Hypocortisolism: An Evidence-based Review

Lena D. Edwards, MD, FAARM, FICT; Andrew H. Heyman, MD MHSA; Sahar Swidan, PharmD

Abstract

Research over the past 8 decades has emphasized the importance of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol regulation in modulating the endocrine, cardiovascular, neurologic, and immune systems. Hypocortisolism, a relative or absolute state of paradoxically low cortisol, is emerging as an important yet incompletely understood maladaptive consequence of chronic stress exposure and HPA axis dysfunction. Many theories attempt to define the etiology through which hypocortisolism arises, yet none predominate due to the complex nature of the stress response and the difficulty in proving definitive cause and effect.

Nonetheless, studies have shown a correlation between hypocortisolism and numerous disease states, such as metabolic syndrome, fibromyalgia, and chronic fatigue syndrome, as well as chronic pain syndromes, cardiometabolic disease, mood disorders, autoimmune diseases, and malignancies. The term adrenal fatigue has been proposed to describe a maladaptive state in which adrenal corticosteroid production is significantly diminished in response to chronic stress. Although review of the medical literature confirms the presence of primary adrenal gland dysfunction in patients with chronic fatigue syndrome and critical illness, a direct cause-and-effect relationship between chronic stress and adrenally mediated hypocortisolism remains unproven.

As such, a more physiological and clinically functional approach is necessary to identify hypocortisolism as the primary clinical aberration rather than to promote "adrenal fatigue" as the all-encompassing mold into which all forms of low-cortisol states must fit. This review discusses the numerous complex factors contributing to the evolution of hypocortisolism, as well as the metabolic and clinical consequences of this physiologic state.

Key Words: adrenal fatigue, adrenal gland dysfunction, hypocortisolism, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, chronic fatigue syndrome, salivary cortisol, subclinical Addison's disease, stress

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The importance of the hypothalamic-pituitary-adrenal (HPA) axis in mediating the stress response and in maintaining physiologic homeostasis has long been described.[1-4] Studies suggest that chronic stress may propagate a systemic cascade of dysfunctional metabolic events initially intended to be adaptive.[5-7] Dysfunction of the HPA axis appears to be a major initiating and contributing factor to this process, ultimately leading to disruption of the normal diurnal cortisol release pattern. The correlation between chronic stress-induced hypercortisolism and aging, hormone deficiencies, and disease development has been confirmed by several investigators.[6-14]

However, there has been an increasing appreciation for the equally dysfunctional state of hypocortisolism, a state of inadequate basal cortisol production, flattened daytime

cortisol production patterns, and inappropriate elevation of cortisol under stressful conditions.[15-25] Although many studies have attempted to characterize the process whereby low cortisol states evolve and are propagated, the extremely complex nature of the stress response has yielded ongoing speculation and investigation.[15,24-27]

Many clinical syndromes, including "burnout," fibromyalgia (FMS), chronic fatigue syndrome (CFS), posttraumatic stress disorder (PTSD), autoimmunity, allergies, inflammation, and chronic pelvic pain, have been associated with HPA axis dysfunction and hypocortisolism.[15-17,19,21,22,24,25,28-30] However, "traditional" medical practice does not routinely recognize hypocortisolism as a potential etiology in patients with these and other medical conditions. Rather, the traditional approach identifies and treats low cortisol states when they are profound and life threatening, as in patients with Addison's disease.

Baschetti describes in several journal articles how many clinical signs and symptoms coexist both in patients with CFS and in those with Addison's disease. As such, he suggests that with such "impressive clinical overlap," clinicians should assess cortisol production in patients with chronic fatigue, even if the classic signs and symptoms of Addison's disease are lacking.[31,32]

The term adrenal fatigue (or hypoadrenia) has evolved to describe a maladaptive state in which adrenal corticosteroid production is significantly diminished in response to chronic stress. The resulting state of adrenal insufficiency then renders the body incapable of mounting and perpetuating an adaptive, chronic "fight or flight" response.[4,33,34] The terms most likely have been influenced by Hans Selye's General Adaptation Syndrome.[4,35,36] In this work, Selye proposed a chronology whereby prolonged physical or emotional stress could transform an initial instinctive alarm reaction into a phase of resistance ultimately culminating in a state of exhaustion.

