

Assessment and Nutraceutical Management of Stress-induced Adrenal Dysfunction

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Summary

Stress, whether chemical, physical, or emotional in origin, creates specific cascades in the human body. Activation of the hypothalamic-pituitary-adrenal axis (HPA) creates an end product of circulating cortisol, which in the short term is useful for adaptation but in the long term can create a myriad of health problems. Chronic activation of the HPA axis initially leads to hyperadrenia in the body's attempt to compensate for the overload of stress. "Adrenal fatigue" has been associated with hypoadrenia. Uncompensated stressors thus cause either hypo- or hyperadrenia and, for purposes of this article, both

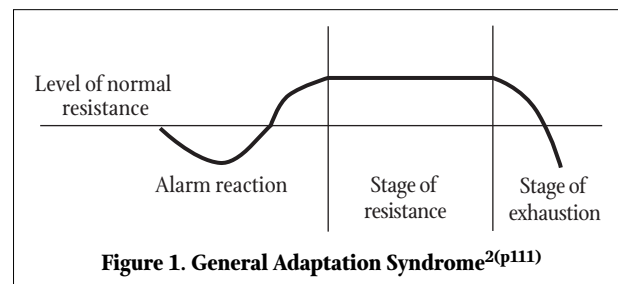
will be referred to as adrenal dysfunction.

Due to chronic activation of the HPA axis, adrenal dysfunction is becoming an ever-increasing vague syndrome presenting to the physician. If adrenal dysfunction is suspected, proper assessment is necessary before attempting to alter adrenal function. Once proper assessment is complete, research has shown that a variety of natural compounds have an impact on adrenal physiology. We will discuss basic stress physiology, clinical assessment of adrenal function, and possible nutraceutical interventions to adrenal dysfunction.

Stress has become the leading health problem in Western society.¹ In spite of work by Hans Selye, considered the father of stress research, in the 1930s to investigate and define the General Adaptation Syndrome (GAS, which is the manifestation of stress in the whole body, as developed over time),² we are more ravaged by the consequences of stress today than at any time in previous history. It is estimated that 75% to 90% of visits to primary care physicians are for stress-related problems.¹ Health and productivity costs of worker stress to American business is estimated at between \$50 billion and \$150 billion per year, and unmanaged reactions to stress have been shown to be greater risk factors for cancer and heart disease than either cigarette smoking or eating high cholesterol foods.³ Much of contemporary stress is psychological rather than physical in origin; yet, according to Selye, all stressors, whether of chemical, physical, or psychological origin, provoke the same responses in the body.²

Selye defined stress as "the non-specific response of the body to any demand,"^{2(p1)} and a stressor as that which produces stress. In human physiology, any stressor, be it a "good" one (excitement, athletic competition, travel, marriage, having a baby) or a "bad" one (tissue injury, pain, hypotension, hypoxemia, hypoglycemia, cold, fever, infection, trauma, emotional distress, burns), stimulates the hippocampus to activate the hypothalamus to secrete corticotropin-releasing factor (CRF), which travels through the hypophysial portal system to the pituitary, stimulating the secretion of adrenocorticotropic hormone (ACTH). ACTH then travels through the systemic circulation to the adrenal cortex, where it induces release of the glucocorticoid cortisol.^{4,7} Immediately upon activation of this pathway, the body begins an alarm reaction:³ gluconeogenesis,⁴ decreased insulin sensitivity,⁸ amino acid mobilization,⁴ protein catabolism,⁴ mobilization of free fatty acids from adipose tissue,⁴ decreased phagocytosis and white blood cell migration,⁴ decreased lymphocyte production,⁴ disappearance of blood-borne eosinophils and lymphocytes,⁴ and increased red blood-cell production.⁴

CRF is controlled through a negative feedback loop of cortisol to the hippocampal neurons, eventually returning the system to homeostasis.⁴ During the alarm reaction, the body's defenses are reduced. According to Selye's GAS theory, when activation becomes chronic, the body transitions from alarm reactions to the stage of resistance in which defenses are elevated and finally to the stage of exhaustion in which defenses are again reduced (see Figure 1).^{2(p111)}



