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Clinical perspective on stress, cortisol and adrenal fatigue

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ABSTRACT

After 30+ years of clinical practice, it is this author's experience that adrenal fatigue is a common stress-related disorder in which the symptoms are strongly influenced by circulating cortisol levels. Although adrenal fatigue has appeared in the medical literature by various names for over 100 years, its prevalence is just now coming to the forefront. Healthcare professionals can make a dramatic difference by monitoring patients' health to check for signs and symptoms of adrenal fatigue. Despite the frequency with which this health condition occurs, even many skilled clinicians have not had the opportunity to learn about it or its importance to their practice. The intent of this article is to provide the practitioner with clinically relevant information about the diagnosis and successful treatment for adrenal fatigue.

What is already known about this topic?

- Adrenal fatigue has appeared in the medical literature by various names for over 100 years.

What this paper adds?

- A new clinical perspective that offers a protocol for diagnosing and successfully treating adrenal fatigue.

1. Introduction

Cortisol plays a crucial role in maintaining health. But in order to do so, circulating levels must be maintained in a fairly narrow range. If levels drop much below optimal, signs and symptoms of adrenal fatigue occur [1]; if they drop precipitously low, as in Addison's disease, it can be life-threatening [2]. If levels climb and remain above optimal for a period of time, signs and symptoms of metabolic syndrome appear [3]; pathologically high, and Cushing syndrome manifests [4].

Regulated by the hypothalamic-pituitary-adrenal (HPA) axis and cortisol carriers in the blood possessing different affinities for cortisol binding, the level of circulating cortisol in a healthy body remains between 15 and 24 mcg/dL, with the adrenals producing 20–25 mg of cortisol over a 24 h period [5]. These optimal circulating levels vary in a diurnal pattern, with low being at approximately 4:30 am and high being 30–45 min after rising. There is also a midafternoon low sometime between 2:00 and 5:00 pm [6], with a duration of 15 min to 2 h.

The feedback loop that controls circulating cortisol must walk a tightrope walk, balancing at varying levels during the 24-h diurnal cycle in order to adequately supply cells, tissues and organs and keep the body functioning optimally. In addition, cortisol – sometimes called the "stress hormone" [7] – must respond appropriately to all stresses impinging upon the host. These stresses can be physical, biochemical, hormonal, physiological, mental, emotional, real or imagined. The combined stresses are sensed by the hypothalamus, which compares the amount of circulating cortisol to anticipated need throughout the entire body and, under normal circumstances, causes adequate, but only adequate, amounts of cortisol to be released from the adrenal cortex. This balancing act is carried out via a negative feedback loop of messenger hormones: corticotropin releasing hormone (CRH) from the hypothalamus → adrenocorticotropic hormone (ATCH – aka corticotropin) from the anterior pituitary → stimulates receptors in the adrenal cortex to prompt cortisol's manufacture and immediate release into circulation → sensed by cortisol receptors in the hypothalamus, thus completing the loop [8]. This occurs every 3–6 s to maintain the proper amount of cortisol in circulation for preserving homeostasis according to the body's total stress and physiological needs.

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This system works with wonderful efficiency as long as the stresses are not too lasting, numerous or severe. But in current modern industrial society, this is often not the case. Stresses are often prolonged, abundant, multiple and intense. In addition, the nutrients used in greatly increased quantities during such high stress states are not replenished by the normal modern diet. Even in 'healthy' foods, nutrient quality has been diminished by the use of chemical fertilizers, which deplete the ground of the minerals and trace minerals necessary for plants to make and store the vitamin and phytonutrient rich food existed previously [9]. Thus, people today experiencing constant and multiple stressors have fewer nutrients to replenish challenged adrenals.

Chronically stressed people are caught in an untenable position. If the adrenals are strong enough to withstand this day after day and cortisol levels remain adequately elevated to handle the multiple stresses, over time the signs and symptoms of metabolic syndrome begin to appear – often taking decades to fully manifest but which can lead to adult onset diabetes [10], heart disease [11] and cancer [12]. If the adrenals are not able to keep up with the demands, adrenal fatigue appears – usually developing more quickly than metabolic syndrome, and which can become so severe as to disable them. As a physician, I have seen many people so depleted by adrenal fatigue they were unable to work or do anything beyond menial house chores, including several whose adrenal fatigue was so severe that they were unable to even dress themselves. In the face of light or moderate intermittent stress, the HPA axis walks the cortisol tightrope walk to maintain balance (homeostasis) while helping the body adapt to the stresses being experienced. With chronic and/or severe stress, this balance can be upset, resulting in either adrenal fatigue or metabolic syndrome.