Selye recognized that the stress response was complex and was directly influenced by both the endocrine system and the nervous system. Moreover, numerous internal and external factors served as influential cofactors in mediating the stress response.[36] Therefore, the assumption that all low cortisol states are secondary to adrenal fatigue not only underestimates the complexity of the stress response, but also ignores the role of the central nervous system and the influence of other metabolic and environmental factors involved in the development of hypocortisolism.

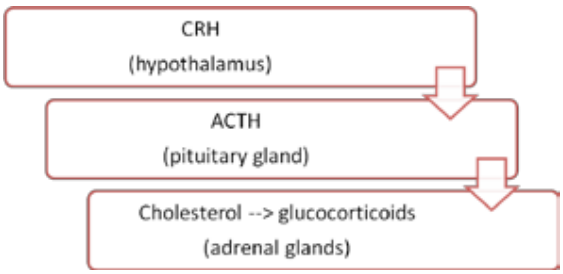
Since the metabolic consequences of hypocortisolism appear to influence the morbidity and mortality of several commonly encountered disease states, a heightened degree of clinical awareness is justified. Patients of all ages and genders may be affected, even though corroborating their symptoms with their often "normal range" laboratory values is challenging. Through a better understanding of the signs and symptoms of hypocortisolism, as well as appropriate laboratory evaluation (ie, salivary cortisol testing), clinicians can more effectively diagnose patients with hypocortisolism and abnormal HPA axis activity and can initiate appropriate treatment if indicated.

Stress, the HPA Axis, and Cortisol

The term stress has been used to describe any entity causing disruption of normal homeostasis.[5,6] However, the ambiguity of this term oversimplifies the intricate nature of the underlying adaptive and maladaptive physiological effects of persistent homeostatic disruption on an organism.[5-7] Consequently, the alternative terms allostasis and allostatic load were proposed to describe the protective maintenance of homeostasis through change or adaptation and the resulting deterioration of an organism to recurrent allostatic exposure, respectively.[5,6,37] Genetic influences, developmental and life experiences, and individual lifestyles and personalities indirectly influence and directly contribute to allostatic load.[5,15,24,38]

The brain is the central regulatory organ in the stress response, not only because it houses essential structures that regulate glucocorticoid release, but also because it determines whether and to what extent a stimulus is potentially harmful.[7,39] Upon exposure to a perceived stressor, stimulation of the pituitary gland by the hypothalamic hormone, corticotropin-releasing hormone, results in pituitary secretion of adrenocorticotropic hormone that, in turn, promotes adrenal gland production of glucocorticoids from cholesterol (Figure 1). Although glucocorticoids are the primary regulators of the physiological reactions to allostatic load, other key mediators include hormones of the sympathetic and parasympathetic nervous system, growth hormone, prolactin, dehydroepidrosterone, excitatory amino acids, and proinflammatory and antiinflammatory cytokines.[6,7,14] Cortisol, the predominant glucocorticoid, can be viewed as the key regulatory hormone responsible for maintaining homeostasis. In addition to cortisol's direct effects on adaptation via redirection of energy and alteration in behavior, it also indirectly affects the release and action of other hormones to reestablish homeostasis.[5-8,14]

Figure 1. The Hypothalamiepituitary-adrenal Axis Cascade



Under normal physiological conditions, cortisol levels typically peak before awakening, then decrease over the course of the day (Figure 2). This diurnal pattern of cortisol release is an important indicator of intact HPA responsiveness.[40] When chronically elevated (Figure 3), cortisol has potent metabolic effects as a catabolic hormone in all organs and tissues except the liver.[41] Systemic effects of elevated glucocorticoids include increased gastric acid secretion, decreased collagen produc-

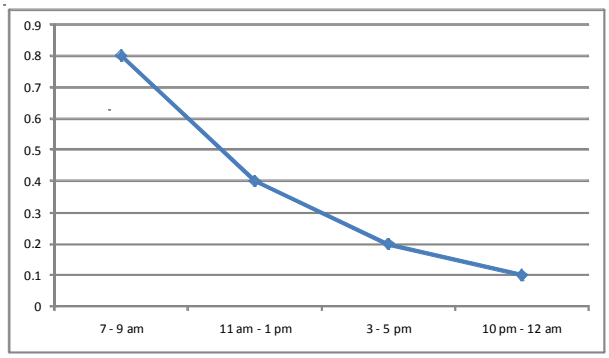


Figure 2. Normal salivary cortisol release pattern measured in µg/dL.