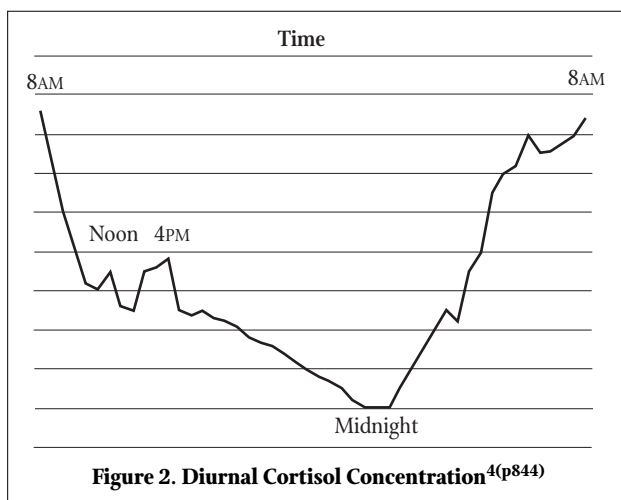
As the body cycles through prolonged or repeated alarm reactions, receptors in the hippocampus become desensitized and damaged (though it is unknown if the damage is permanent), leading to a feed-forward overproduction of cortisol.⁹ Depending on vitality of the individual, cortisol levels may remain high for extended periods with a long stage of resistance, or they may rapidly drop, leading quickly to exhaustion. In the exhausted condition, acute exposure to more stress may act to suppress production of cortisol.¹⁰

Providing levels return to normal reasonably quickly, acute activation of the hypothalamic-pituitary-adrenal axis (HPA) axis presents minimal detrimental effect on the body. However, long-term activation or adrenal exhaustion and hypo-activation have been associated with a myriad of disease processes (see Table 1).¹¹ Elevated levels of circulating cortisol have a direct inhibitory effect on all levels of the reproductive,¹²⁻¹⁴ growth hormone,^{15,16} and thyroid axes.¹⁷

At rest, the body undergoes a specific diurnal pattern of cortisol

Increased Stress System Activity	Decreased Stress System Activity
Anorexia nervosa	Atypical depression
Chronic active alcoholism	Chronic fatigue syndrome
Chronic excessive exercise	Cushing's syndrome
Hyperthyroidism	Hypothyroidism
Malnutrition	Nicotine withdrawal
Melancholic depression	Obesity
Obsessive-compulsive disorder	Post-traumatic stress disorder
Panic disorder	Seasonal depression
Pre-menstrual tension	Vulnerability to inflammatory diseases
Severe chronic disease	
Vulnerability to addiction	

secretion, peaking in the early morning, slowly declining throughout the daytime, and increasing again overnight, with a small mid-afternoon spike (see Figure 2).^{4(p844)} When this pattern is disrupted, whether by increased secretion of cortisol induced by acute or chronic stress or by decreased secretion in the stage of exhaustion, symptoms dependent on the genetic composition and environment of the individual will develop (see Table 2).^{18,19} A thorough case history detailing possible acute or chronic stressor exposure (see Stress Factor Questionnaire on p. 20) is invaluable not only in determining the presence of adrenal dysfunction, but also in preparing a treatment plan to assist the patient in finding new methods of managing or reducing the body's reaction to stress. While conventional thought would classify symptoms according to pattern, anecdotal evidence has shown that pattern recognition by case history is but minimally effective. Due to difficulties distinguishing patterns from symptoms, it is important for the clinician to have reliable tests available to correlate with the patient's case history.



Afternoon low between 3-4 PM	Difficulty getting up in the morning
Anhedonia	Fatigue not relieved by rest
Anxiety	Feeling better after eating
Cognitive dysfunction	Increased effort to do everyday tasks
Confusion	Increased fears
Craving salt or sugar	Increased recovery time
Dark circles under eyes	Increased symptoms with skipped meals
Decreased ability to handle stress	Insomnia
Decreased libido	Lethargy
Decreased memory recall	Orthostatic hypotension
Decreased productivity	Pain
Decreased tolerance	Pre-menstrual tension
Depressed mood	
Difficulty concentrating	

Adrenal Function Assessment

Assessment of the HPA axis is accomplished by any of several conventional methods, including insulin-tolerance test, CRH stimulation, and ACTH stimulation, all of which require venous sampling and, ironically, can induce cortisol secretion simply by the process of sample collection.²⁰ Serum cortisol is 90% to 94% bound by plasma proteins,^{4,21} and its level can be affected by certain medication use or disease states.^{19,20,22} Salivary-cortisol levels represent the unbound fraction of circulating cortisol.²³ In multiple analyses of salivary-cortisol testing compared to plasma-cortisol testing, salivary- and plasma-cortisol levels maintained a similar profile of stimulation and recovery.^{20,24,25} Thus, salivary-cortisol assessment appears to be sufficient for assessing HPA-axis status.

