

HPA-D Diagnosis Review

Three basic categories of assessment

1. Signs, symptoms, and history
2. Laboratory tests
3. Perceived stress questionnaires

Although it's not desirable to make a diagnosis based on symptoms alone, it's important to know that not all patterns of HPA axis dysfunction will show up in lab test results. Remember, cortisol signaling issues can be tissue-specific, not just systemic, which means that you can't necessarily detect them in saliva, blood, and urine.

Increased salivary, serum, or urine cortisol levels may be compensated for by glucocorticoid receptor resistance in specific tissues, and that won't show up on a lab test.

On the other hand, low cortisol may be compensated for by upregulated receptor function in particular tissues, which would not be detected by commercial lab tests.

This means that HPA axis dysfunction is a clinical diagnosis, and history, signs, and symptoms play a very important role.

RISK FACTORS FOR HPA AXIS DYSFUNCTION

Trauma (<i>including early life</i>)	Circadian disruption
Poor diet	Mental/emotional stress
Food intolerances	Environmental toxins
Chronic illness	Chronic infections
Inappropriate physical activity	Injury
Poor sleep	Lack of social support

“RED FLAG” SYMPTOMS OF HPA AXIS DYSFUNCTION

Difficulty falling or staying asleep	Impaired exercise tolerance or recovery
Waking up feeling tired even after 7-8 hours of sleep	Weakened immune system
Afternoon energy crashes	“Brain fog” and memory issues
“Second wind” late at night	Extreme hunger, irritation, or agitation before meals
Waking up with heart pounding in middle of the night	Postural hypotension
Inability to handle stress	

OTHER SIGNS AND SYMPTOMS OF HPA-D

Muscle fatigue/weakness/pain	Increased or decreased appetite
Headaches	Difficulty with word recall
Teeth grinding	Dizziness
Cold/clammy hands and feet	Dry skin
Dry mouth/problems swallowing	Loss of muscle tone
Digestive distress	Dark circles under the eyes
Shortness of breath	Weight gain
Depression and/or anxiety	Frequent urination

PERCEIVED STRESS IS ONE OF THE FOUR MAJOR HPA AXIS TRIGGERS

- It may seem unnecessary to assess perceived stress. It’s pretty obvious when we’re stressed out, right? But patients often have differing levels of awareness around this.
- Humans are remarkably adaptable. We get used to our circumstances. They quickly become the new normal, and we don’t realize anything is awry. This is why I suggest using questionnaires to assess perceived stress and stress inventories.
- When patients see a very high score on these assessment tools, they’re more likely to treat it as a real problem.

PERCEIVED STRESS SCALE (PSS)

- The 10-question version is the most commonly used in clinical settings and is included as a handout for this ADAPT course.
- It measures the degree to which situations in one’s life are appraised as stressful, and it is designed to assess how unpredictable, uncontrollable, and overloaded respondents find their lives to be.

PSS SCORES

- Obtained by reversing the numeric responses
- An answer of zero equals four points, an answer of one equals three points, two equals two points, an answer of three equals one point, and then an answer of four equals zero points—for questions four, five, seven, and eight, and then summing across all of the scale items. The perceived stress scale is not a diagnostic instrument, there are no score cutoffs, only comparisons within groups shown below.

Norm Table for the PSS 10 item inventory			
Category	N	Mean	S.D.
Gender			
Male	926	12.1	5.9
Female	1406	13.7	6.6
Age			
18-29	645	14.2	6.2
30-44	750	13.0	6.2
45-54	285	12.6	6.1
55-64	282	11.9	6.9
65 & older	296	12.0	6.3
Race			
white	1924	12.8	6.2
Hispanic	98	14.0	6.9
black	176	14.7	7.2
other minority	50	14.1	5.0

Another useful assessment tool for perceived stress is the Holmes and Rahe Stress Inventory. The PSS tells you the relative amount of stress a person is under. The Holmes and Rahe inventory does this too, but in the process of filling it out, the patient gains insight into what the major stressors in their life are.

Markers that research suggests are most effective for evaluating HPA-D are free cortisol, metabolized cortisol, the diurnal free cortisol and free cortisone rhythm, the cortisol awakening response or CAR, DHEA, and the DHEA-to-cortisol ratio.

