From Stages to Patterns: Science-Based HPA Axis Assessment

The 3-Stage model of “adrenal fatigue” has long been considered a staple of the functional medicine community. Based upon the pioneering work of the father of stress, Dr. Hans Selye, using animal models, it has served the purpose of helping clinicians observe the progressive impacts of stress on the body, and the subsequent physiological changes. However, like all models and theories, this premise has evolved, leaving behind much of its value. This doesn’t mean that it is no longer of any use. Any theory that helps us understand a phenomenon has a place in clinical practice.

However, by updating the model, it becomes more powerful and helps hypothalamic-pituitary-adrenal (HPA) axis assessment gain more credibility in the medical and scientific communities. With clinicians, patients, and laboratory leaders alike understanding and implementing the latest research from the scientific community, and its clinical applications, that we can push HPA stress testing into the mainstream - and entrench it firmly where it belongs – in evidence-based territory, helping patients in a significantly more successful manner.

3-Stage Model vs. Current Scientific Literature on HPA Axis Function

The 3-Stage model attempts to describe the progression of stress-related dysfunction of the HPA axis by making assumptions about the adrenal glands and other physiology that we now know to be inaccurate. While the 3-Stage model can be helpful, dispelling its inaccuracies and understanding the current knowledge will only further our progress as health professionals.
Stage 1 Assumptions and Current Scientific Understanding:

As the above diagram shows, in what is considered Stage 1 of the 3-Stage model, initial exposure to chronic stressors typically results in elevated cortisol while DHEA levels remain constant or decline. The cause of the stress and vitality/age of the patient will determine if DHEA levels will be lower than expected or “normal.”

3-Stages Assumption: The adrenal glands are being assaulted by a stressor which causes a prolonged stimulus to adrenal glands to produce excessive prolonged cortisol. The adrenal glands cannot meet this demand indefinitely and eventually other pathways are compromised to facilitate cortisol demand. This is where the theory of “pregnenolone steal” comes into play.

The theory is that all steroidal hormones are derived from a common precursor, pregnenolone, and that increased demand for production of cortisol diminishes the total available pool of raw material needed to produce other hormones. While an increase in cortisol is a common characteristic in early to midterm stress progression, the notion that there is a limited “pool” of raw material for all hormones to work with is simply incorrect. The transformation of cholesterol to pregnenolone occurs in the mitochondria of the cell and there is no known pool or mechanism of physiology whereby a cell can transfer pregnenolone to the mitochondria of other cells.

Current scientific understanding: Prolonged stressors do affect the HPA axis mechanism; cortisol is often initially driven higher. This is caused by adrenocorticotropic hormone (ACTH) production and HPA axis activation. As Stage 1 begins to transition we see an adaptation by the HPA axis. This can be caused by an adaptation to a specific stressor (overcoming a fear of public speaking, for example), a down-regulation of the HPA to prevent damage from excessive cortisol, or both.

Stage 2 Assumptions and Current Scientific Understanding

As we see in the figure above, in Stage 2, chronic stress progresses to a more permanent down-regulation of cortisol production, but total cortisol levels are still often within laboratory reference ranges. This is differentiated from Stage 1 in that DHEA-S levels are now lower than expected. Additionally, we may see a history of chronic stress side effects and nuanced changes to cortisol diurnal rhythm.

3-Stages Assumption: A transitory phase, it is thought that ACTH levels remain high, or even increase. However, the adrenals' ability to respond to ACTH stimulation is lessened. “Pregnenolone steal” is thought to contribute to the maintenance of normal cortisol levels at the expense of DHEA, meaning DHEA levels are low or borderline low. This is often thought of as “adrenal fatigue.”

Current scientific understanding: There is no evidence to suggest that the zona fasciculata (the part of the adrenal glands where cortisol is produced) becomes insensitive to ACTH or fails to respond over time. Therefore, lower cortisol levels are most likely due to a reduction in ACTH caused by a down-regulation of the HPA axis. This down-regulation is a normal reaction to repeated bouts of elevated cortisol or exogenous glucocorticoids.

