KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

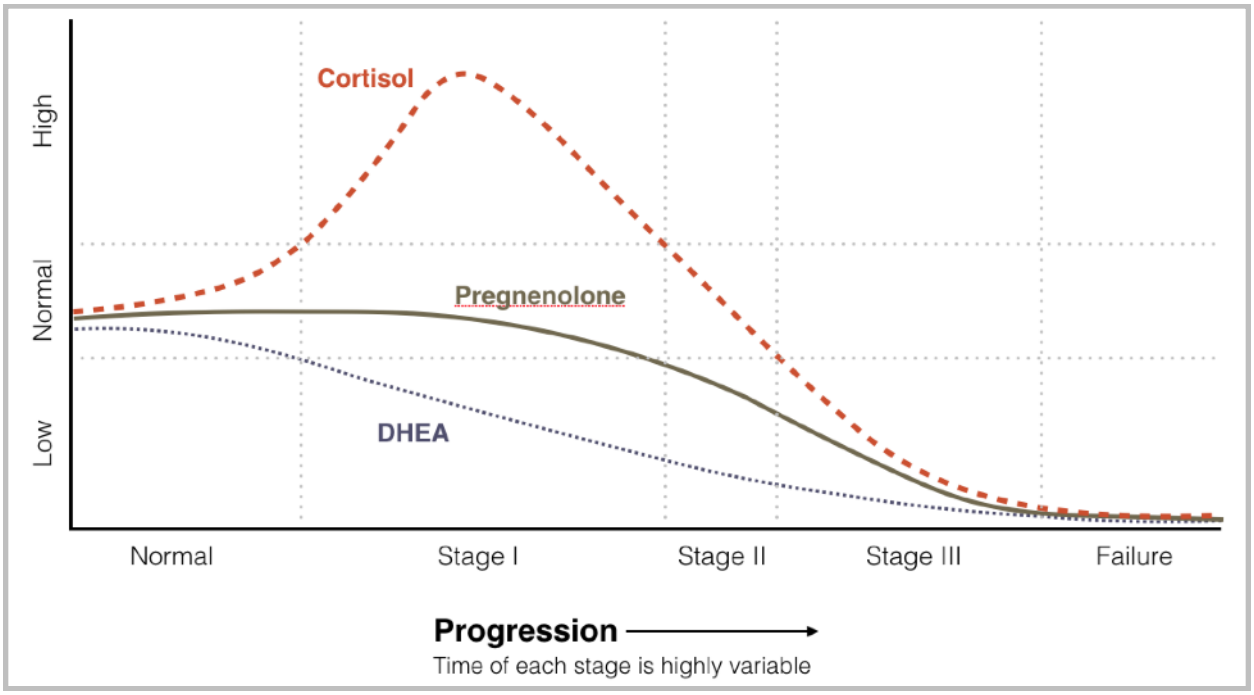
HPA-D or Adrenal Fatigue Review

This week I'm going to argue that the concept of adrenal fatigue is not supported by the current scientific evidence. It should be replaced by more specific terms that are in line with decades of research on how stress impacts physiology.

ADRENAL FATIGUE

Hans Selye proposed the general adaptation syndrome. Acute or chronic stressors eventually cause the HPA axis to move from being hyperresponsive in the early stages to hyporesponsive in later stages, shown below.