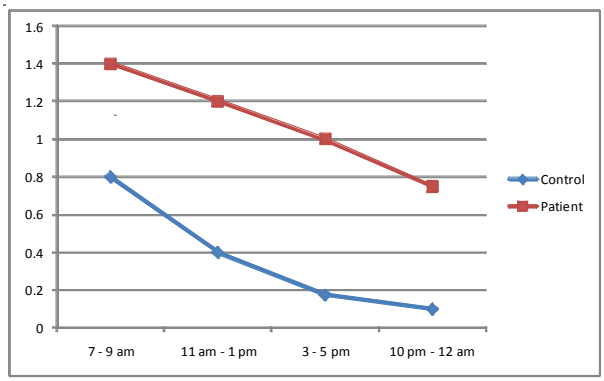


Figure 3. Salivary cortisol pattern displaying hypercortisolism in a 38-year-old, depressed male. Salivary cortisol measurement is in µg/dL.

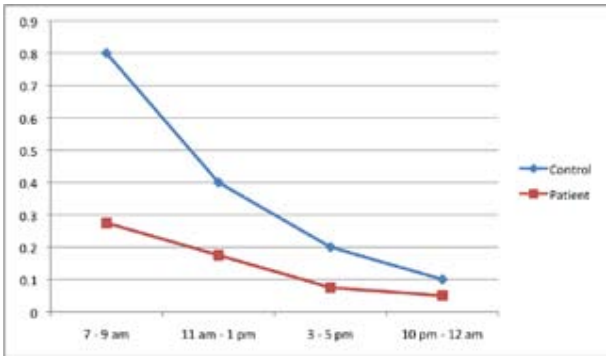


Figure 4. Blunted awakening salivary cortisol level in a 45-year-old premenopausal patient with chronic fatigue syndrome. Salivary cortisol measurements are in µg/dL.

tion, reduced diuresis, reduced bone formation, hyperglycemia, and hippocampal neuronal damage.[10-12,40-43]

Cortisol also impairs thyroid hormone production and function and causes numerous aberrations in immune system regulation and function.[14,44-48] Figure 4 displays abnormally flattened daytime cortisol release patterns consistent with hypocortisolism. The metabolic and clinical consequences of low cortisol states and flattened daytime production patterns are discussed in detail below.

Proposed Theories on the Pathophysiological Evolution of Hypocortisolism

The process by which hypocortisolism evolves remains a subject of ongoing study. Since integrity of HPA axis function and predictable patterns of diurnal cortisol release are essential for maintaining homeostasis during periods of chronic stress, much of the available research on hypocortisolism and stress-induced disease has focused on disturbances in these latter mechanisms.[7,9,10,14-16,20,21,24,25-29,30,46,48-51]

Developmental. Hellhammer and Wade propose a developmental model whereby hypocortisolism may develop via hypoactivity of the HPA axis after prolonged periods of chronic stress. After an initial period of HPA axis hyperactivity and cortisol hypersecretion, hypocortisolism may ultimately develop as a type of maladaptive "over compensation" of the self-preservation mechanisms designed to protect the metabolic machinery (in particular, the brain) from the effects of persistent cortisol elevation.[25,50]

Corticotropin-releasing Factor (CRF) Receptor Downregulation. An increase in hypothalamic release of CRF with subsequent adaptive downregulation of CRF receptors at the level of the pituitary gland also has been proposed. Although not yet demonstrated in human studies, animal studies have shown this to occur.[51-53] Yehuda et al and others have postulated that an increase in the sensitivity of the HPA axis to cortisol during periods of excessive glucocorticoid production induces negative feedback control on further release of stimulating hormones, thereby resulting in hypocortisolism.[24,26,28,40,54]