Additionally, low cortisol levels may be due to an increase in Cortisol Binding Globulin (CBG), whereby salivary (free) cortisol levels are lower while total serum cortisol may remain elevated.
Again, this is a protective mechanism designed to reduce cortisol’s damaging effects and decrease the need for long-term down regulation of ACTH. Lower DHEA levels are a natural product of 1) prolonged chronic stress activation (Stage 1) and 2) Declining ACTH secretion (Stage 2). Aging can also result in lower DHEA levels and may be a contributing factor depending on the patient. Note that BioHealth DHEA-S references ranges are age and gender specific to help in more accurate diagnostic data.

**Stage 3 Assumptions and Current Scientific Understanding**

In the figure above we see that Stage 3 consists of low total cortisol and low DHEA-S. In the literature this is referred to as “burnout.” Burnout is often defined (although not in all cases) as having a low sum of total cortisol, a flat cortisol awakening response, or a low cortisol response to a laboratory psychosocial stress test such as the TSST (Trier Social Stress Test).

3-Stages Assumption: The 3-Stage model predicts a progression of stress-related adaptations which moves the body from Stage 2 to Stage 3, if left unchecked. The model assumes that ACTH levels are constant and it is a failure on the part of the adrenal glands to be able to keep up with the cortisol levels demanded. This stage is often termed “adrenal exhaustion.” However, this stage can be differentiated from true adrenal insufficiency conditions by evaluating ACTH levels and the body’s response to ACTH injections. True adrenal insufficiency is a serious problem; if one has it, life-long hydrocortisone therapy is often required.

**Current Scientific Understanding:** While cortisol levels may reach the point of being considered hypocortisol, with associated low levels of DHEA, this is not due to adrenal gland resilience to ACTH, but rather chronic HPA axis down-regulation and metabolic dysfunction. The depletion of metabolic reserves means that treating patients at this point can be extremely challenging and often require years of work to regain metabolic reserves and regain adequate protection from stress. Metabolic reserve can be thought of as the ability of the cells and organs to withstand repeated (chronic) demands to meet physiological needs.

**Assessing HPA Function Using the Latest Research**

Given that the latest scientific literature has debunked many of the assumptions that the 3-Stages Model was predicated on, what is the most reliable, scientific, and accurate way for a clinician to assess HPA axis function? The answer is combination of the most reliable staples of functional medicine theory with the latest advancements in the research. Combined, we believe this to be the absolute best way to assess HPA function outside of a controlled research setting.

**The Elements That Need To Be Assessed Are:**

**Diurnal Cortisol Rhythm**

The most common analyte for measuring HPA axis function is cortisol. Used in thousands of studies and clinical trials, it has established itself as the go-to marker for assessing status, reactivity and function of the HPA axis. The production of cortisol has a predictable diurnal pattern and can be intentionally suppressed or stimulated with various interventions making it easy to study.
One of the most important features of the HPA axis is its circadian rhythm, which results in a predictable diurnal cortisol secretion pattern. There should be a dramatic difference between awakening levels of cortisol and evening levels (greater than 5-fold).

**Cortisol Awakening Response**

Cortisol Awakening Response (CAR) is the predictable rise and fall cortisol within one hour of waking. The CAR is caused by two phenomena: First, the natural propulsion of rising cortisol that starts hours before waking, due to normal circadian HPA axis activity (namely ACTH). Second, a temporary (30-45 minute) further increase of up to 50% in cortisol secretion due to light activation of the suprachiasmatic nucleus (this does not occur when awakening from a nap).

The CAR has been used significantly more than overall diurnal salivary cortisol in the clinical literature to define specific stress-related HPA axis dysfunctions that affect cortisol output. It is affected by overall HPA reactivity, and analogously, it acts as a mini stress test for the HPA axis upon awakening. In those with PTSD and chronic fatigue we see a blunted CAR. We also see higher a CAR on workdays (stressful) as opposed to days off (usually more relaxed, suggesting CAR is partially dependent on perception/anticipation of stress).

In an ideal CAR, cortisol will increase 35%-60% about 30 minutes after awakening (when it peaks) and start to drop closer to awakening levels at 60 minutes after awakening.