Since resting cortisol presents a specific diurnal pattern, it is vital to obtain multiple samples throughout the day; a single sample is not adequate to discern the patient's diurnal pattern of cortisol secretion. It is also recommended that the patient sample on an "average" day, since altered levels of stress will alter the lab results. Salivary-cortisol testing negates the necessity of the patient making multiple visits for venous sampling since the sample can be taken by the patient and is a cost-effective method of determining diurnal cortisol patterns.^{20,24,25}

Diet and Lifestyle Modifications to Promote Adrenal Health

In a healthy person, adrenal reaction to stress is well under control. However, today, seldom do we find true health. Following are ways that you can counsel your patients to avoid diminishing and start improving their adrenal health.

Diet and Caffeine

Cortisol and blood glucose levels have an intimate relationship. During times of stress, cortisol mobilizes glucose into the bloodstream by gluconeogenesis, decreased insulin sensitivity, amino acid mobilization, and protein catabolism. Hypoglycemia causes the release of cortisol.⁸ Because of this relationship, diet plays a key role in adrenal health. Skipping meals or eating meals or snacks rich in simple carbohydrates can create a hypoglycemic state, which induces the stress mechanism and release of cortisol.

Stress Factor Questionnaire

Name: _____ Date: _____

Respond with respect to your current state of health and any existing health challenges.

0 – Definitely not a factor

1 – Possibly a factor, but I don't really think so

2 – Possibly a factor, I just don't know

3 – I think this could be a factor

4 – I feel that this is a significant factor

5 – I know this is a key factor

Structural/Physical Stress

- Physical work habits
- Inherited weakness in your structure
- Insufficient rest
- Altered joint mobility / mechanics
 - Foot, ankle, knee mechanics
 - Hip, pelvic, spinal mechanics
 - Wrist, arm, shoulder mechanics
- Poor postural habits
- Insufficient or improper exercise
- Past surgeries
- Past injuries (auto, sport, etc)
- Birth trauma

Mental/Emotional/Spiritual Stress

- Home environment (past or present)
- Work environment (past or present)
- Social/Community environment (past/present)
- Social activities (or lack thereof)
- Recreational activities (or lack thereof)
- Low self-esteem
- Insufficient love
- Values / rules conflicts
- Religious conflict
- Mental / emotional relaxation
- Insufficient creative expression
- Financial
- Career fulfillment
- Relationship with family
- Relationship with significant others
- Relationship with coworkers
- Relationship with friends
- Sufficient happiness and joy
- "Self-talk" (your inner dialogue and internal evaluations)

Chemical Stress

- Food allergies or intolerances
- Food and/or beverage choices
- Eating habits (too rushed, skipped meals, etc)
- Inefficient digestion
- Low nutrient levels
- Drug use (prescription, recreational; past or present)
- Alcohol use (past or present)
- Chemical exposure (work, hobbies, etc)
- Inherited weakness in your body chemistry
- Air quality (smoke, dust, dirt, etc)
- Water quality

Electromagnetic Stress

- Not enough time spent out of doors in contact with nature
- Too much time spent indoors
- Poor home ventilation
- Poor office / workplace ventilation
- Too much time spent on video display terminal
- Too much time spent in front of television or other electrical equipment and/or appliances
- Overhead lighting
- Previous radiation therapy / exposure
- Exposure to other electromagnetic fields (microwaves, high-tension wires, etc)
- Do you sleep on a heated waterbed or under an electric blanket? (Yes / No)
- Do you regularly use a cell phone? (Yes / No)
- Do you spend time in close proximity to where the electrical power supply enters your home or office? (Yes / No)