SELYE'S GENERAL ADAPTATION SYNDROME

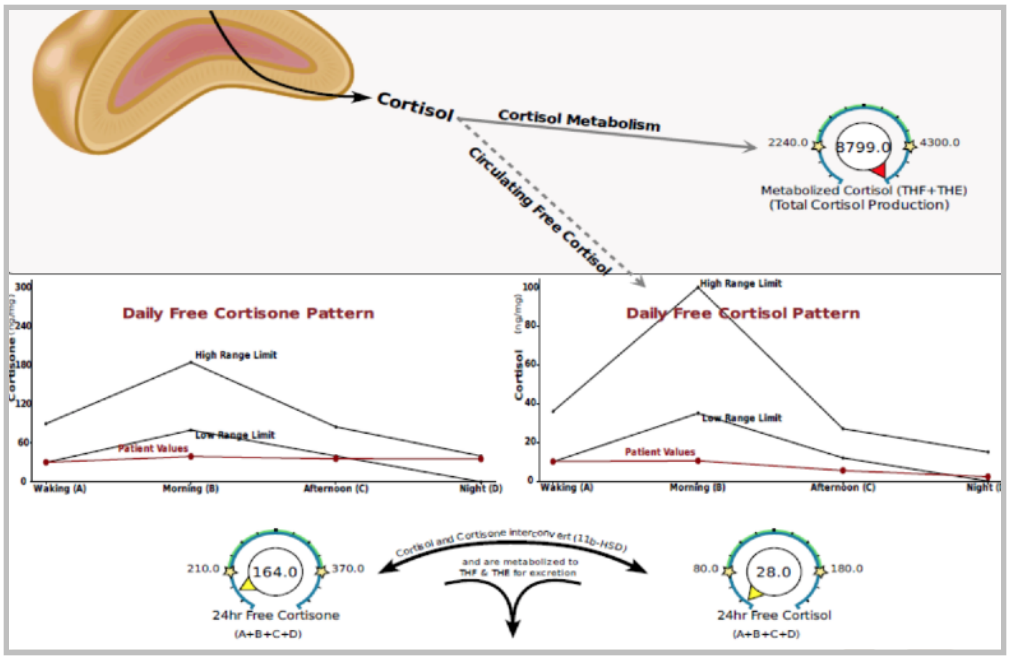


- Stage one: Increase in cortisol and a decline in pregnenolone and DHEA. This stage could last many months or even years.
- Stage two: An adaptation occurs that results in reduced cortisol production such that cortisol may actually even be in the normal range. What distinguishes stage two from normal HPA axis function would be the lower levels of DHEA and pregnenolone.
- Stage three: All three hormones continue to fall until they reach failure or exhaustion.

ADRENAL FATIGUE CONCEPT

- Many people who are diagnosed with or self-diagnose adrenal fatigue don't actually have low cortisol.
- Salivary cortisol testing, particularly the adrenal stress index, is commonly used to identify adrenal fatigue.
    - Cortisol measured in saliva is free, and this is the most potent form because only free cortisol has cell signaling effects and is available to activate the cellular transcription response.
    - Free cortisol is only about 3 to 5 percent of the total cortisol in the body at any given time. The rest of the cortisol in the body is cleared by several metabolic pathways before it's conjugated and excreted into the urine.
    - In the serum, cortisol is bound to cortisol-binding globulin, and cortisol binding globulin varies a lot, even among healthy individuals, and is affected by many disease states and drugs.
    - Free cortisol is not the best marker for overall cortisol production.
    - Measuring the metabolites of cortisol (as measured in the DUTCH test), since most cortisol is excreted in the urine, is the best way of estimating overall production.

Studies have found that many people who have low free cortisol actually have high total cortisol. This is observed in subjects who have insulin or leptin resistance and are overweight, which, of course, accounts for about two-thirds of the U.S. population right now. It can also be caused by things such as chronic stress, glucocorticoid use, including steroid inhalers for things such as asthma, hyperthyroidism, and chronic fatigue syndrome.



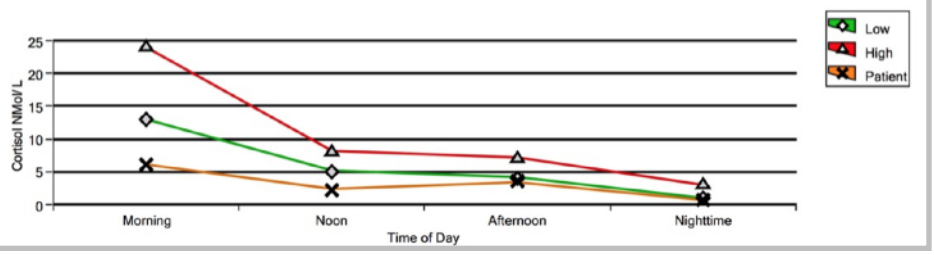
Above is an example of a patient who has low free cortisol, low free cortisone, a flattened diurnal cortisol rhythm and would be diagnosed with so-called adrenal fatigue.

However, their metabolized cortisol level on the upper right is two times the upper end of the lab range, and this person does not have low total cortisol. In fact, they have very high total cortisol production.

