

## Adrenal Disease

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The adrenals are two crescent-shaped glands that sit on top of each kidney. The adrenal glands secrete hormones directly into the bloodstream. They are divided anatomically and functionally into two main parts: the medulla (middle) and the cortex (rind) (Clayman 1989). Additionally, each division of an adrenal gland consists of internal layers that produce different hormones.

The inner part, or adrenal medulla, manufactures epinephrine and norepinephrine, also known as commonly known as adrenaline and noradrenaline. These hormones are the "fight or flight" hormones that are released in potentially life-or-death situations. Their release increases one's heart rate, and blood pressure, and diverts more blood to the brain, heart, and skeletal muscles. This is important when discussing stress.

The adrenal cortex surrounds the adrenal medulla and responds to a different type of stress. This is where the steroid hormones are made. These include cortisone, hydrocortisone, testosterone, estrogen, 17-hydroxy-ketosteroids, DHEA, pregnenolone, aldosterone, androstenedione, progesterone, and some other intermediate hormones. Many of these hormones are also made elsewhere in the body, but aldosterone, cortisone, and hydrocortisone are made only in the adrenal glands.

The hormone aldosterone, together with the kidneys, regulates the balance of sodium and potassium in the body. This regulation is critical to many areas of physiological function, including the ability to react to stress, maintain fluid balance, and regulate blood pressure.

Two disorders often associated with impaired function of the adrenal glands are Addison's disease and Cushing's syndrome.

### **ADDISON'S DISEASE: ADRENAL INSUFFICIENCY**

Addison's disease is a profound chronic adrenal failure caused by damage or disease of the adrenal gland, resulting in a deficiency of cortisol. This disease is sometimes called chronic adrenal insufficiency or hypocortisolism. The most important job of cortisol is to help the body respond to stress. Among its other vital tasks, cortisol is partly responsible for:

- Maintaining blood pressure and cardiovascular function
- Balancing the effects of insulin in breaking down sugar for energy
- Slowing the immune system's inflammatory response
- Regulating the metabolism of proteins, carbohydrates, and fats

Addison's disease is characterized by muscle weakness, reduced blood sugar, nausea, loss of appetite, weight loss, and low blood pressure, which can impact the act of standing, causing dizziness or fainting. Skin changes also are common in Addison's disease, with areas of hyperpigmentation or dark tanning that are mostly visible on scars, skin folds, toes, lips, mucous membranes, and pressure points, such as the elbows, knees, and knuckles.

### **CUSHING'S SYNDROME: OVERPRODUCTION OF CORTISOL**

The overproduction of cortisol by the adrenal glands leads to Cushing's syndrome (Clayman 1989). Cushing's syndrome also results when glucocorticoid drug hormones (such as hydrocortisone, prednisone, methylprednisolone, or dexamethasone) are

taken in excess for a prolonged period of time. These steroid hormones are often used to treat inflammatory-related illnesses such as asthma, rheumatoid arthritis, systemic lupus erythematosus, and some allergies.

The overproduction of cortisol in the adrenal glands can happen in two ways. A pituitary tumor could be producing too much ACTH (adrenocorticotropic hormone, produced by the pituitary gland), stimulating the adrenals to grow and to produce too much cortisol, or a benign or malignant tumor outside the pituitary such as in the lung, thymus gland, pancreas, or other organs can produce too much ACTH. The pituitary form is classically called Cushing's disease.

Cushing's syndrome is characterized by central obesity; sparing of the arms and legs (thin extremities); a round, reddish moon face; buffalo hump; and a protuberant abdomen. Many people with Cushing's syndrome experience severe fatigue, weak muscles, ulcers, thin skin, high blood pressure, and high blood sugar. Irritability, anxiety, and depression are also very common. Women with Cushing's syndrome will usually have excess hair growth (hirsutism) on their face, necks, chests, abdomens, and thighs. Their menstrual periods may become irregular or stop. Men may have decreased fertility and desire for sex.