Repeated exposure to acute or chronic stressors increases cortisol levels, thereby forcing blood glucose levels up regardless of where they begin. To properly address adrenal health, patients should be counseled to choose a diet balanced with proper levels of complex carbohydrate (45%), protein (30%), and fat (25%).¹⁹

Along with a macronutrient-balanced diet, it is also important to avoid intake of chemical stressors, including drugs and alcohol. Caffeine is an especially prevalent drug in America, where it is estimated that 85% of adults consume some sort of caffeinated beverage, including coffee, tea, and soft drinks, on a daily basis.²⁶ Caffeine, in addition to being a central nervous system stimulant and raising blood pressure, also exaggerates the stress response, amplifying cortisol production many hours after ingestion.²⁷ In addition, these amplification effects persist with regular use of caffeine.²⁷ Caffeine should be avoided by individuals who are under chronic stress, as well as by those who wish to avoid adrenal dysfunction.

Exercise and Stress-reduction Techniques

Exercise, although itself a stressor, actually rebalances cortisol levels.¹⁹ In pre-industrialized societies, physical stress was much more prevalent than today. Seeing a predator and running from it was simultaneously the stressor and the stress reliever. With a sedentary society experiencing increasing levels of psychological stress, the relief of physical exertion is much less common. Exercise causes cortisol release, but then it works on the body by changing receptor sensitivity to cortisol.²⁸ Repeated studies have shown that athletically trained individuals exhibit higher levels of cortisol during exercise with a quicker recovery than non-trained individuals, and are much less susceptible to dexamethasone (a corticosteroid that is used to suppress the output of ACTH and cortisol) suppression tests.²⁹⁻³¹ Exercise-induced cortisol elevations are hypothesized to create a less-inflammatory state in the body by immune suppression.²⁹⁻³¹ Stress-reduction techniques such as yoga,³² spa bathing,³³ qigong,³⁴ and relaxation programs³⁵ have all been demonstrated to reduce cortisol levels, both during the activity and for a significant interval after.

Nutraceutical Management of Adrenal Dysfunction Adaptogens

Adaptogens are natural herbs that have non-specific, normalizing effects on physiology; they influence normal body functions only enough to encourage non-specific resistance to stressors.³⁶ Adaptogens include herbs—*Eleutherococcus senticosus*, *Ginkgo biloba*, *Ocimum sanctum*, *Panax ginseng*, *Rhodiola rosea*, and *Withania somnifera*—and the mushroom *Cordyceps sinensis*. Following is a short description of each.

Eleutherococcus senticosus (Siberian ginseng) has been long used in Chinese herbal medicine to enhance general health, longevity, appetite, and memory. While only distantly related to *Panax ginseng* (see below), it was popularized in Russia in the 1950s due to the relative scarcity and cost of panax.^{37,38} The active portion of *Eleutherococcus* are the glycosides eleutherosides A through M.³⁹ *Eleutherococcus* is known to have antistress³⁹ and antifatigue³⁹ effects as well as immunomodulatory properties.³⁹ A study examining the effects of *eleutherococcus* on steroidal hormone indices of

stress showed an increase in cortisol production in endurance athletes. The authors suggest a threshold may exist below which *eleutherococcus* increases and above which it decreases the stress response.⁴⁰ Another study showed an improvement in quality of life for elderly patients given *eleutherococcus* but only during the first 4 weeks of treatment. By the end of 8 weeks, the treatment group had returned to baseline scores.⁴¹ This suggests that a pulsed dose may be more effective than continued use.

Ginkgo biloba has been used for several thousand years by the Chinese for various maladies, including vertigo, short-term memory loss, and lack of attention or vigilance.⁴² Standardized extracts of ginkgo have been shown to possess antioxidant⁴³ and neuroprotective properties, including slowing the progression of dementia.⁴⁴ Recent studies have shown ginkgo to possess antistress properties as well.⁴⁵ When subjects were given a single dose of ginkgo extract and then exposed to a memory and handgrip test, their levels of post-test salivary cortisol were significantly lower than those who were treated with placebo, yet there was no change in resting salivary cortisol compared to placebo.⁴⁵ Another study comparing acute and chronic stressors in rats treated with ginkgo, panax, or placebo showed that ginkgo was effective in reducing corticosterone levels in rats subjected to acute stress, although it had little or no effect when rats were exposed to chronic stress.⁴²