Inadequate Glucocorticoid Signaling. A state of relative hypocortisolism may arise during periods of normal or even elevated cortisol levels, essentially becoming a state of cortisol resistance. In such situations, inadequate glucocorticoid signaling has been suspected. Failure in proper communication pathways between the hormonal message and the target tissues may be multifaceted. Decreased glucocorticoid bioavailability accounts for one possible mechanism and may develop secondary to decreased adrenal cortisol production, alterations in cortisol binding protein levels, enzymatic conversion of cortisol to other hormones, or action of the "multidrug resistant pump," which potentiates cortisol exit from the cell.[55-59] "Relative" hypocortisolism may arise as an alternate mechanism representing failure of glucocorticoid action at the cellular level, secondary either to a reduction in the number of receptors or a decrease in receptor sensitivity.[27,59] Finally, receptor dysfunction may occur as a consequence of decreased glucocorticoid binding affinity, decreased receptor

DNA binding, receptor thermolability, impaired translocation of the receptor into the nucleus, or alteration of appropriate interaction of proteins with coactivators.[27,59-64]

Intrinsic Adrenal Gland Dysfunction. This also has been proposed as a cause of hypocortisolism, but limited data exists in comparison with other proposed mechanisms, particularly in cases of stress-induced hypocortisolism. Scott and colleagues found patients with CFS and abnormal endocrine parameters to have a significant reduction in adrenal gland volume compared with control subjects. The authors postulate that in the face of adrenocortical atrophy, glucocorticoid production would diminish and compensatory glucocorticoid receptor upregulation does not occur.[65]

Another study by Cleare et al found CFS patients to have impaired adrenal cortical function as evidenced not only by decreased basal cortisol levels, but also by blunted cortisol responses to stimulation testing.[66] A 2005 study by Segal et al found adolescent CFS subjects given low doses of dexamethasone had lower peak and mean cortisol levels, reduced cortisol areas under the curve, and longer time to peak cortisol, suggesting adrenal dysfunction.[67] Intensive care unit patients with critical illnesses also have been shown to exhibit hypocortisol states, which are felt to be secondary to primary adrenal insufficiency.[68-71]

Adaptive Response. In response to recurrent or ongoing infectious assaults, hypocortisolism may occur as an adaptive survival mechanism to promote a more vigorous immune response.[27,72] Glucocorticoids are the most potent inhibitors of proinflammatory cytokines. During periods of acute illness, levels of cortisol increase in order to suppress immune overreactivity, thereby preventing tissue destruction.[7,25,27] Raison and Miller suggest that in individuals suffering from recurrent or smoldering infectious processes, reduced glucocorticoid signaling may eventually occur resulting in impairment of the normally adaptive inhibitory mechanisms.[27]

The term sickness response has been coined to describe the anorexia, fatigue, sleep disturbances, anhedonia, hyperesthesia, and cognitive difficulties often accompanying the body's response to infection via elevated immune activity. In his 1988 paper, Hart wrote that the sickness response results from the body's adaptive attempts to ration and prioritize its defenses to better eliminate the pathogen.[72] Many symptoms of the sickness response mimic those of stress-related bodily disorders, and an association between hypocortisolism-induced FMS and the sickness response has been observed.[73]

Additionally, studies have shown that patients with PTSD and hypocortisolism also appear to have an increased capacity to produce proinflammatory cytokines and thus manifest many of these same symptoms.[22,74,75,76]

Metabolic Sequelae of Hypocortisolism

Every organ system is adversely affected by chronic psychological and physiological stressors, and the subsequent damaging effects on normal cellular function are extensive.[6,8,77-83] Research has shown that short-lived physiological stressors can actually promote cellular longevity through cellular development of stress-induced resistance. However, under conditions of prolonged physiological stress, the normal cellular restorative and protective mechanisms are hindered, resulting in abnormal cellular function, premature cell aging, and cell death.[8,77-79] In addition, the set points and response profiles of certain regulatory systems are altered, thereby impairing recovery from subsequent stressors.[8,28,80,81]