## ADRENAL FATIGUE

Constant stress and poor nutrition can weaken the adrenal glands. When stress continues over prolonged periods of time, the adrenal glands can deplete the body's hormonal and energy reserves, and the glands may either shrink in size or hypertrophy (enlarge). The overproduction of adrenal hormones caused by prolonged stress can weaken the immune system and inhibit the production of white blood cells that protect the body against foreign invaders (in particular lymphocytes and lymph node function). Adrenal dysfunction can disrupt the body's blood sugar metabolism, causing weakness, fatigue, and a feeling of being run down. It can also interfere with normal sleep rhythms and produce a wakeful, unrelaxing sleep state, making a person feel worn out even after a full night's sleep.

If a person succumbs easily to allergies and infections, feels constantly drained and exhausted, and experiences low blood sugar and blood pressure, the culprit may be weak adrenals. Adrenal insufficiency is sometimes linked to chronic fatigue. In some fatigued patients, thyroid problems may overlap adrenal problems. In these cases, the status of the adrenal glands and the thyroid gland must be assessed. The appropriate treatment should be undertaken only after this determination is made. If adrenal fatigue is suspected, the patient should be evaluated by a physician with experience in recognizing and treating adrenal fatigue and issues of the relative Addisonian state. It is very important to make sure that full-blown Addison's disease is not the problem, since it must be treated vigorously (Ehlert et al. 2001; Tsigos et al. 2002). In most communities, a qualified internist or internal medicine subspecialist will begin the investigation.

## DIAGNOSIS

### ■ Factors that May be Overlooked in Diagnosis

If disturbed adrenal function is suspected, the levels of hormones such as hydrocortisone, aldosterone, epinephrine, and ACTH may be measured in blood, plasma, and urine. There are also tests (by injection) to measure the effects of substances that normally modify the production of a specific hormone. One test is called the ACTH challenge test. When ACTH is injected, there should be an increase in adrenal hormone output. If this does not happen, adrenal fatigue is probable. These tests are also helpful in localizing the underlying cause of a particular disorder (e.g., to distinguish between Cushing's syndrome caused by an adrenal tumor from that caused by pituitary disease). Conversely, a very high potency corticosteroid (dexamethasone) can be used to assess the suppressability of cortisone production in Cushing's syndrome.

If disease of the adrenal glands is suspected, imaging studies (abdominal x-ray, MRI, CT scan, arteriography, radionuclide scanning, and IV scanning of the position of kidneys using an IV dye) may show the presence of adrenal calcification, a tumor, atrophy, or the overgrowth of a gland.

### **Factors that May be Overlooked in Diagnosis**

Cortisone is produced mainly in a reversible reaction from cortisol; it is also secreted in small amounts from the adrenal cortex. The term hydrocortisone refers to both naturally produced cortisone and the pharmaceutical preparation used to treat various inflammatory disorders. Naturally produced hydrocortisone is a glucocorticoid, meaning that it helps to regulate normal blood glucose concentration by converting amino acids and fatty acids to glucose, when needed, in a process called gluconeogenesis.

Synthetic hydrocortisone drugs (corticosteroids) became available in the late 1940s and were heralded as a miraculous treatment for rheumatoid arthritis due to their suppression of the immune system. However, it did not take long to learn that there was a serious price to pay for chronic corticosteroid use. People taking synthetic hydrocortisone developed many symptoms and physical abnormalities such as the symptoms of Cushing's syndrome, resulting from the body's overexposure to corticosteroids.

As a result of these adverse reactions, an often irrational approach developed in the medical community to the question of relative adrenal function. A person who has total failure of the adrenal glands is said to have Addison's disease even though low steroid levels can also be caused by failure of the hypothalamus, thalamus, and pituitary areas of the brain. In this case, the adrenal glands still function. In the case of Cushing's syndrome, the disease may manifest due to physical abnormality or as the result of corticosteroid use.