Ocimum sanctum (Holy basil or tulsi) is used in Ayurvedic medicine and has been shown to have antistressor effects.⁴⁶ Sembulingham, et al, subjected rats to acute or chronic noise stress, with and without *ocimum* administration. Those rats that had been pretreated with *ocimum*, whether exposed to acute or chronic noise, had significantly reduced levels of corticosterone.⁴⁶

Panax ginseng (Korean, Chinese, or red ginseng), the first clinically used adaptogen, has clear antistress action. *Panax* contains several active principals, including saponins (ginsenosides), polysaccharides, flavonoids, and volatile oils.⁴⁷ Standardized extracts usually contain about 4% to 7% ginsenosides.^{38,47} While the mechanisms behind the action of *panax* remain unclear, its ability to improve resistance to stress has been well documented. One such study showed the ability of subjects to withstand cold-water immersion for significantly longer periods of time when given *panax* compared to placebo and to withstand cold and flu season with fewer symptoms compared to those who did not consume *panax*.⁴⁸ Toxicity and adverse effects with *panax* are similar to those with placebo.⁴⁹

Rhodiola rosea (golden root and Arctic root) has been used by traditional medical systems in Eastern Europe and Asia for stimulating the nervous system, relieving depression, enhancing work performance, improving sleep, eliminating fatigue, and preventing altitude sickness.³⁸ Its active adaptogenic constituents include p-tyrosol, salidroside, rhodionoside, rhodiolin, rosin, rosavin, rosarin, and rosiridin.^{38,50} Standardized extracts usually contain 1% to 3% rosavin.⁵⁰ *Rhodiola* has been shown to increase resistance to a variety of chemical, biological, and physical stressors. In a test of “to the limit” swimming, *rhodiola* significantly increased the swimming time of rats.⁵¹

Withania somnifera (ashwagandha, Indian ginseng, winter cherry) has been used in Ayurvedic medicine for thousands of years as an aphrodisiac, liver tonic, anti-inflammatory agent, and astringent.

gent.⁵² The active constituents are withanolides, the most active of which are withaferin A and withanolide D.⁵³ In a study comparing withania and panax, both chronic and acute stress effects were reduced by both herbs almost equally.⁵⁴

Cordyceps sinensis, an ascomycetes fungus (mushroom), has been traditionally used in Chinese society for its immunomodulation effects. Researcher Leu, et al, using different fractions of cordyceps, showed both inhibition and promotion of corticosterone production in rats under non-stressful conditions. Adrenal weight also varied depending on the fraction of cordyceps used and age of mice.⁵⁵ Administering the hot-water fraction of cordyceps to mice, Koh, et al, found the treated mice had increased swimming endurance, decreased stress indicators, and decreased adrenal weight when compared to placebo.⁵⁶

HPA-axis Potentiators

Glycyrrhiza glabra (licorice, sweetwood) has been used in traditional medicines as an expectorant and carminative (easing passage of gas through the alimentary system).⁵⁷ The HPA-active constituent is glycyrrhizin,⁵⁷ which is a potent 11beta-hydroxysteroid dehydrogenase (11B-HSD) inhibitor.⁵⁸ 11B-HSD catalyzes the conversion of active cortisol to inactive cortisone. Two different isoenzymes are present in the body. Type 1 is widely distributed but concentrated in the liver and adipose tissue, whereas type 2 is found predominantly in mineralocorticoid target tissues (ie, kidney, colon, and salivary glands). Inhibition of this enzyme enables an increase in circulating cortisol, potentiating the stress reaction.⁵⁹

For patients with adrenal exhaustion, glycyrrhiza can be used to increase cortisol levels, either throughout the day using repeated doses or for a short time with a single dose. Timed supplementation with glycyrrhiza should be correlated with salivary hormone testing since, depending on the dose, its half-life ranges from 3.5 to 30 hours.⁶⁰ However, caution must be used in overtly hypertensive individuals. Glucocorticoid (cortisol) and mineral corticoids (aldosterone) both have an affinity for mineralocorticoid receptors (MR). In mineralocorticoid tissues of the kidney, colon, and salivary gland, type 2 11B-HSD protects the mineralocorticoid receptor from over-stimulation by elevated circulatory levels of cortisol. When 11B-HSD is inhibited, the MR receptors may be continually stimulated, causing a hypermineralocorticoid state.⁵⁸