**DHEA Sulfate**

DHEA-S is a neurosteroid that supplies 50% of the androgens in men, 75% of the active estrogens in premenopausal women and 100% in postmenopausal women. The more stable, sulfated form of DHEA, DHEA-S, provides a more reliable measure of DHEA levels than DHEA itself and salivary levels are ~1% of free serum levels and .05% of total serum DHEA-S levels. DHEA-S decreases with age and supplementation may be beneficial (if test results and symptoms show a need) for a wide range of symptoms, such as, but not limited to, sexual performance, bone mineral density, cardiovascular function and mental performance.

**Cortisol to DHEA-S Ratio**

This ratio of biomarkers has been studied extensively and can be thought of in a simplified sense as the ratio of catabolic to anabolic hormone. Because DHEA-S has a modulating/down regulation effect on cortisol, the ratio of the two is an important one. As one ages DHEA-S levels drop and the ratio of cortisol to DHEA-S increases. Therefore, it is helpful if DHEA-S results are delineated by age, as well as gender (reference ranges). Finally, it is helpful when looking at this ratio to look at them as a molar ratio taken off the 30-minute waking sample, when DHEA-S and cortisol are at their highest.

**Perceived Stress Scale**

The human stress response is designed to quickly activate and help protect us from harm. The classic fight or flight analogy of being chased by a bear in the woods often comes to mind. Unfortunately, this system cannot tell the difference between real and perceived threats. Concerns
over money, relationships, or even choosing what clothes to wear, all act on the HPA axis to increase activation which may eventually lead to dysfunction, depending on intensity and duration. Since determining all causes of stress (perceived or real) is essential to repairing HPA axis dysfunction, how does one determine perceived stress and what effect it’s having on the body?

The Perceived Stress Scale (PSS) has been in use since 1983 and assesses the level of control people feel over their lives. Because perception and anticipation of stress adversely impact the HPA axis (most easily seen in the CAR) the combination of the PSS and CAR results make for an efficacious way to determine the effects and impacts of a patient’s mental and emotional stress. For more info (link to paper).

Sample Patterns of HPA Axis Dysfunction

The following are samples of patterns that you may see when doing an HPA axis assessment, which may point to specific aberrations. These patterns include a minimum of 6 cortisol data points (including the cortisol awakening response, discussed in the next section) and a waking DHEA Sulfate measurement. With the patterns, we’re not relying on conveniently fitted reference range criteria (such as the 3-Stage model), but rather on dynamics which combine diurnal cortisol patterns, DHEA-S levels, and the CAR.

**Ideal**

Overview: An ideal healthy individual with low mental and emotional stress, no trauma history, getting 8 hours of sleep and taking no medication that influences HPA axis function.

CAR (if tested): Cortisol should increase by 35%-60% from the time of waking to the peak approximately 30 minutes later. It should then drop at by minute 60 to levels closer to waking.
Diurnal cortisol rhythm: There should be a natural circadian-driven progression from around minute 30 (peak), throughout the day, with the biggest drop happening after around 3 hours after waking. There should be a substantial (more than 500%) difference from 30 minutes post waking to the nighttime measurement.

DHEA-S: Since this decreases over time, appropriate DHEA levels are age dependent.

Cortisol:DHEA-S ratio: This ratio will naturally change with age as DHEA-S decline but a typical “healthy” ratio is 4:1 to 6:1.

**Hyper Cortisol, High CAR (only)**

Overview: What was often deemed Stage 1 we see many people with increased HPA activation due to excessive perception/worry about the upcoming day’s events. People with depression or premenopausal women who are ovulating may have elevated CAR. Others, with sleep issues, may also have elevated CAR, although, depending on the abnormality (sleep-apnea and limited sleep) may be associated with blunted CAR.

CAR: Waking levels may start higher than reference ranges and exceed a 60% increase by minute 30 in those with high levels of perceived stress.

Diurnal cortisol rhythm: Morning cortisol may exceed the reference ranges and will often be higher at different intervals throughout the day as well. Older people will typically have higher levels of cortisol.