When a physician evaluates a patient relying solely upon laboratory data, the patient is considered either normal or having Addison's disease or Cushing's syndrome. There may be no analysis of other contributing factors. This protocol is directed only at the function of the adrenal glands. However, just as in thyroid dysfunction (see the Thyroid Deficiency protocol), normal laboratory tests do not exclude what some physicians refer to as adrenal fatigue (or relative Cushing's or Addisonian states).

The association of impaired immune function and the administration of synthetic corticosteroids have blurred an important fact. Decreased levels of corticosteroids also impair immune function. What further complicates the matter is the fact that it is now thought that the continual overproduction of cortisol, not in the range that would produce Cushing's syndrome, contributes to immune suppression, atherosclerosis, brain cell injury, and accelerated aging.

## DRUG TREATMENTS

- Addison's Diseases
- Cushing's Syndrome

### Addison's Disease

- Adrenal Cortical Extract
- Hydrocortisone

#### ***Adrenal Cortical Extract***

A few physicians recommend adrenal cortical extract (ACE), which contains all the corticosteroids in the proper proportions. ACE used to be widely available in this country, but at the present time it is not. Complementary physicians may have had experience with it. At times of increased stress, the addition of adrenal glandulars may be advisable but must be monitored carefully. Long-term use is not recommended and is likely hazardous. (The FDA removed all products containing adrenal cortex from market in 1997 due to concerns regarding contamination.)

#### ***Hydrocortisone***

Cortisol is usually replaced orally with hydrocortisone tablets. The doses of this medication are adjusted to meet the needs of individual patients. During a critical stage, when blood pressure and blood sugar are dangerously low and potassium levels are high, therapy can involve the injection of hydrocortisone, saline, and dextrose.

#### ***Cushing's Syndrome***

Treatment of Cushing's syndrome will depend upon the cause of the disorder. If the disorder is caused by long-term corticosteroid use, the drug must be slowly decreased and the patient weaned under medical supervision. If it is caused by a pituitary or adrenal tumor, surgery is necessary to remove it. In Cushing's syndrome caused by an ectopic ACTH-secreting tumor, the tumor is resected. For a year after cessation of high-dose corticosteroid therapy, even minor illnesses can cause a full-blown Addisonian collapse. If the tumor is malignant and has metastasized and resection is not possible, treatment may include a combination of chemotherapy, immunotherapy, and radiation therapy.

Drugs such as ketoconazole, aminoglutethimide, or metyrapone may also be given to suppress cortisol metabolism and secretion. The European drug KH3 (the active ingredient is procaine), which can block some of the cell-damaging effects of cortisol and help protect against cortisol toxicity, is beneficial for Cushing's disease. KH3 has been also known for its beneficial effects in aging and depressed people (Cohen et al. 1974; Hall et al. 1983). A suggestion would be to take 1-2 KH3 capsules in the morning on an empty stomach and 1-2 KH3 capsules in mid-afternoon, also on an empty stomach.

# Adrenal Disease

## NATURAL SUPPLEMENTS TO TREAT ADDISONIAN STATES

- DHEA
- Licorice
- Pantothenic Acid
- L-Theanine

### DHEA

Aging and diseases associated with aging can cause a decline in critical hormones produced by the adrenal glands. Pregnenolone is converted into crucial antiaging hormones such as dehydroepiandrosterone (DHEA), estrogen, progesterone, and testosterone. DHEA supplementation may help to partly rectify hormone imbalances caused by age-induced adrenal insufficiency.

An article in the journal *Clinical Endocrinology* described a study of the effect of oral DHEA replacement therapy in women with Addison's disease (Gebre-Medhin et al. 2000). The researchers found that DHEA and DHEA-sulfate (DHEA-S) levels were restored to normal in those patients receiving 50 mg of DHEA, whereas the DHEA-S level was slightly above the normal reference value in those receiving 200 mg of DHEA. Circulating levels of androgens (androstenedione, testosterone, and testosterone/SHBG ratio) were normalized in all patients. No serious side effects were seen, but some of the patients experienced increased apocrine sweat secretion (apocrine glands are in the armpit, anal, genital, and breast areas and produce a strong odor), itchy scalp, and acne, all of which were reversed when DHEA was discontinued. The authors concluded that a daily replacement dose of 50 mg of DHEA results in near physiological levels of DHEA, DHEA-S, androstenedione, and testosterone in women with Addison's disease without severe side effects (Gebre-Medhin et al. 2000).