Evidence exists implicating hypocortisolism in disease development and stress-related bodily (physiological and psychological) disorders.[5-7,15,16,19,21,24,25,27-30,49,53] A key component of the maladaptive physiological responses fueled by hypocortisolism is an increase in proinflammatory cytokines and immune system activation. This increase is due in part to loss of counterregulation by normal glucocorticoid activity.[15,25,27,46] Proinflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 (IL-6) not only suppress lymphocyte function but also disrupt T-cell signaling and inhibit natural killer cell activity.[25,46,84] Consequently, the upregulation of numerous inflammatory pathways increases susceptibility to the development of autoimmune diseases, mood disorders, malignancies, chronic pain, atopy, allergies, and asthma.[6,14,15,19,21,22,24,85-90] Studies also have found elevated levels of proinflammatory cytokines in patients with stress-related disorders, including PTSD, CFS, and FMS.[22,75,76,91-95]

Breast cancer patients who demonstrate significant post-treatment exhaustion have been shown to have significantly altered HPA axis activity in combination with elevated IL-6 levels and flattened cortisol curves with an apparent consequential increase in mortality and metastases.[87,88,90] Furthermore, the more flattened the cortisol curve, the worse the prognosis and the earlier the mortality.[87] Additional studies have found elevations not only in interleukin-1 and natural killer cell levels, but also in the levels of antinuclear autoantibodies, thyroid antibodies, and prostaglandins in patients with PTSD,[84] in patients with intrusive traumatic memories,[93] in sexually abused girls,[89,94] and in patients with CFS, FMS, and chronic pelvic pain.[28,90-95]

The hypocortisol state also permissively allows an in increase in sympathetic tone and catecholamine activity secondary to the absence of normal cortisol-mediated suppression.[37,85] Increased levels of catecholamines have been observed in patients with both PTSD and FMS.[96-101] Furthermore, exaggerations in sympathetic tone fueled by underlying hypocortisolism further potentiate the production of already elevated levels of proinflammatory cytokines. This mechanism is thought to contribute to glucose dysregulation, obesity, and damage to peripheral tissues such as the heart and bones.[102-109]

Finally, alterations in rhythmicity of cortisol release have been associated with various negative outcomes, including tumor growth and early mortality in cancer.[87,90] Diseases such as obesity, increased coronary artery calcification, and metabolic syndrome have been linked to circadian abnormalities in cortisol, particularly flattened cortisol curves.[102,103]

Clinical Manifestations of Hypocortisolism

The symptomatology of adrenal insufficiency and hypo-

Table: Signs and Symptoms of Hypocortisolism
General: fatigue, fever, weakness, myalgia, arthralgia, sore throat, headaches, dizziness upon standing, chronic pain
Gastrointestinal: anorexia, nausea, vomiting, diarrhea, abdominal or flank pain
Psychiatric: depression, apathy, irritability, sleep disturbances, difficulty concentrating, difficulty with memory, confusion, stress sensitivity
Cardiovascular: increased heart rate, postural hypotension, orthostatic tachycardia, hypovolemia, depressed myocardial contractility
Laboratory: hypoglycemia, hyponatremia, hyperkalemia, hypercalcemia, neutropenia, eosinophilia, hyperprolactinemia, hypothyroidism, leukocytosis, lymphocytosis

cortisolism states have been outlined in the critical care literature.[68-71] The term critical illness-related corticosteroid insufficiency (CIRCI) has been adopted to define a state of inadequate glucocorticoid activity secondary to both target tissue cortisol resistance and suboptimal serum levels of free cortisol.[70] Adrenal infarction, adrenal hemorrhage, coagulopathies, metabolic acidosis, and lack of substrate needed for cortisol production have been implicated as potential causes of CIRCI.[68-71,110] Clinically, critically ill patients display such findings as eosinophilia, hypoglycemia, and hypotension, symptoms also observed in Addisonian patients.[68,70,111]

In an outpatient clinical setting, patients with hypocortisolism may complain of subtle symptoms such as low-grade fever, easy fatigability, myalgias, weight loss, and muscular weakness—symptoms also seen in patients with both Addison's disease and CFS. Other complaints may include abdominal pain, nausea, vomiting, mood changes, and symptoms of hypoglycemia and postural hypotension (see Table).[31,32,111,112] Signs and symptoms of the aforementioned hypocortisol-associated disease states may also coexist and influence the clinical presentations in these patients.