Another factor that contributes to the adrenal fatigue concept is different ranges used by labs that do saliva testing can indicate different results.

Functional Adrenal Stress Profile - 201

Parameter	Result	Reference Range	Units
Cortisol - Morning (6 - 8 AM)	**6.1***	13.0 - 24.0	nM/L
Cortisol - Noon (12 - 1 PM)	**2.2***	5.0 - 8.0	nM/L
Cortisol - Afternoon (4 - 5 PM)	**3.6***	4.0 - 7.0	nM/L
Cortisol - Nighttime (10 PM - 12 AM)	**0.7***	1.0 - 3.0	nM/L
Cortisol Sum	**12.6***	23.0 - 42.0	nM/L
DHEA-S Average	4.41	2.0 - 10.0	ng/mL
Cortisol/DHEA-S Ratio	**2.86***	5.0 - 6.0	Ratio



Above is a result on this slide from BioHealth, and you see low cortisol in the morning and at all four time points and a low estimated sum cortisol. It's suggestive of so-called adrenal fatigue.

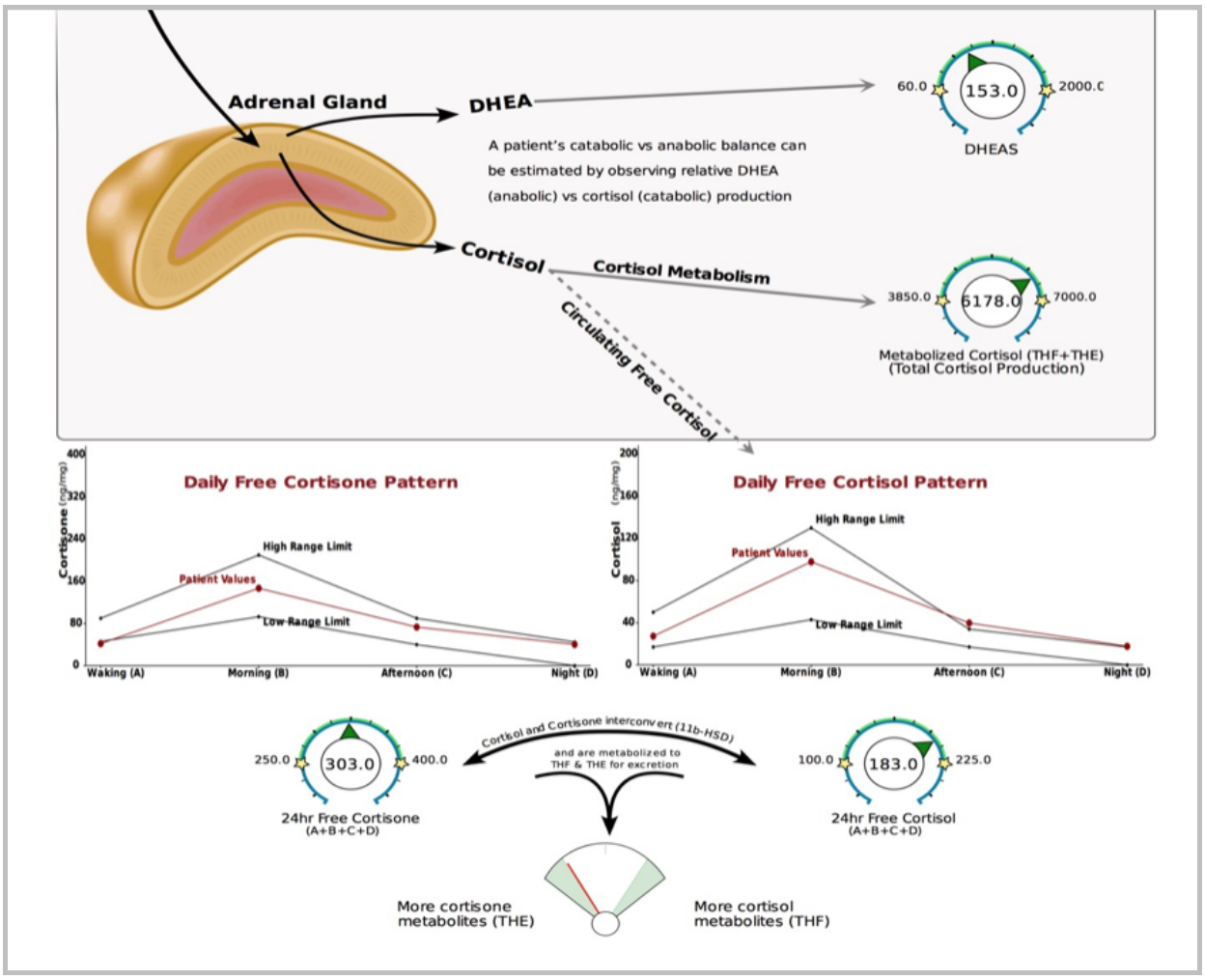
Tests Ordered

Salivary Cortisol X4, Timed

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Salivary Cortisol X4, Timed					
#1 Salivary Cortisol	0.020		ug/dL		01
Draw date/time: 11/09/15 - 00:01					
Reference Range:					
Children and Adults:					
8:00a.m.:	0.025 - 0.600				
Noon:	<0.010 - 0.330				
4:00p.m.:	0.010 - 0.200				
Midnight:	<0.010 - 0.090				
#2 Salivary Cortisol	0.141		ug/dL		01
Draw date/time: 11/09/15 - 08:00					
#3 Salivary Cortisol	0.058		ug/dL		01
Draw date/time: 11/09/15 - 12:00					
#4 Salivary Cortisol	0.123		ug/dL		01
Draw date/time: 11/09/15 - 16:00					

Above is a LabCorp result from the same exact patient, drawn on the same day at the same time. Here we see all of the four values are within the laboratory reference range.

It's very difficult to compare results from saliva labs, but I was able to convert the results from LabCorp and BioHealth into the same units. I found that the low end of the range is 0.025 for LabCorp, but 0.472 for BioHealth (almost 20 times higher lower end of the range). These differences in lab ranges make reliable evaluation difficult.



Above is the same patient's results on the same day from the DUTCH test. We actually did a three-split sample. The metabolized cortisol levels are at the upper end of the range. Then the 24-hour free cortisol is at the upper end of the range and is elevated in the afternoon, and 24-hour free cortisone matches. In addition, the DUTCH hormone test uses a tighter range, which is appropriate as oftentimes the functional lab ranges are a little bit tighter because we're looking for optimal function rather than just disease.