Another article described a randomized, double-blind study in which 39 patients with Addison's disease received 50 mg of oral DHEA daily for 12 weeks (Hunt et al. 2000). After DHEA treatment, levels of DHEA-S and delta- (4) -androstenedione rose from subnormal to within the adult physiological range. Total testosterone increased from subnormal to low normal with a fall in serum sex hormone-binding globulin in females, but with no change in either parameter in males. In both sexes, psychological assessment showed significant enhancement of self-esteem with a tendency for improved overall well-being. Mood and fatigue also improved significantly, with benefit being evident in the evenings. The authors concluded that DHEA replacement corrects this steroid deficiency effectively and improves some aspects of psychological function. These positive effects, in the absence of significant adverse events, suggest a role for DHEA replacement therapy in the treatment of Addison's disease. Studies suggest that low DHEA-S might be a prognostic marker and a sign of exhausted adrenal glands (Hunt et al. 2000; Beishuizen et al. 2002). ( Before taking DHEA or pregnenolone, refer to the Foundation's precautions in the DHEA Replacement Therapy protocol and to the Autoimmune Diseases protocol for additional suggestions . ) .

Even mild Addison's disease requires expert physician intervention and supervision. Glucocorticoid and mineralocorticoid component drugs are prescribed for Addison's disease. Once cortisol levels are stabilized, the serum levels of DHEA should be evaluated to determine if DHEA replacement therapy is warranted. In the majority of cases, Addison's disease is caused by an autoimmune attack on the adrenal glands. DHEA has been shown to suppress inflammatory cytokines and thereby down-regulate autoimmune reactions in the body. In the past, infection, such as tuberculosis or meningitis, was the main cause.

### Licorice

Licorice (*Glycyrrhiza glabra* and *Glycyrrhiza uralensis*) is grown in Europe and Asia . Licorice is a highly prized medicinal ly in Chinese medicine. It is used in almost all of the Chinese patent herbal formulas. *Glycyrrhiza* may be taken in a variety of ways, including as a tea. It helps to reduce the amount of hydrocortisone broken down by the liver, thereby reducing the workload of the adrenal glands. Licorice is a well-loved candy for children, although most commercial brands no longer contain real licorice. Instead commercial products use anise seed and sugar, which taste similar. It is best to stay with teas or supplements. Licorice was prescribed for Addison's disease until the 1930s. Licorice is also a demulcent (an oily substance that reduces irritation), which makes it soothing to the digestive tract. Deglycyrrhized licorice (DGL) is made by removing the glycyrrhizin. For the adrenal effects, only real licorice should be used, not DGL.

Long-term use of licorice containing more than 1 gram of glycyrrhizin (the amount in approximately 10 grams of licorice root) daily can cause increased blood pressure and water retention (edema) (Schambelan 1994). High doses of licorice should only be taken under the care of a qualified health professional.

### Pantothenic Acid

Pantothenic acid (vitamin B5) activates the adrenal glands. It is a precursor of acetyl CoA (a part of the Krebs's cycle which produces cellular energy) and acetylcholine (a primary neurotransmitter). Pantothenic acid deficiency results in adrenal insufficiency, which is characterized by fatigue, headache, sleep disturbances, nausea, and abdominal discomfort (Tarasov et al. 1985; Smith et al. 1996; Murray et al. 1997).

## **L-Theanine**

L-theanine is an amino acid found in green tea that produces a calming effect in the brain. It works by increasing gamma-aminobutyric acid (GABA) that is a relaxer and creates a sense of well-being. L-theanine may be taken to help modulate mood and relieve stress in many health conditions (Abe et al. 1995; Kobayashi et al. 1998; Juneja et al. 1999).