HPA-axis Inhibitors

N-3 fatty acids (fish oils) are known to be cardiovascular protective.⁶¹ A recent study by Delarue, et al, evaluated the effect of n-3 fatty acids on the HPA axis. After 3 weeks of supplementation with 7.2 g of fish oil per day, the cortisol response to stress was significantly blunted. While the mechanism is not clearly understood, it is believed to be exerted at the level of the central nervous system.⁶²

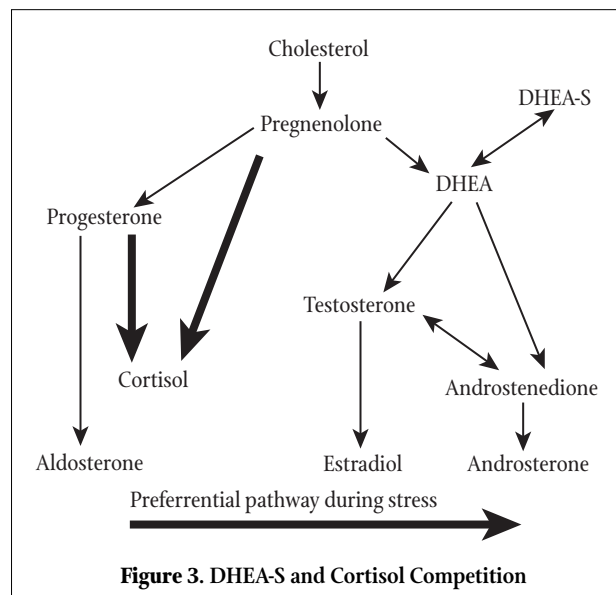
Phosphatidylserine (PS) is a naturally occurring phospholipid found in cell membranes. Often used for improved cognitive function, PS has been shown to have potent inhibitory effects on the HPA axis.⁶³⁻⁶⁵ Monteleone, et al, showed positive inhibitory effects of PS to physical stress on both ACTH and cortisol following a single bolus injection⁶³ and 10 days of oral administra-

tion.⁶⁴ Research results are unclear as to optimal oral dosing. Monteleone, et al, found oral dosages of 400 mg/day displayed no statistical difference from placebo, while administration of 800 mg/day had significant inhibitory effects on the HPA axis.⁶⁴ However, for Hellhammer, et al, 400 mg/day was the most effective dose to blunt effects of psychological stress.⁶⁵ While the mechanism of action of PS is not clearly understood, it is speculated that due to the prevalence of PS in cellular membranes, supplemental PS alters membrane structure and receptor activity. Alternatively, it may also have effects on the neurotransmitter systems that regulate the HPA axis.⁶³⁻⁶⁵

Hormones

Dehydroepiandrosterone (DHEA) is a c19 steroid derived from pregnenolone, which itself is derived from cholesterol through side-chain cleavage by cytochrome p450scc. Released in response to ACTH, DHEA (along with its sulfated form, DHEA-S) is often considered the “mother steroid” because of its subsequent conversion into progesterone, estrogens, and testosterone.^{66,67} It has also gained notoriety as an “antiaging” hormone, since we see a marked decline in serum DHEA-S concentration in the aged.⁶⁸

Under normal circumstances, DHEA-S is secreted synchronously with cortisol in the adrenal cortex in response to ACTH stimulation, showing a similar diurnal variation.⁶⁹ As shown in Figure 3, it directly competes with cortisol for the precursor molecules of pregnenolone and 17-OH-progesterone.⁶⁶ Due to this competition, prolonged exposure to stress with its subsequent overproduction of cortisol may decrease DHEA-S production. This DHEA-S “steal” by the body, preferentially secreting cortisol at the expense of DHEA-S, may then alter concentrations of estrogens and testosterone, since these hormones are made directly from DHEA-S.⁷⁰ In adrenal exhaustion, the adrenal cortex is unable to maintain normal cortisol levels in response to stress.⁷¹ However, it may still possess the ability to make either normal or diminished amounts of DHEA-S, prompting the need for diagnostic testing of DHEA-S levels before supplementation is begun.^{72,73}