DHEA-S: Although there is not a diagnostic correlation between CAR and DHEA-S, higher levels of DHEA-S at waking is typically seen in those (young) with ideal CAR patterns.
Hyper-Cortisol (with Diurnal Drop)

Overview: This occurs when cortisol is elevated at all or most time points, but the diurnal rhythm is still intact. Unlike those with Cushing Syndrome (high cortisol, no diurnal drop) this pattern indicates that the circadian control is still intact even if the feedback inhibition is sub-optimal. This is a common pattern in those with depression, older adults with poor health and subjects with high levels of life stress.

CAR: Waking levels may start higher than reference ranges and exceed a 60% increase by minute 30 in those with high levels of perceived stress. Older people will have higher cortisol levels in general but the difference between waking and 30 minute (peak) levels may be less (percentage wise).

Diurnal cortisol rhythm: While cortisol will be higher at all intervals, excessive spikes may be due to exercise or lack of blood sugar control.

DHEA-S: Levels may be up after a strong stressor (like waking) but most will have lower DHEA-S levels than healthy peers.
**Hyper-Cortisol Spikes Due to Rigorous Exertion**

Overview: The figure above show the diurnal curve for young men engaged in rigorous sports training on both training days and rest days. There is a noticeable spike in cortisol after training is completed. It’s important that collection occurs at least two hours after any exercise and that rigorous exercise is refrained from on a day of saliva collection.

CAR: This won’t be influenced.

Diurnal cortisol rhythm: Cortisol is fairly low given the health and age of the subjects.

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**Late Evening Elevated Cortisol (Insomnia-Inflammation)**

Overview: Inflammation activates the HPA axis. Typically people with inflammation have a flatter total diurnal curve that worsens as the inflammation becomes chronic.

CAR: Much like the flat diurnal curve, those with chronic inflammation often have blunted CAR. If inflammation affects sleep it may further worsen the CAR.

Diurnal cortisol rhythm: Those with chronic inflammation may have either lower or higher levels of cortisol depending on whether the nature of the inflammation is chronic or acute. Even those with down-regulated HPA axis function may still have elevated nighttime cortisol.

DHEA-S: DHEA-S may be lower than the reference ranges because of HPA axis dysfunction.
However, if they are not, it is a sign that HPA axis still has decent responsiveness.

**Diurnal Cortisol with Blunted CAR**
Overview: Blunted CAR occurs often in those with high levels of prolonged life stress, seasonal affective disorder, PTSD and chronic fatigue. Poor sleep can also lead to a blunted CAR. Finally, blunted CAR is associated with true adrenal insufficiency.

CAR: Waking levels may be normal but the movement between waking and 30 minutes is not as robust as it should be.

Diurnal cortisol rhythm: Blunted CAR is typically associated with low total cortisol. Those with sleep issues or inflammation may have blunted CAR yet high nighttime cortisol.

DHEA-S: These levels are typically below healthy age and sex adjusted peer values. However, those with PTSD may have higher levels of DHEA-S than ref ranges would indicate.

**Hypocortisolism**

Overview: This pattern consists of all or most intervals have low cortisol and total cortisol is often below or near the reference range.

Diurnal cortisol rhythm: Hypocortisolism describes any condition in which cortisol is low, has a flat diurnal curve or blunted cortisol release. Research has shown that those exposed to frequently stressful environments, those with unpredictable schedules, and those with past trauma, are often hypocortisolimic. Flatter diurnal curves typically represent a further progression of HPA axis dysfunction than ones that are still intact and may have a higher risk of chronic disease dysfunction.
DHEA-S: Will typically be lower than age and sex adjusted peer values due to down-regulation of the HPA axis. Those with PTSD may have normal or even elevated levels.

**Where do We Go from Here?**

So, do we completely abandon the 3-stage model? It may be better to say that we evolve from staged thinking to looking at common patterns as points of reference, not as rules. We cannot fit a human being’s cortisol patterns into a neat box and arrive at an immediate conclusion. As a rule-of-thumb, clinicians should rely upon all of their diagnostic and history-taking skills, in addition to laboratory findings, to assess the status of the HPA axis.