CORTISOL

There are four primary methods of assessing cortisol levels:

1. Serum
 - a. Total cortisol levels represent both bound cortisol, which is 95 percent of the cortisol in the body, and unbound or free cortisol, which is 3 to 5 percent of the cortisol in the body.
 - b. Most of that cortisol is bound to cortisol-binding albumin or globulin and is not bioavailable. We know that several conditions and medications affect cortisol-binding globulin levels, so using total serum cortisol is not a great idea.
 - c. Free cortisol can be calculated from measurements of total cortisol plus cortisol-binding globulin.
2. Hair
 - a. Cortisol accumulates in the hair via passive diffusion from the blood.
 - b. Being investigated as a historical measure of HPA-D.
 - c. Possible for about 6 centimeters worth of hair, equivalent to six months of cortisol production.
3. Saliva
 - a. Saliva only contains free cortisol
 - b. It's a noninvasive, time-specific marker that allows you to capture the diurnal rhythm of cortisol production in a convenient setting, and you can, through those four different readings, estimate total cortisol production.
4. Urine cortisol
 - a. 24-hour collection.
 - b. Urine contains free cortisol, but it also contains many cortisol metabolites, such as cortisone.
 - c. Assuming normal cortisol clearance rates, most cortisol synthesized by adrenal glands will be metabolized in the liver and cleared in the urine within 90 minutes. Urine cortisol is a reflection of cortisol production over 90 minutes.
 - d. Precision Analytical's test called DUTCH—dried urine test comprehensive hormones— involves collection of a small amount of urine on filtered paper four times a day. This allows estimate diurnal production, like saliva, but it also provides information on both total free cortisol and overall cortisol using metabolites as well as free cortisone and metabolized cortisone.

One of the most commonly used markers for HPA axis function in the scientific literature is called the cortisol awakening response, or CAR.

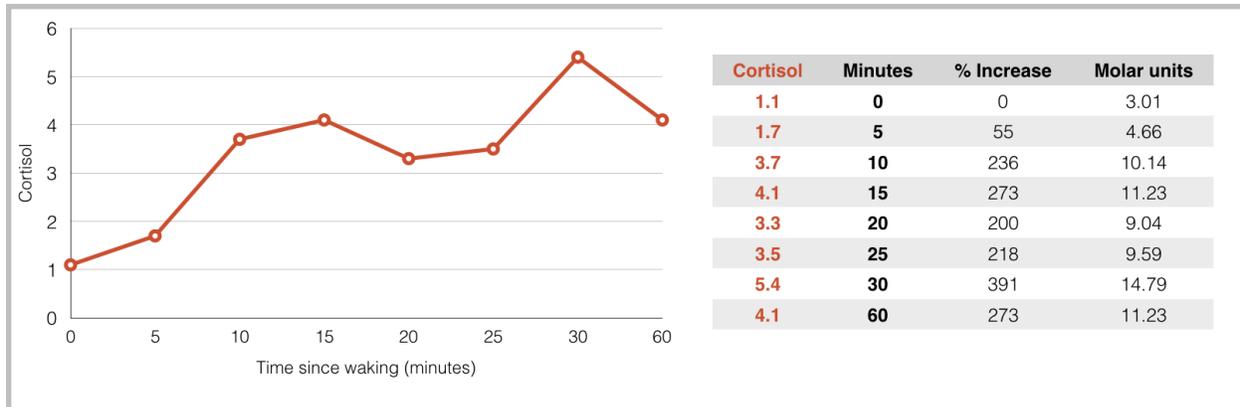
- CAR is the increase of cortisol that occurs in the morning just after awakening.
- The proper procedure for capturing the cortisol awakening response would be testing at waking, and then again at 30, 45, and 60 minutes.
- Rising cortisol begins several hours before awakening due to normal HPA axis activity, and then there is a transient 30- to 45-minute additional increase of up to 50 percent in cortisol secretion when light comes into the retina and activates the suprachiasmatic nucleus.
- CAR is a marker of how the HPA axis responds to stress.
 - For example, lower CAR is observed in people with PTSD, chronic fatigue, and burnout, and it's higher in people with ongoing job stress and higher levels of perceived stress.

CAR TESTING CHALLENGES

Remember, more than 50 percent of the cortisol we produce in a given day is produced within 30 to 45 minutes of waking up. If a patient misses that cortisol produced during the CAR, the estimate of the patient's total cortisol production may be low when they don't actually have low cortisol. At the time of this recording, the DUTCH Plus test is the only lab that includes a cortisol awakening response but unfortunately, it is not yet available as a stand alone test. It can be an optional add-on for their other panels.