While DHEA-S supplementation is warranted after determination of a deficiency, caution should be used when recommending this hormone. Repeated studies have shown that DHEA supplementation has different effects on each gender: Doses as low as 50 mg per day in women have been shown to increase testosterone, androstenedione, and dihydrotestosterone to above physiological levels.^{74,75} Since DHEA-S supplementation can also potentially increase estrogens and their subsequent metabolites, it is recommended that additional DHEA-S metabolite testing be conducted shortly after initiating treatment with this hormone, particularly with women. Specific testing of estrone, estradiol, estriol, and testosterone should be performed.

Supplementation of DHEA without first determining a deficiency is unwise, and continued supplementation without determining which metabolites of DHEA-S are being produced can be, at the least, cosmetically undesirable, causing facial hair and acne. It can also be potentially dangerous, stimulating growth of estrogen-dependent cancers.⁶⁶ While these effects are most notably seen in women, elevations in estrogens have been found in men supplemented with DHEA as well.⁷⁶

Pregnenolone, as a precursor to both DHEA-S and cortisol, is also an option for supplementation in cases of severe adrenal fatigue. As with DHEA-S supplementation, care should be taken when recommending this hormone, since we cannot predict which metabolites will form after supplementation begins. If pregnenolone is chosen as a treatment option, further salivary testing of estrone, estradiol, estriol, and testosterone should be completed, particularly with women, shortly after supplementation has begun to assess the patient's levels of potentially dangerous metabolites.^{66,67}

Vitamins and Minerals

When a person is undergoing stress, adequate production of cortisol requires a variety of vitamins and minerals. A deficiency of any single nutrient can diminish conversion of cholesterol to cortisol (For a suggested nutritional protocol for adrenal stress, see Table 3).

B-complex vitamins have been widely used as antistress vitamins. Due to their involvement in energy production, they are required to catalyze any anabolic pathway. In the adrenal cortex, the B vitamins are required for, among other things, steroid biosynthesis. Several studies have shown adrenal hypofunction and increased response to stress with deficiencies of riboflavin (B₂),^{19,77-79} pantothenic acid (B₅),^{19,79,80} pyridoxine (B₆),^{19,79,81,82} biotin,⁷⁹ and nicotinamide.^{19,79,83} Much caution is warranted in dosing pyridoxine, however, as there have been reports of irreversible neurological damage with doses as low as 100 mg/d.⁷⁹

Vitamin C (ascorbate), in addition to being one of the most potent antioxidants,⁷⁹ is also vital for adrenal cortex function.⁸⁴ Ascorbate is necessary for conversion of cholesterol into pregnenolone, one of the initial steps in cortisol, DHEA-S, and sex-hormone production. A deficiency of ascorbate will create hypofunction of the adrenal cortex.^{84,85} Ascorbate is best used buffered in combination with bioflavonoids.¹⁹

Vitamin E, as an antioxidant, has been shown to protect the body from a wide range of free radical effects.⁷⁹ Numerous studies

Table 3. Suggested Nutritional Protocol for Adrenal Stress*

Ascorbic acid	1000 mg
Balanced B-complex including:	
Bioflavonoids	500 mg
Biotin	2000 µg
Calcium	400 mg
Copper	1 µg
Magnesium	400 µg
Mixed carotenoids	5000 IU
Nicotinamide	20 mg
Pantothenic acid	750 mg
Pyridoxine	50 mg
Vitamin A (retinol)	2500 IU
Vitamin E w/mixed tocopherols	400 IU
Zinc	10 µg
*All dosages are oral, twice daily (BID)	

have shown that acute or chronic exposure to stress increases free radical formation throughout the body but specifically in the adrenal cortex. In response to stress, Vitamin E has been shown to protect the adrenal cortex from free radical damage and reduce cortisol production.^{19,85-89}