2. Adrenal fatigue

In adrenal fatigue cortisol levels are no longer able to rise adequately to meet the demand and people begin noticing signs and symptoms that give them a clue something is not right. In a nutshell, adrenal fatigue is the persistent suboptimal functioning of the adrenal glands, especially under stress. A more formal and elegant definition was put forth by Charles Sajous, an eminent physician early in the last century who, in 1930, wrote:

> "Functional hypoadrenia [the term used for adrenal fatigue at that time] is the symptom-complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration or any other factor which, without provoking organic lesions in the organs or their nerve-paths is capable of reducing their secretory activity." [13]

Adrenal fatigue is not Addison's disease, which is the virtual failure of the adrenals primarily caused by either an infectious or autoimmune process that damages and often destroys the glands [referred to above by Sajous as "organic lesions"]. Stress rather than pathological damage is the primary cause of adrenal fatigue [14,13]. When the amount of stress continually exceeds the capacity of the adrenals to secrete sufficient hormones to make the physiological, and biochemical compensations necessary for that level of stress, adrenal fatigue occurs. In adrenal fatigue, the adrenals function but not optimally.

3. Frequency of adrenal fatigue

In a 1974 publication, John Tintera, MD, a specialist in low adrenal function, said that conservatively about 16% of the population has some moderate to severe degree of hypocortisolism [a term used at that time for adrenal fatigue] but in actuality, the figure should be 67%, if all the related groups were included [15]. Although there has been no rigorous study of the frequency of low adrenal function, from the author's four decades of clinical experience, Dr. Tintera's higher estimate seems relatively accurate, especially in these stressful times. Most relevant for the physician is the knowledge that this health condition is common enough to be seen regularly by every practitioner. In contrast, the incidence of Addison's disease is approximately 4–11 cases per 100,000 (.00004–.0001% of the population) [16].

4. Unique fatigue pattern of adrenal fatigue

There are many signs and symptoms of adrenal fatigue, yet there is no single pathognomonic indicator, except possibly its unique pattern of fatigue. Although fatigue is a common complaint heard by physicians – 85% of patients complain of fatigue as one of their major symptoms – there seems to be no other fatigue pattern like it.

- Early morning fatigue even with sufficient sleep [17] – need caffeine or other stimulants to get going [18] and some do not actually feel fully awake until after noon meal.
- Midmorning low – often compensated for by more caffeine plus sugar with fat, e.g. coffee and doughnuts to temporarily compensate for the hypoglycemia due to low cortisol.
- Afternoon low between 2:00 and 5:00 pm [19,20] – lasts from 15 min to 2 h and ranges from simply wanting to take it easy for a few minutes to having to lie down.
- Substantially improved energy after 6:00 pm – usually feel better than have all day.
- 'Second wind' of renewed energy around 11:00 pm (if still awake) – lasts until 1:00–2:00 am.
- Much more refreshed in morning if able to sleep in about 2 h beyond usual rising time [1].

5. Other common signs and symptoms of adrenal fatigue

The distinctive pattern of fatigue when combined with the symptoms below forms a syndrome that healthcare professionals can readily learn to recognise.

- Needs caffeine or other stimulants to get going and often to keep going during the day.
- Decreased stamina and energy – feels run down and exhausted much of the day [21].
- Decreased productivity [22].
- Decreased resilience – takes longer to recover from illness and rebound from stress [14].
- Craves salt or salty foods [22].
- Hypoglycemia and its symptoms, especially under stress (Cortisol plays intimate role in maintaining adequate blood sugar.) [22].
- Does not feel rested or refreshed even with 8 h sleep.
- Decreased libido.
- Increased frequency and/or severity of respiratory illnesses [23].
- Increased difficulty focusing, concentrating, remembering (fuzzy-headed) [22].
- Increased irritability and/or intolerance [14,22].
- Increased perimenopause or PMS symptoms [22].
- Feels overwhelmed [22].
- Mild depression [22].

6. Causes of adrenal fatigue

There are many causes of adrenal fatigue but by far the most common is any type of stress that is chronic, prolonged or severe [24]. In modern life, there are often multiple stresses occurring in

tandem. The patient may be unaware of some of these stresses but their adrenals, being the glands of stress, have to compensate for each and every stress – physical, biochemical, hormonal, thermal, internal, external, emotional, mental, or toxic in origin, including overuse of drugs, alcohol and sugar. Through a carefully orchestrated stress response system of the hypothalamic-pituitary-adrenal (HPA) axis, the body strives to maintain homeostasis in the midst of these ongoing and varied stresses [25].

