Changing Paradigms in “Adrenal” Stress Assessment

In this Article
• Is it Adrenal Fatigue?
• Does Pregnenolone Steal Actually Exist?
• Updating the 3 Stage Model of HPA Dysfunction
• What is Cortisol Awakening Response?

For integrative health professionals, there has been no lab assessment more appreciated for its value in helping to evaluate a patient’s core health status than the adrenal stress profile. This test typically includes four measurements of saliva, performed throughout a single day, to evaluate cortisol diurnal rhythm, as well as DHEA Sulfate (DHEA-S).

While valuable as a clinical tool for many years, the body of current scientific literature does not support many of the concepts and terminology in popular use, where such testing is concerned. It’s time for health professionals, laboratories, and the public alike, to catch up to the research, and reconsider the ideas and words used to describe stress-related health concepts.

Terms such as adrenal stress and adrenal fatigue, and other variations, require clarification in our lexicon. But more significantly, the physiology of the stress response system, as well as the body of research by those investigating its workings, demands fresh attention. When put under scrutiny, it becomes clear that improvements in communication, models and thinking need to be made across all disciplines concerned with using salivary cortisol/DHEA-S analysis in the clinical setting.

Is it Adrenal Fatigue?

In this adapted excerpt from his groundbreaking book The Role of Stress and the HPA Axis in Chronic Disease Management, Thomas Guiliams, PhD, best answers this question:

“Sometimes, when we endeavor to understand and describe complicated medical topics, there is a temptation to find a simple explanation to cut through the complexity. These explanations can help bridge the knowledge gap for a while, but as our knowledge grows, they lose some of their original usefulness (e.g., the notion of “good” and “bad” cholesterol). In some cases, those over-simplified explanations actually become a hindrance to helping clinicians and patients understand the important mechanisms and solutions related to chronic conditions.

The use of terms like “adrenal fatigue” and “adrenal exhaustion” to summarize the complex dysfunctions related to the stress response is one such explanation. Though these terms have helped dispel the notion that only extreme issues related to adrenal function (Addison’s disease or Cushing’s disease) are of clinical importance, and have become surrogate descriptions for stress-related outcomes, they should now be replaced by more accurate and medically appropriate terms, like HPA axis dysfunction, adrenal insufficiency, or where applicable, hypocortisolism.
While it is true that the most common laboratory method to assess the function of the HPA axis is through the measurement of hormones secreted by the adrenal glands, primarily cortisol and DHEA(S), the mechanisms that control the level of these hormones resides mostly outside of the adrenal gland. Low cortisol and DHEA(S) levels may indeed be related to chronic stress, but as a result of HPA axis adaption (down-regulation) to protect tissues from excess cortisol, have little to do with the inherent capability of the adrenal gland to produce these hormones (see adrenal insufficiency below). While many clinicians (and laboratories) still refer to this as “testing the adrenals,” it is much more accurate to say that such testing is assessing the status of the HPA axis using adrenal hormone measurements as surrogate markers.

Using descriptive and accurate terms helps clinicians and patients better understanding the pathophysiology caused by stress and the stress response system. In most cases, issues related to perceived stress, glycemic control, circadian rhythm, cortisol feedback control (in the hypothalamus and/or pituitary), inflammatory signaling, or tissue-specific glucocorticoid effects will have much more to do with a treatment protocol than direct support of adrenal function.

Related to this is the ability of the clinician to interface appropriately with the vast amount of literature that describes patient outcomes related to stress and HPA axis function. The term “adrenal fatigue” is virtually absent from the peer-reviewed literature and has even caused the Endocrine Society to warn the public against the diagnostic “myth” of adrenal fatigue and to cast suspicion upon clinicians using such terms.

**Correcting the Terminology**

**HPA Axis Dysfunction** (or Maladaptation): This term is much more appropriate to describe the many consequences that link stress (allostasis) with the myriad of measurable negative outcomes related to the stress response. The majority of these outcomes can be linked in some manner to processes controlled by the HPA axis. Alternatively, some refer to these as “disorders of the stress system” or the “consequences of the maladaptation to stress.”

**Hypocortisolism**: This is the most descriptive term to use when measured cortisol is well below the laboratory reference range. Still, it is a relative term and does not necessarily implicate dysfunction or “fatigue” of the adrenal gland. Extreme hypocortisolism is associated with Addison’s disease and other forms of primary and secondary adrenal insufficiency. Reduced HPA axis function resulting in low cortisol levels is common in PTSD, fibromyalgia, chronic fatigue syndrome, certain affective disorders, and individuals with high psychosocial “burnout”. Other specific terms for different stress-related HPA axis phenomena include hypercortisolism, loss of HPA circadian function, and low circulating DHEA(S).
**Adrenal Insufficiency:** This is a clinical manifestation that results in a deficient production or action of glucocorticoids, a condition that has potential life-threatening consequences. Primary adrenal insufficiency (i.e., Addison’s disease) describes diseases intrinsic to the adrenal cortex primarily caused by autoimmune adrenalitis. Secondary adrenal insufficiency relates to insufficient pituitary ACTH or intrinsic defects in the adrenal responsiveness to ACTH. Tertiary adrenal insufficiency results from impaired synthesis of hypothalamic CRH or AVP.

Given the facts, it’s time to get away from talking about adrenal fatigue and adrenal stress, and instead refer to HPA axis dysfunction. By using scientifically accurate terminology we promote wider acceptance of the very substance of the concept across all healthcare disciplines.