Vitamin A (retinoic acid/retinol and carotenoid precursors), like vitamins C and E, is a potent antioxidant.⁷⁹ It has also been shown to be essential in the production of steroid hormones.⁹⁰ In rats fed a diet deficient in retinoic acid, the adrenal cortex showed considerable stunting and did not produce normal amounts of corticosteroids.⁹¹ Vitamin A is essential for conversion of pregnenolone into cortisol. Even mild deficiencies of vitamin A cause significant blunting of cortisol production.⁹⁰ Research shows only retinoic acid or retinol to have a positive impact on adrenal health.⁹⁰ However, research also shows that we should be cautious of vitamin A toxicity above 5000 IU/day.⁷⁹ Therefore, a mixture of retinol/retinoic acid with mixed carotenoids would be preferred.

Macro-minerals such as calcium and magnesium are vital for all energy production and anabolic processes. Magnesium is a necessary cofactor for activation of many processes and is specifically needed to activate and transport pyridoxine (vitamin B₆).⁹² Deficiencies, especially of magnesium, will cause negative changes throughout the HPA axis.^{93,94} While a balance of 2:1 calcium to magnesium is considered normal, it may be appropriate in cases of severe stress or depletions to decrease the ratio to 1:1.

Micro-minerals, specifically zinc, copper, manganese, selenium, molybdenum, chromium, and iodine, are also important cofactors for adrenal cortex function.^{19,95-97}

Treatment, Safety, and Efficacy

Initially, treatment should include identification of all possible stressors with either elimination or reduction of those that can be eliminated or reduced. Specific stress-reduction

techniques such as those listed previously have been shown to be safe and effective when done specifically and consistently. Patients should also be extensively counseled in such dietary interventions as meal-component balance and glycemic load to control blood-sugar fluctuations.

As a general “tonic” for adrenal stress, a regimen of vitamins and minerals as outlined in Table 3 is appropriate. Should the patient not be willing to complete adequate testing, this protocol, for most patients, should not only be safe but should have a positive impact in the adrenal glands’ ability to produce adequate cortisol and DHEA. However, if the clinician suspects chronic adrenal fatigue with severe hypoadrenia, the protocol will not be enough to enhance the production of cortisol or DHEA.

By definition, the adaptogens are considered safe and effective for either the hyper- or hypoadrenia patient. However, anecdotal evidence has occasionally shown adaptogens to cause increased symptoms in some hyperadrenia patients. Therefore, clinicians should counsel patients placed on adaptogens to be vigilant for symptoms such as insomnia, hyperexcitability, anxiety, or difficulty concentrating.

HPA-axis potentiators and inhibitors such as glycyrrhiza, n-3 fatty acids (at cited doses), and PS, due to their ability to significantly change circulating levels of cortisol, should be used with caution only after appropriate testing indicates the need. Such potentiators and inhibitors are dose-time specific in relationship to laboratory analysis so as to avoid increasing or decreasing cortisol at inappropriate times. Studied doses of n-3 fatty acids were 7.2 g/day, which are significantly above most supplemental recommendations and so have few cautionary concerns.

The hormones pregnenolone and DHEA, while very effective at increasing levels of cortisol and DHEA, have the highest potential for side effects and so should be used with the most caution due to their potential for increasing levels of androgen or estrogen metabolites.

Conclusion

Adrenal dysfunction is a prevalent, if often subclinical, condition in Western societies that can create a milieu of vague signs and symptoms that are often overlooked in the traditional medical setting.¹⁹ Due to increasing psychological stressors, sedentary lifestyle, poor diet, and abuse of adrenal stimulants, we should expect the prevalence of adrenal dysfunction to increase even more. In its extreme states, specific disorders may present, but, in our desire to alleviate symptoms of disorder, the underlying adrenal dysfunction may be forgotten.¹¹ A clinician looking for adrenal dysfunction must not only take a thorough case history but be willing to evaluate the patient with laboratory tests to correctly diagnose the condition. Without this step, any treatment plan is purely speculative.

By far the most important component of any treatment plan for adrenal dysfunction is improving the person’s diet and lifestyle. Stress-coping mechanisms are vital in helping reduce the acute stress response and preventing adrenal exhaustion. While nutraceutical interventions are effective at rebalancing adrenal function, only by improving the individual’s ability to cope with stress will there be long-term improvement in adrenal function.

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