Many of the cases of adrenal fatigue the author has seen clinically are triggered by motor vehicle accidents; severe injuries – especially head injuries and severe burns; deep emotional trauma such as divorce, extended periods of overwork without sufficient time for relaxation; poor and irregular eating habits; and chronic lack of sleep. I have observed that there are certain groups that tend to suffer from adrenal fatigue more frequently because of the constant stress they are under. Examples are caregivers, social workers, police, doctors, nurses, single moms, people working two jobs, lawyers, and the self-employed.

7. Treatment for adrenal fatigue

As incapacitating and severe as adrenal fatigue can be and as bad as it can make people feel, its saving grace is that the right kind of therapy is nearly always successful. Fortunately, most aspects of this therapy are already used by many conscientious practitioners: lifestyle modification, stress management techniques, adjustments to diet, and nutritional supplementation. When targeted specifically for adrenal fatigue in a cohesive programme and implemented for an adequate time period, these components are usually enough to successfully treat 80–90% of patients suffering from adrenal fatigue. In the most severe cases, there may also be a body burden that must be addressed before full recovery is possible.

The criteria I use clinically to indicate success in adrenal fatigue treatment is that the patient not only feels good but is also able to maintain a normal life and activity level without reliance on the daily use of supplements. That is, the consistent practice of healthy lifestyle, stress management and dietary behaviours combined with the essential physiologically restorative support of targeted supplementation has allowed the body to recover its natural stress resilience. As a result, the patient is now able to maintain in a stressful world.

8. Lifestyle modification

An unhealthy lifestyle is how many people slip into adrenal fatigue. Although lifestyle modification alone is insufficient for full recovery, it constitutes an important leg in the triad of the therapeutic protocol for adrenal fatigue.

1. Look for ways to decrease the stress load: mental, emotional, physical.
2. Minimise commitments.
3. Create a minimum of 2 h of free (uncommitted) time every day.
4. Eliminate or minimise emotional stressors. Creating a **Good for Me**, **Bad for Me** chart is the best place to begin. In one column, patients list all the things that make them feel good, alive, healthy and happy. In another column they list all the things that make them feel bad, drained or unhealthy. After prioritising the items in each column from most to least influential, they write out a plan to increase the top item on the Good side and decrease or eliminate the top item on the Bad side, and commit to implementing this plan within 10 days. At 3-week intervals, they do the same with each subsequent item on each side while keeping the prior plans moving forward. Usually, after the first three items on each side have been addressed and successfully dealt with, their attitude and stress load is much improved.
5. Sleep in late whenever possible.
6. Minimise or eliminate energy robbers. In many lives, there are what I call "energy robbers". These are people who are draining for the patient to be around (sometimes even by phone or mail). The patient needs to minimise contact with these energy robbers or they will continue to sap energy and be an impediment to healing.
7. Laugh as much as possible. Make it a point to laugh every day. Actually prescribe laughter as part of the patient's therapy. Humorous books, movies, stories, YouTube clips, jokes, memories, anything that makes them laugh. Remember that laughter is parasympathetic, and as such automatically induces relaxation [26,27].
8. Schedule regular therapeutic sessions that help decrease stress, increase relaxation and keep the autonomic nervous system in better balance: chiropractic care, massage, Reiki, acupuncture, aromatherapy, etc.
9. Exercise moderately daily. Any activity that moves the body and gets heart rate to just over 100 beats per minute seems beneficial as long as it does not leave the patient more depleted within 90 min of exercising or the next morning.

9. Dietary changes

Poor eating habits and food choices not only leave the body without essential nutrients but also disrupt or create a burden on the stress response, digestive, energy production and other homeostatic systems. There are specific dietary guidelines that form the second important leg of the therapeutic triad.

1. Combine protein, unrefined carbohydrate (whole grain or whole grain products) and good quality oil or fat at every meal and snack.
   a. Protein – At least some daily protein needs to be from an animal source such as poultry, fish, pork, beef, etc. In my four decades of clinical experience, I've yet to see a person with more than very mild adrenal fatigue fully recover by only consuming vegetable protein. As I was a vegan when I first discovered this, it was difficult to admit but for some yet unknown reason, animal protein appears to be an essential part of the dietary recovery protocol for adrenal fatigue.
   b. Fat – Preferably plant source (seed and nut oils), cold-pressed and must be fresh.
2. Eat before 10:00 am and again before noon.
3. Have 5–6 servings of vegetables daily.
4. Avoid fruit (high potassium, low-sodium) in the morning.
5. Salt drinking water to taste. This is often very revitalizing, especially in the morning and during the low energy periods of the day (midmorning and midafternoon).
6. Eat meals at regular times during the day.
7. Chew food 30 times per mouthful to help digestion and absorption.
8. Avoid junk food. This includes all food made with white flour or sugar, hydrogenated/partially fat, or artificial sweeteners.

