known steroid use), a serum specimen was analyzed for dexamethasone by LC-MS/MS, and found to be significantly elevated at 105 ng/dL (2.68 nmol/L) (RI, <20 ng/dL, <0.51 nmol/L). The high serum dexamethasone level explained her presentation with Cushingoid symptoms and her suppressed ACTH and cortisol concentrations.

As the patient denied any steroid intake, the source of the dexamethasone was sought. She admitted to taking a number of supplements for her eyes, thyroid, and arthritis. She was requested to provide a list of all supplements, including pictures of the supplement bottles. None of her supplements listed any glucocorticoids as ingredients.

A notification from the Food and Drug Administration (FDA) was released on April 20, 2022, warning consumers about a product called "Artri-King," which contained diclofenac and dexamethasone, despite not being listed on the product label (4). Artri-King is a dietary supplement promoted as a treatment for arthritis, muscle aches, osteoporosis, bone cancer, and other painful conditions. It was noticed that one of our patient's supplements is also sold as a dietary supplement "for people suffering from osteoarthritis (stiffness and pain when moving joints)." This similarity in claims of the two products made us suspect that dexamethasone was contained in the product used by our patient. To confirm our suspicion, we purchased a bottle of the same supplement she used for her arthritis online, which contained 90 capsules of 750 mg. The contents of 1 capsule were added to 3 mL pooled serum and mixed using a vortex mixer several times during a 3-h period. After centrifugation, 1 mL of the supernatant was mixed with 1 mL of the pooled serum. Both this latter sample and the neat serum were then analyzed for dexamethasone by LC-MS/MS in the same laboratory that tested our patient's sample. The dexamethasone concentration was 101 ng/dL (2.57 nmol/L) in the sample which contained the supplement extract, whereas it was undetectable in the neat serum. This confirmed that dexamethasone was indeed contained in the supplement, although it was not listed as an ingredient.

The patient was advised of the presence of dexamethasone in one of her supplements, which she said she had taken twice weekly for 1 year. Given that her biochemical testing indicated she had HPA axis suppression, she was advised to reduce the dosage to once weekly for 2 weeks, then 1 capsule every other week for another 2 weeks, after which her early morning cortisol would be checked to evaluate HPA axis recovery. Assessment of her bone density by dual-energy X-ray absorptiometry was also recommended, given the duration of dexamethasone exposure. Unfortunately, the patient was unable to return for follow-up because of a change in her insurance coverage.

POINTS TO REMEMBER

- Biochemical evidence of hypercortisolism is expected in patients with clinical suspicion of Cushing syndrome.
- In the absence of increased serum/urine cortisol concentrations despite clinical symptoms of Cushing syndrome, exogenous use of steroids should be suspected.
- Undisclosed drugs contained in dietary supplements can cause diagnostic confusion and unnecessary clinical and laboratory workup.

The United States has a massive supplement industry, with over 4000 products on the market in 1994, and more than 29 000 by 2005, representing an average of 1000 new products each year, and an almost 20-fold increase in the number of supplements from 1994 to 2002 (5,6). Dietary supplements are not required to receive FDA approval before marketing, as the FDA does not provide oversight of supplements for safety and/or effectiveness, and has minimal influence over any claims to "diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases" (5). It is therefore possible that unauthorized constituents, including prescription drugs, may be present in supplements, and in some cases may enhance their effectiveness—we are not aware of any reliable agencies or third-party organizations that regularly verify dietary supplement contents for consumers. It is also difficult for agencies to test for hidden drugs in a supplement without knowing what to look for, given the thousands of possible hidden compounds. This is challenging for healthcare providers, since hidden drugs in supplements may cause severe health problems and unpredictable drug–drug interactions (7–10). In this particular case, hidden dexamethasone in the supplement not only contributed to the patient's clinical symptoms but also generated misleading laboratory results, leading to initial misdiagnosis and unnecessary workup. This case is not unique, as there are multiple reported cases of supplements that contain undisclosed prescription drugs (7–10). As healthcare professionals, it is our responsibility to

report concerns to the FDA to enable proper investigation and increase consumer awareness of the dangers of unregulated supplement use.

Nonstandard Abbreviations: RI, reference interval; ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal.

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Commentary on Low Cortisol in a Cushingoid Patient

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In 2021, the Centers for Disease Control reported that 58% of adults in the United States had used a dietary supplement in the last 30 days. Use of these supplements is higher in women (64%) than men (51%). Among women over 60 years of age, an astonishing 80% report the use of dietary supplements (1). The most common supplements are those containing vitamins (most notably, vitamin D) and omega-3-fatty acids. Tens of thousands of products are available in the dietary supplement market, which is projected to reach $56.7 billion in the United States by the year 2024. These products are not regulated by the U.S. Food and Drug Administration (FDA), although the agency has a mechanism for reporting adverse events encountered with the use of supplements. However, any degree of surveillance by the FDA only occurs after these products are already on the market, so potentially dangerous supplements are in the hands of consumers before any federal interventions are possible.

Dexamethasone is a synthetic derivative of cortisol that is fluorinated at the carbon-9 position and contains a double bond between carbons 1 and 2 on the steroid backbone. Dexamethasone has approximately 25 times the glucocorticoid activity of cortisol and is used in a common provocative test to assess the integrity of the hypothalamic–pituitary–adrenal axis. The drug is useful for suppressing adrenocorticotropic hormone (ACTH) release and measuring the cortisol response because it does not cross-react with immunoassays for cortisol. The undocumented addition of dexamethasone to a dietary supplement, which the authors note had been previously reported, creates a substantial risk of adverse

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