**Does Pregnenolone Steal Actually Exist?**

For many years, clinicians have surmised that when DHEA levels (or other steroidal hormones) are low that it’s due to a phenomenon known as “pregnenolone steal.” 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. This figure from Dr. Guilliams’ book illustrates this point, demonstrating the hormone synthesis know to occur from each of the glandular zones.
So why do we often see increases/decreases in cortisol and a decline in DHEA when the body is under chronic stress? The amount, as well as the type of stressor, and age of the person, factor strongly into whether DHEA levels are normal or in a state of decline. With cortisol, the body may begin to adapt to chronic stressors (depending on their nature) and/or the body will down-regulate the HPA axis, often in an attempt to spare it from the harm caused by prolonged levels of high cortisol.

By using the right vernacular and having a more accurate understanding of the physiological processes that produce stress-related changes in hormone production, the clinician is better able to assess and hopefully help their patients resolve underlying issues related to stress-driven health conditions.

**Updating the 3 Stage Model of HPA Dysfunction**

The three-stage model (loosely based on Hans Selye’s GAS theory of chronic stress in animal models) has become a common way for clinicians to explain the progression of HPA dysfunction (or maladaptation to stress) using total cortisol sum and DHEA-S value(s). Many laboratories offering such tests categorize patients into a particular stage based on their test results. Some sources, particular those of independent clinicians’ websites, promote additional stages of “adrenal fatigue,” in some cases describing as many as 9 stages. However, all explanations of staged models are based on a number of untested or disproven suppositions from animal models or assumptions based on biochemical pathways – and even a bit of poetic license.

The 3 stage model tries to define progressive stages of chronic stress using incorrect terms and ideas like “adrenal stress,” “adrenal fatigue,” and “adrenal exhaustion.” However, as we discussed in the section “Is it Adrenal Fatigue?” it is understood that these concepts are misleading and/or incorrect.

So, do we completely abandon the staging 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.

Recent research into HPA axis assessment is helping to evolve the 3 stages model into a more science-based concept in which we can better assess HPA axis function by looking at cortisol/DHEA-S test results in terms of patterns. 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, but rather on dynamics which combine diurnal cortisol patterns, DHEA-S levels, and the cortisol awakening response.

For information on how to transition from the staged model of thinking to pattern-based concepts, read the article “From Stages to Patterns: Science-Based Interpretation of Cortisol and DHEA-S.”

**What is Cortisol Awakening Response?**

Cortisol Awakening Response (CAR) is a phenomenon that has been well researched and studied in the scientific community for many years. The CAR is defined by the predictable rise in cortisol that occurs immediately after wakening. It is a result of two processes: 1) The gathering propulsion of increasing
cortisol levels several hours before awakening due to normal circadian HPA axis function, 2) A short term (30-45 minutes) increase of up to another 50% of cortisol levels due to light activation of the suprachiasmatic nucleus (this does not occur when awakening from a nap). Together these processes form the CAR, a measurement that has been used by the scientific research community significantly more than diurnal cortisol measurement to assess stress-related HPA axis dysfunctions.

The CAR is very difficult to capture using the most common patient instructions. Mistiming the collections by even 5 or 10 minutes can lead to results that are substantially different than if collected properly. Ideally, CAR measurement collections must start within 5 minutes of awakening. Another sample should be collected at 30 minutes post-awakening and another at 60 minutes post-awakening. In research settings there may be further delineation, with samples taken at 15 minutes intervals, but in the clinical setting, collections at 0, 30 and 60 will yield an accurate CAR measurement.

Beyond Diurnal Cortisol Rhythm: DCR/CAR

The importance of the CAR lies in its ability to more comprehensively evaluate the dynamics of the HPA axis than diurnal cortisol rhythm alone. The CAR is impacted by overall HPA reactivity as well as a person’s internalization or perception of stress. One can make the analogy that awakening acts as a mini stress test for the HPA axis. For example, an elevated CAR may be indicative of one’s inability to adequately manage stress while a blunted CAR may indicate such tangible conditions as “burnout,” chronic fatigue syndrome, or PTSD. Depressive disorders may result in a higher CAR while seasonal affective disorder typically shows up as a lower CAR.

By combining the CAR with a salivary diurnal cortisol rhythm (DCR/CAR) and Perceived Stress Survey (PSS), we are able to get substantially greater insight into a person’s HPA axis health and what might be driving dysfunction than if anyone one aspect was used alone. Because perceived stress increases HPA axis activation, being able to quantify one’s perception of stress, and the ability to associate it with specific life events, gives the clinician much more insight into the types of therapies or treatments likely to help the patient.

The DCR/CAR based pattern model is a vast improvement upon the 3 stage model. Instead of focusing on incremental stages of maladaptation based on inconsistent cortisol sums and lack of precision for the critical morning measurement, the CAR puts the dynamic output of cortisol in the first hour of awakening into context with remaining cortisol values throughout the day. This graph shows an example of cortisol output related to CAR:

Note (in ideal subjects) the cortisol spike that normally occurs in the first 30 minutes after awakening followed by an approximate decline of 30-60% within an hour. From there, the cortisol values follow a normal diurnal pattern of slow decline, to the lowest point in the late evening when the body should be heading to a state of rest and repair.

There are many factors that can lead to cortisol output problems, such as unhealthy lifestyle habits, chronic infections, inflammation, blood sugar imbalance, excessive alcohol use, and so on. However,
until recently with the discussion of the CAR pattern model, it has been difficult to grasp the relevance of perceived stress on the cortisol output, and the events that occur upon awakening as they set the tone for cortisol activity throughout the day. For this reason, patients undergoing saliva testing to evaluate HPA axis function should complete subjective questionnaires, including the PSS.

**In Conclusion**

It is an exciting time for clinicians, labs, and patients. Advancements in numerous diagnostic disciplines are coming to fruition and fostering new opportunities (and tools) for promoting health and wellness. We at BioHealth hope you will embrace the changes being made in stress assessments and help to make functional medicine practices more widely accepted on their scientific merit, as well as their tangible influence on improving patient care.