10. Dietary supplements

My professional experience with most dietary supplements that were supposed to treat adrenal fatigue has been disappointing. However, there are a few that truly work. Remember – the goal of supplementation is more than just getting your patient feeling better, it is to provide the specific, targeted support the adrenals and HPA axis need to heal to the point where the dietary supplements are no longer needed. I have witnessed this many

hundreds of times and know that the right supplements are often the most critical leg of the triad, especially in the early phases of treatment. Below are some tips for locating the best ones for adrenal fatigue patients.

1. Particular B vitamins are required in higher quantities by the adrenals and stressed cells.
   a. Niacin (B3) is needed in quantities of 125–150 mg/day to help the multiple NADP–NADPH enzymes of the adrenal cascade function optimally.
   b. Pyridoxine (B6) is essential to the transamination and hydroxylation reaction of tissue repair and is needed in quantities of 50+ mg per day.
   c. Pantothenic acid is a precursor to the Krebs cycle and is needed in quantities of 1200–1500 mg/day for recovery from stress and adrenal fatigue.
   d. The other B vitamins should be present to work with these vitamins and to act as cofactors for the enzymatic reactions needed to facilitate recovery from adrenal fatigue and stress.
   e. For best results, B vitamins (and other water-soluble vitamins) should be in a sustained-release format to allow even absorption and increased tissue saturation.
2. The adrenals need more vitamin C than any other organ or tissue in the body, especially during times of stress [28,29].
   a. To adequately treat stressed states and adrenal fatigue, use 2500–4000 mg/day in a sustained release to enhance absorption and minimise loss through excretion [30].
   b. A pH balanced vitamin C helps avoid stomach irritation and mitigate tendency towards acidity in adrenal fatigue.
   c. Bioflavonoids help enhance the antioxidant power of the ascorbic acid [31].
3. Other dietary supplements that are helpful include:
   a. Magnesium (citrate) – 400 mg before bedtime to promote sleep and relaxation.
   b. Vitamin E (as mixed tocopherols) for its antioxidant properties in the adrenals and elsewhere [32].
   c. Digestive aids to facilitate digestion, which is often compromised by stress.
4. To help balance HPA axis function, and promote evenness and calmness during the day, and sound sleep at night, I found four herbal tinctures work well together:
   a. *Eleutherococcus senticosus*.
   b. Ashwagandha (*Withania somnifera*).
   c. Maca (*Lepidium meyenii*).
   d. Licorice (*Glycyrrhiza glabra*).

With implementation of this treatment protocol, my clinical experience has shown subjective improvement within 4–6 weeks, clinical changes within 8 weeks, and laboratory changes within 12 weeks. But feeling better and clinical improvements are not healing. It takes time to fully recover from adrenal fatigue and this must be explained to the patient. I have found that mild adrenal fatigue, with proper treatment, takes about 6 months; moderate, 1 year to 18 months; and severe, up to 2 years or longer. It is not that patients will continually feel bad during this time – most will, in fact, begin feeling better within a few weeks – but they must allow this much time to fully recover. The most beautiful thing is that patients can – and most will – fully recover if treated properly.