Although patients with low cortisol states may present with any of the symptoms mentioned previously, Fries, Heim, and others have identified the hypocortisolemic symptom triad, consisting of high stress sensitivity, fatigue, and pain, as the most common presenting symptoms.[24,25] Reportedly, 20% to 25% of patients with stress-related bodily disorders present with symptoms of chronic fatigue, chronic pain, functional bowel disturbances, and atypical depression within the clinical context of hypocortisolism.[22,25,28,86,113,114] Blunted morning cortisol levels and flattened daytime cortisol curves also have been found to be associated with suboptimal physiological and psychological development and a diminished sense of well-being.[115]

Diagnostic Modalities

Cortisol measurements can be obtained through various biological samples, including serum, urine, and saliva. Cortisol is 90% to 93% bound to cortisol-binding globulin (CBG) in the circulation.[116,117] Fluctuations in CBG due to drugs and disease alter accuracy of measured total cortisol while free cortisol is independent of changes in CBG.[118]

Numerous studies report salivary cortisol to be ideal for evaluating bioavailability and accurately reflecting serum hormone activity because it houses the free and biologically active rather than the protein-bound fraction of the hormone.[119,120] Salivary cortisol concentrations are not influenced by parotid flow rate, food, dental care, or storage conditions.[120] Obtaining saliva samples offers several advantages, such as simplicity and cost effectiveness, and stress-free collection for study subjects.[121] Saliva samples can be safely frozen or refrigerated, easily transported, and have been successfully used in large-scale epidemiologic studies and clinical trials.[122]

Aberrant peaks and troughs replacing normal cortisol curve patterns are less well understood in the context of diseases states. However, specific findings such as low cortisol levels on awakening, flattened diurnal patterns, and abnormal sleep/wake cycles have both diagnostic and prognostic value, as previously discussed. Multiple salivary cortisol samples measured in a single day allow for accurate assessment and abnormalities of rhythmicity. In addition, they provide prognostic information unavailable from traditional single-serum samples or 24-hour urine collections.[118,121]

Conclusion

Because of the extensive nature of this topic, this paper provides an initial introduction and general overview of hypocortisolism. Numerous theories attempt to define the cascade of events leading to the evolution of hypocortisolism. However, the complex nature of the stress response has made definitive explanation of this disorder elusive. Nonetheless, the metabolic and clinical consequences that arise secondary to hypocortisolism are perhaps more important to consider. Clinicians have traditionally been trained to identify and treat the extremes of endocrine diseases. Although the importance of identifying patients with subtle symptoms of hypocortisolism has historically been unrecognized, ongoing research appears to be promoting increased awareness.

The stress response is complex and vulnerable to damage with prolonged perturbation. There are important and often deleterious metabolic consequences on every organ system with exposure to chronic stressors. Initial clinical manifestations of hypocortisolism and stress-related bodily disorders can often be vague. Therefore, clinicians must remain aware of possible presenting symptoms and employ appropriate diagnostic methods (salivary cortisol) for confirmation.

The mechanism by which hypocortisolism evolves remains ill defined. However, much of the available medical literature identifies the primary instigator of low cortisol states and abnormal diurnal cortisol release patterns to be HPA-axis dysregulation. Although adrenal fatigue or burn out of the adrenal gland subsequent to chronic stress has been proposed as one mechanism by which hypocortisolism develops, current medical research does not support this claim. Clinicians and patients should avoid global use of this term because it underestimates the complexity of HPA-axis dysfunction and the other processes by which hypocortisolism can evolve.

HPA-axis dysregulation and hypocortisolism are extremely important conditions that have not received appropriate attention until recently. We are in complete agreement with Gunner and Vazquez that "hypocortisolism may be a fairly common phenomenon associated with stress and challenge in human development" and that this condition is observed with adequate frequency to warrant our attention.[15] In light of current corroborating research on this topic, patients deserve more thoughtful consideration and evaluation when presenting with the metabolic and clinical consequences of chronic maladaptive stress responses.

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