As an alternative option, you can test CAR using a pre-existing saliva test from any of the major labs.

1. Order a kit from one of the labs.
2. Have the patient rinse their mouth and collect saliva for two to three minutes right after waking.
3. Then collect again at 30 minutes, 45 minutes and 60 minutes.
4. Patients can drink a little water between each collection but should not eat.
5. Healthy CAR should show a 350 to 600 percent increase in the first 30 minutes.



You can use the results to calculate a percentage increase regardless of the units.

DHEA:

For DHEA and DHEA sulfate, assessment options include serum, saliva, and urine. Note that the concentration of DHEA sulfate is 300 times higher than DHEA in serum.

Serum:

- DHEA and DHEA sulfate are often combined into a measurement called DHEA (S).

Saliva:

- Testing of DHEA in saliva is somewhat controversial, in part because we understand so little about DHEA.
- Salivary DHEA sulfate levels are only 2.5 times higher, versus 300 times in serum, than salivary DHEA.
- Also, levels of DHEA (S) drop quickly in the first hour after awakening, and this can make timing difficult.

Urine:

- DHEA sulfate can be measured but not DHEA.
- Some studies suggest that a combination of DHEA sulfate, androsterone, and etiocholanolone may be a more accurate indication of total DHEA production.

The **cortisol-to-DHEA ratio** is another important marker to consider.

- It can be an indicator of catabolism versus anabolism.
- Anabolism means building things up, tissue repair, growth, and recovery.
- Catabolism means breaking things down and is defined as breaking down molecules into smaller units that are oxidized to release energy.

- Clinically, I use the ratio as a rough relative guide. If DHEA is low or low-normal and cortisol is high or high-normal, the ratio is out of whack.

SALIVA VERSUS DUTCH TESTING:

Saliva pros

- Noninvasive
- Can be done at home
- Not stress-inducing
- Reflects specific time points
- Measures free/unbound cortisol
- Has potential of capturing CAR

Saliva cons

- Nonstandardized
- Improper test collection methods
- Does not measure cortisol metabolites
- Labs don't provide cortisone results

DUTCH pros

- Has advantages of saliva (easy to collect, noninvasive, captures diurnal rhythm) and urine (measures metabolites such as A-THF, cortisone)
- Differentiates between free/total cortisol
- Measures not only DHEA-S but also etiocholanolone and androsterone
- Measures sex hormones and sex hormone metabolites
- Captures CAR with DUTCH Plus test

DUTCH cons

- Not as much research correlating urine cortisol with disease, though there is quite a bit on obesity, depression, chronic fatigue, etc.
- Not much research on dried urine
- Each sample represents two-hour previous average rather than single time point

COMPARISON OF HPA AXIS ASSESSMENT METHODS

	Serum	Saliva	Urine (24hr)	Dried Urine
Adrenal Hormones	Yes	Yes	Yes	Yes
Diurnal Free Cortisol Pattern	No	Yes	No	Yes
Cortisol Metabolism	No	No	Yes	Yes
Sex Hormones	Yes	Yes	Yes	Yes
Sex Hormones Metabolites	Yes	No	Yes	Yes
Easy Collection	No	Yes	No	Yes
Can Capture CAR	No	Yes	No	No*

Internal research at Precision Analytical that's ongoing suggests that the morning cortisol value correlates pretty well with the cortisol awakening response

This week, we showed an example of a patient who did three split samples on the same day with the following results:

1. BioHealth: Low cortisol suggestive of adrenal fatigue.
2. LabCorp: Results in the normal range.
3. DUTCH: Cortisol was in the normal range, and free cortisol is a touch on the high side in the afternoon.

Given all this, which method should you use in clinical practice? I prefer the DUTCH Plus test that now includes a saliva cortisol awakening response (CAR).

ANALOGY:

- A house of mystery with about 10 windows; seven of the windows are boarded up, and saliva allows us to look into two windows.
- Urine testing allows us to look into one of those two windows, which is overall free cortisol, and a third window which is total production.
- DUTCH gives us all three windows, the diurnal pattern, the overall free cortisol levels, and total cortisol production, but we still can't see into the windows of tissue sensitivity, receptor response to both cortisol and ACTH.