## **NATURAL SUPPLEMENTS TO TREAT CUSHING'S SYNDROME**

- DHEA
- Vitamin C
- Phosphatidylserine
- Melatonin

## **DHEA**

DHEA may help to protect against the overproduction of cortisol from the adrenal glands and enhance the immune system. This is an important factor since too much cortisol accelerates aging and causes immune system disorders. Studies show that DHEA deficiency may actually debilitate immune status (Wisniewski 1993; Morio et al. 1996).

## **Vitamin C**

Studies show that vitamin C and aspirin can attenuate and influence cortisol, inducing an anti-inflammatory response to prolonged exercise and stress. Vitamin C has been shown to reduce the elevation of cortisol in response to heavy exercise. In human studies, 3000 mg of vitamin C daily mitigated a rise in blood pressure, cortisol, and subjective response to acute psychological stress ( Di Luigi et al. 2001; Peters et al. 2001a, 2001b; Brody et al. 2002).

## **Phosphatidylserine (PS)**

Phosphatidylserine is a phospholipid that is a structural component of the biological membranes in animals and plants. In studies, supplemental PS has been shown to improve mood and blunt the release of cortisol in response to physical stress (Monteleone et al. 1990; Kelly 1999; Benton et al. 2001).

## **Melatonin**

Melatonin is secreted by the pineal gland and functions to regulate circadian rhythm and induce sleep. Melatonin circadian secretion in patients with pituitary- or adrenal-dependent Cushing's syndrome was shown to be significantly lower compared to healthy control groups. Studies also have shown that nightly administration of 2 mg of melatonin increased the DHEA-S-cortisol ratio after 6 months of treatment (Soszynski et al. 1989; Bruls et al. 2000; Pawlikowski et al. 2002).

## **NATURAL SUPPLEMENTS TO TREAT ADRENAL FATIGUE**

After an evaluation by a physician, if stress is determined to be the cause of adrenal fatigue, the first goal is to relieve the stressful situations as much as possible. Consider lifestyle changes, including diet modification and exercise. Limit the consumption of processed foods, and avoid alcohol and tobacco use because these substances put extra stress on the adrenal glands. Many supplements recommended for either Addison's disease or Cushing's syndrome may also be taken for general adrenal fatigue because they can help to support healthy adrenal function, reduce stress, and blunt the release of excess cortisol during stress. Consider the following:

- Vitamin C, 3000 mg a day
- DHEA, 50 mg a day
- L-theanine, 100-400 mg a day
- Pantothenic acid (vitamin B5), 1500 mg a day
- Melatonin, 300 mcg-6 mg (at bedtime)
- Phosphatidylserine capsules, 300 mg a day

## DIET AND ADDISON'S DISEASE

A possible link between gluten sensitivity (celiac disease) and Addison's disease has been proposed. An article in the *Journal of Endocrinological Investigation* described a patient with celiac disease and multiple endocrine disorders, including autoimmune Addison's disease and hypothyroidism (Valentino et al. 1999). Over a 3-month period, on a gluten-free diet, the patient showed a marked clinical improvement accompanied by a progressive decrease in the need for thyroid and adrenal replacement therapies. After 6 months, the serum IgA antiendomysium antibody test (used to confirm celiac disease) became negative. After 12 months, a new jejunal biopsy showed complete mucosal recovery. (The jejunum is the middle third of the small intestine.) After 18 months on a gluten-free diet, the antithyroid antibodies titer decreased significantly, and thyroid substitutive therapy was discontinued. The authors proposed a link between autoimmune endocrine disease and celiac disease, noting that celiac disease is one of the causes for the failure of substitute hormonal therapy in patients with autoimmune thyroid disease (Valentino et al. 1999).

According to the National Adrenal Diseases Foundation (Great Neck, NY), individuals who have Addison's disease as well as other diseases of the adrenal glands are often misdiagnosed or go for long, distressful periods without a correct diagnosis.