SALIVA CORTISOL TESTING OFTEN RETURNS FALSELY LOW VALUES, ESPECIALLY IN THE MORNING.

- About 30 to 45 minutes after we wake up, light activation of the suprachiasmatic nucleus leads to an increase of up to 50 percent in cortisol secretion. This is called the cortisol awakening response, or CAR.
- The cortisol that is produced during the CAR within the first 30 to 45 minutes of awakening accounts for more than half of the total cortisol reported on a full day's saliva test.
- This means that the timing of the first sample collected is absolutely crucial to getting accurate results because the adrenal stress index estimates the total cortisol production for the day based on those four readings.
- This is a huge problem because labs only suggest doing the waking sample during a window of time, for example between 6 to 8 a.m. with no regard for waking time.

The term "adrenal fatigue" is virtually absent from the scientific literature, whereas there are thousands of studies detailing the effects of stress on human physiology via dysregulation of the HPA axis. Things such as high cortisol, cortisol resistance, or disruption of the diurnal rhythm are far more common than low cortisol as a mechanism.

Even if cortisol is low in some patients, it's rarely because the adrenals are fatigued or exhausted and unable to produce it. Instead, the control mechanisms for cortisol are mostly found in the brain and the central nervous system, as well as in local tissues.

SEVERAL MECHANISMS THAT LEAD TO LOW CORTISOL INCLUDE:

Developmental factors

- The theory is that early life stress can permanently program the HPA axis to a maladaptive response.

CRH receptor downregulation

- Animal studies have shown a decrease in CRH receptor sensitivity in the pituitary gland after prolonged exposure to stress.
- Other studies have shown an increase in the sensitivity of HPA axis to cortisol during periods of stress leads to downregulation of further release of cortisol.

Impaired cortisol signaling

- Refers to a group of related dysfunctions; chronically high cortisol levels will lead to cortisol resistance.