References

[1] Wilson JL. Adrenal fatigue: the 21st century stress syndrome. Petaluma, CA: Smart Publications; 2001.
[2] Erichsen MM, Løvås K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol 2009;160(February (2)):233–7. http://dx.doi.org/10.1530/EJE-08-0550 [Epub 2008 Nov 14].
[3] Boulogne A, Vantyghem MC. Presse Med 2004;33(June (10)):666–72. 681.
[4] Walker BR. Cortisol—cause and cure for metabolic syndrome? Diabet Med 2006;23(December (12)):1281–8.
[5] http://www.globalrph.com/corticosteroids.htm.
[6] Jacobs D, editor. Laboratory test handbook. 4th ed., Hudson, OH: Lexi-Corp.; 1996. p. 112–4.
[7] http://www.psychologytoday.com/blog/the-athletes-way/201301/cortisol-why-the-stress-hormone-is-public-enemy-no-1.
[8] Hyman SE. How adversity gets under the skin. Nat Neurosci 2009;12:241–3.
[9] Hunt J. Harmful Effects of Chemical Fertilizers. http://www.ehow.com/list_7387433_harmful-effects-chemical-fertilizers.html#ixzz2z0UQM3g7.
[10] Aldhahi W, Mun E, Goldfine AB. Portal and peripheral cortisol levels in obese humans. Diabetologia 2004;47(May (5)):833–6 [Epub 2004 Apr 17].
[11] Chan DC, Watts GF. Dyslipidaemia in the metabolic syndrome and type 2 diabetes: pathogenesis, priorities, pharmacotherapies. Expert Opin Pharmacother 2011;12(January (1)):13–30. http://dx.doi.org/10.1517/14656566.2010.502529 [Epub 2010 Jul 14].
[12] Reynolds RM. Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis—2012 Curt Richter Award Winner. Psychoneuroendocrinology 2013;38(January (1)):1–11. http://dx.doi.org/10.1016/j.psyneuen.2012.08.012 [Epub 2012 Sep 19].
[13] Sajous CEdeM. The internal secretions and the principles of medicine, vol. 1. Philadelphia: F.A. Davis Company; 1920. p. 83.
[14] Harrower HR. Minor adrenal insufficiency as a major clinical problem. In: Harrower HR, editor. Endocrine pointers. Glendale, CA, USA: Harrower Laboratory Inc.; 1933. p. 105–20.
[15] Tintera J. Hypocortisolism. 8th printing, Mount Vernon, NY: Adrenal Metabolic Research Society of the Hypoglycemia Foundation; August 1974. 17.
[16] Stewart PM. The adrenal cortex. In: Larson PR, et al., editors. Williams textbook of endocrinology. 10th ed., Philadelphia: Saunders; 2003. p. 507.
[17] Yamamoto T. History of stress-related health changes: a cue to pursue a diagnosis of latent primary adrenal insufficiency. Intern Med 2014;53(3):183–8.
[18] Harrower H. Endocrine pointers. Glendale, CA, USA: Harrower Laboratory Inc.; 1933. 115.
[19] Groves RW, Toms GC, Houghton BJ, Monson JP. Corticosteroid replacement therapy: twice or thrice daily? J R Soc Med 1988;81(September (9)):514–6.
[20] Tintera J. Hypocortisolism. 8th printing, Mount Vernon, NY: Adrenal Metabolic Research Society, Hypoglycemic Foundation Inc.; 1974. 5.
[21] Tintera J. Hypocortisolism. 8th printing, Mount Vernon, NY: Adrenal Metabolic Research Society, Hypoglycemic Foundation Inc.; 1974. p. 1–15.
[22] Tintera J. Hypocortisolism. 8th printing, Mount Vernon, NY: Adrenal Metabolic Research Society, Hypoglycemic Foundation Inc.; 1974. p. 3 & 5.
[23] Harrower HR. Minor adrenal insufficiency as a major clinical problem. In: Harrower HR, editor. Endocrine pointers. Glendale, CA, USA: Harrower Laboratory Inc.; 1933. p. 109.
[24] Harrower HR. An endocrine handbook. Glendale, CA, USA: Harrower Laboratory Inc.; 1939. p. 13–22.
[25] http://dujs.dartmouth.edu/fall-2010/the-physiology-of-stress-cortisol-and-the-hypothalamic-pituitary-adrenal-axis#.U08jISKPLmQ.
[26] Berk LS, Tan SA, Fry WF, Napier BJ, Lee JW, Hubbard RW, et al. Neuroendocrine and stress hormone changes during mirthful laughter. Am J Med Sci 1989;298(6):390–6.
[27] Cousins N. Anatomy of an illness. New York: Norton; 1979.
[28] Patak P, Willenberg HS, Bornstein SR. Vitamin C is an important cofactor for both adrenal cortex and adrenal medulla. Endocr Res 2004;30(November (4)):871–5.
[29] Padayatty SJ, Doppman JL, Chang R, Wang Y, Gill J, Papanicolaou DA, et al. Human adrenal glands secrete vitamin C in response to adrenocorticotrophic hormone. Am J Clin Nutr 2007;86:145–9.
[30] Groff JL, Gropper SS, Hunt SM. The water soluble vitamins. In: Advanced nutrition and human metabolism. Minneapolis: West Publishing Company; 1995. p. 221–37.
[31] Vinson JA, Bose P. Comparative bioavailability to humans of ascorbic acid alone and in a citrus extract. Am J Clin Nutr 1988;48(September (3)):601–4.
[32] Doroshkevich NA, Antsulevich SN, Vinogradov VV. Effect of alpha-tocopherol on adrenal cortex functions under stress. Ukr Biokhim Zh 1991;63(September–October (5)):79–83.