Symptoms of adrenal diseases often mirror those of chronic fatigue syndrome, including steadily worsening exhaustion, a loss of appetite, and weight loss. In Addison's disease, blood pressure is low and becomes even lower when the person stands, producing lightheadedness. Because of salt loss, a craving for salty foods is common. Darkened skin may appear as an inappropriate tan on a person who is ill (NADF 1998).

Cushing's disease is the symmetrical overproduction of cortisol by the adrenal glands. Cushing's syndrome is a constellation of signs and symptoms due to chronic overexposure to adrenal corticosteroids. Symptoms may include central obesity, wasting of the arms and legs (thin extremities), a reddish moon face, buffalo hump, a protuberant abdomen, and pigmented stretch marks (striae). Many people experience severe fatigue, weak muscles, high blood pressure, and high blood sugar. Irritability, anxiety, and depression are also common.

Adrenal fatigue can be caused by constant stress or poor nutrition, which can deplete and weaken the adrenal glands. There are many symptoms associated with this disorder, mostly fatigue and weakness. In some fatigued patients, thyroid problems overlap or are concomitant with adrenal problems.

- If you suspect that you have some form of adrenal disease, seek professional medical treatment from a physician.
- Identify and relieve sources of stress. Consider meditation or other stress-relieving exercises.
- Consider lifestyle changes such as diet and exercise.
- Obtain baseline corticosteroid, DHEA, and pregnenolone levels.
- Avoid smoking. Nicotine in tobacco initially raises cortisol levels, but chronic use results in low DHEA, testosterone, and progesterone levels.
- Consider laboratory testing for celiac disease (gluten sensitivity) and starting a gluten-free diet.
- If available, consider physician-administered injections of ACE (adrenal cortical extract) from a reliable source for 3-7 days.
- Hydrocortisone tablets (one of several forms available by prescription) may be taken up to 4 times daily for 3-7 days to treat Addison's disease (adrenal insufficiency). Physician supervision is mandatory.

The following natural supplements are recommended for Addison's disease:

- DHEA, 50 mg daily and/or pregnenolone 50 mg daily, based on appropriate laboratory tests (see the DHEA Replacement Therapy protocol for more information and precautions).
- Licorice tea or capsules to provide glycyrrhizin, no more than 1000 mg of glycyrrhizin should be taken in a given day and physician supervision is advised to guard against blood pressure increase and water retention.
- Pantothenic acid (vitamin B5), 1500 mg daily.
- Vitamin C, 1000-3000 mg daily, in divided doses.
- L-theanine may be taken to help modulate mood and relieve stress, one 100-mg capsule up to 4 times a day.
- Phosphatidylserine, 100-300 mg daily.

The following natural supplements are recommended for Cushing's syndrome:

- DHEA, 50 mg daily, or pregnenolone, 50 mg daily, based on appropriate laboratory tests (see the DHEA Replacement Therapy protocol for more information and precautions).
- Vitamin C, 4000 mg daily, in divided doses.

- One enterically coated aspirin tablet (325 mg). (Enteric coatings prevent the tablet from dissolving in the stomach.)
- Phosphatidylserine, 300 mg daily.
- Melatonin, 300 mcg-6 mg nightly.

Physician supervision is essential. To guard against underlying micronutrient deficiencies that could contribute to adrenal disease, take a high-potency multinutrient supplement such as Life Extension Mix (3 tablets 3 times a day).

### FOR MORE INFORMATION

Contact the American College for the Advancement of Medicine, (800) 532-3688, for a physician in your area who practices complementary medicine. Contact the National Adrenal Diseases Foundation for support, information, and education for individuals who have Addison's disease as well as other diseases of the adrenal glands, (516) 487-4992.

### PRODUCT AVAILABILITY

DHEA and pregnenolone capsules, licorice capsules, pantothenic acid (vitamin B5), vitamin C powder and capsules, phosphatidylserine (PS) capsules, melatonin, and L-theanine can be ordered by telephoning (800) 544-4440 or by ordering online. ACE is not approved by the FDA for conventional use at this time.



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