Decreased cortisol bioavailability

- One cause of increased levels of cortisol-binding globulin.
- Another cause is the increase of the conversion of cortisol, which is the more active form, into cortisone.

Maladaptive response

- In people suffering from recurrent or chronic infections or chronic inflammation, the body may reduce cortisol production or signal an attempt to deal with the infection.

Enhanced sensitivity to negative feedback

- Associated with conditions such as rheumatoid arthritis, PTSD, sexual abuse, burnout syndrome, and chronic pelvic pain

None of these mechanisms leading to low cortisol has anything to do with the adrenals being fatigued or unable to produce it.

There is some evidence that low cortisol may occasionally be caused by a reduced ability of the adrenal glands to produce it. A few studies in chronic fatigue syndrome have suggested low cortisol is caused by adrenal insufficiency, and these studies measured free cortisol but not total cortisol. It may just be that in these studies they're not measuring total cortisol, so it only appears that cortisol is low.

PREGNENOLONE STEAL

- Pregnenolone is the precursor of all steroid hormones, and in times of stress, pregnenolone is diverted into the production of cortisol at the expense of DHEA, testosterone, and estrogen.
- It is true that chronic stress can lead to a drop in DHEA, but this effect is not caused by a reduced availability of pregnenolone because it's being "stolen" for cortisol production. That theory assumes that there's a single pool of pregnenolone in the adrenal glands from which both DHEA and cortisol are produced.
- DHEA and cortisol are produced in the mitochondria of individual cells, not from a central pool of pregnenolone.
- Cortisol and DHEA are produced in different parts of the adrenal cortex.
    - DHEA is produced in the zona reticularis.
    - Cortisol is produced in the zona fasciculata.
- There is no known mechanism by which pregnenolone can be stolen from inside of the mitochondria of cells in the zona reticularis, which are producing DHEA, and be transferred to the mitochondria of cells in the zona fasciculata to produce cortisol.
- Cortisol production is regulated primarily by cell-specific enzyme concentration and signaling coming from outside of the adrenal glands themselves.
- The amount of cortisol produced is significantly higher than the amount of DHEA produced.
- If there were an adrenal pregnenolone pool that had enough pregnenolone to handle the higher levels of cortisol, then that pool would also be available for the much smaller amount of DHEA we need when cortisol synthesis decreases even a little.
- Finally, there's no convincing research suggesting that oral pregnenolone supplements increase DHEA levels.

So what does lower DHEA when cortisol is high? It is governed by regulatory processes such as negative feedback inhibition, receptor signaling, and genomic regulation of enzymes.

ADRENAL FATIGUE THREE-STAGE MODEL

1. This is a complicated process with multiple contributing factors, and thus, it is just not as neat and tidy as in this three-stage model.
2. Not everybody progresses through it in the proposed adrenal fatigue order.
3. Even when people do progress from a hypercortisol state to a hypocortisol state, they may do that at very different rates.

WHY DOES THIS MATTER?

1. A clear understanding of what's actually happening leads to more appropriate and better treatment outcomes.
    a. For example, if a patient has low free cortisol but high metabolized cortisol, and they are misdiagnosed with adrenal fatigue and given supplements or even medications to increase cortisol, that's not going to help in most cases, and it may even cause harm.
    b. It may distract us from the true cause of the problem.
    c. A patient may have very low free cortisol and a flattened cortisol rhythm, but their metabolized cortisol is high-normal, as is their DHEA. This is not adrenal fatigue but early insulin and leptin resistance.
2. If we want to maintain credibility among patients and other medical providers and continue to advance functional medicine, we need to align our diagnostic and therapeutic methods as much as possible with research related to the HPA axis.

If it's not adrenal fatigue, what should we call it? I think more appropriate terms for the syndrome that we're referring to would be HPA axis dysfunction or HPA axis maladaptation.

WHY DOES THIS MATTER SO MUCH?

1. It brings us into alignment with the current evidence base, and that allows us to leverage the vast amounts of research connecting stress and the HPA axis function with disease outcomes.
2. A more accurate framework helps clinicians and patients to better understand what is happening.
3. It leads to better treatment outcomes and prevents harm.

Based on all the above, I would argue that it's time to lay the adrenal fatigue concept to rest.