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1 Overview

Summary and Quick Facts for Common Adrenal Disorders

- Disordered adrenal function can lead to a barrage of significant complications, including diabetes, high blood pressure, prolonged fatigue, and depression. Addison's disease and Cushing's syndrome are two major adrenal gland disorders, and they can be deadly if left untreated.
- This protocol will provide an overview of adrenal function and examine the development and consequences of the two primary adrenal disorders – Addison's disease and Cushing's syndrome. Conventional strategies for managing adrenal disorders will be discussed, as well as emerging medical approaches and scientifically studied natural therapies.
- Nutritional interventions may play a supportive role in the treatment of adrenal disorders. Furthermore, emergent treatment strategies such as stimulation of adrenal stem cells for Addison's disease and the drug pasireotide for Cushing's syndrome represent the potential next generation of minimally invasive treatment strategies for these debilitating conditions.

What are Adrenal Disorders?

Adrenal disorders are conditions that arise when adrenal gland function is impaired. The adrenal glands are hormone-producing glands that regulate several bodily functions via the secretion of the following hormones:

glucocorticoids (eg, cortisol), mineralocorticoids (eg, aldosterone), catecholamines (eg, epinephrine), and adrenal androgens (eg, dehydroepiandrosterone [DHEA]).

Disordered adrenal function can have significant adverse effects. Two major adrenal gland disorders are Addison's disease (reduced adrenal function, often autoimmune) and Cushing's syndrome (overactive adrenal function, often due to a tumor).

Natural interventions such as **melatonin**, **calcium**, and **vitamin D** may help support adrenal function.

What are the Causes and Risk Factors for Adrenal Disorders?

- Autoimmune disease
- Genetic abnormalities
- Tumor
- Overtreatment with glucocorticoid medications
- Certain drugs that interfere with adrenal hormone production

What are the Signs and Symptoms of Adrenal Disorders?

Addison's disease:

- Weakness and fatigue
- Low blood pressure upon standing
- Skin hyperpigmentation and bluish discoloration inside the mouth

Cushing's syndrome:

- Rounded "moon" face
- Weight gain around the trunk with slender arms and legs
- Skin appears bruised
- Muscle weakness
- Anxiety and/or depression
- Abnormal hair growth and menstrual disorders in women
- Reduced libido in men

What are Conventional Medical Treatments for Adrenal Disorders?

Addison's disease:

- Hormone replacement therapy (eg, hydrocortisone or other glucocorticoids)

Cushing's syndrome:

- Surgery to remove tumor, if possible
- Mifepristone to treat high blood sugar in people with Cushing's who are not surgical candidates or who had failed surgeries
- Adrenal enzyme inhibitors (eg, ketoconazole) for patients with nonresectable tumors
- Mitotane to prevent the production of steroids in patients who cannot be cured surgically
- Pasireotide, a drug that can bind to adrenal cortex tumor cells and prevent the release of adrenocorticotropic hormone (ie, the hormone that regulates production and secretion of adrenal hormones)

What are Emerging Therapies for Adrenal Disorders?

- Stem cell therapy

What Dietary and Lifestyle Changes Can Be Beneficial for Adrenal Disorders?

- Avoid simple carbohydrates
- Maintain a healthy, well-balanced and steady diet; avoid "yo-yo dieting"
- Limit intake of stimulants (eg, caffeine)
- Exercise regularly
- Manage stress effectively; work to maintain a positive attitude and good self-esteem

- Get enough good quality sleep

What Natural Interventions May Be Beneficial for Adrenal Disorders?

- **Melatonin**. Cushing's syndrome is associated with low melatonin levels and disruption of its circadian secretion. A study in healthy men showed that melatonin reduced cortisol secretion in response to an ACTH stimulation test.
- **Calcium and vitamin D**. Vitamin D supports calcium absorption, and its deficiency can contribute to osteoporosis. High cortisol levels and long-term glucocorticoid treatment lead to osteoporosis as well. Vitamin D and calcium supplements are recommended for people receiving long-term corticosteroids.
- **Potassium**. Potassium levels are low in individuals with Cushing's syndrome, and low potassium levels are a significant determinant of cardiovascular complications in this population. People on ketoconazole treatment for Cushing's syndrome should avoid potassium supplements, however, since it can also increase potassium levels.
- Other natural interventions that may help people with adrenal disorders include **vitamin A**, **curcumin**, **licorice**, **DHEA**, **pantothenic acid**, and **coenzyme Q10**.

2 Introduction

The adrenal glands are a pair of triangular-shaped, hormone-producing glands; one is located on top of each kidney. They regulate several fundamental aspects of human physiology via secretion of specific hormones including ***glucocorticoids*** (eg, cortisol), ***mineralocorticoids*** (eg, aldosterone), ***catecholamines*** (eg, epinephrine), and ***adrenal androgens*** (eg, dehydroepiandrosterone [DHEA]) (Rakel 2012; Brender 2005; PubMed Health 2011a; NICHD 2010; Charmandari 2011; Gurnell 2008).

- **Glucocorticoids** help regulate blood sugar, blood pressure, fat and protein metabolism, and immunity (Charmandari 2010).
- **Mineralocorticoids** help regulate kidney and cardiovascular function (via maintenance of salt and water balance within the body) (Farman 2001).
- **Catecholamines** help regulate the "***fight or flight***" response to stress (Arun 2004; PubMed Health 2011a).
- **Adrenal androgens** are precursors to sex hormones such as testosterone and estrogen (Gurnell 2008).

Disordered adrenal function can lead to a barrage of significant complications, including diabetes, high blood pressure, prolonged fatigue, and depression (Ten 2001; Pozza 2012). **Addison's disease** and **Cushing's syndrome** are two major adrenal gland disorders, and they can be *deadly* if left untreated (Ten 2001; Lovås 2002; Pivonello 2008).

Typical conventional treatment strategies for Addison's and Cushing's comprise side-effect-laden drugs that may require regular clinical monitoring, or invasive surgical procedures (van der Pas 2012, Tritos 2012). However, emergent treatment strategies such as stimulation of ***adrenal stem cells*** for Addison's disease and the novel drug ***pasireotide*** for Cushing's syndrome represent the potential next generation of minimally invasive treatment strategies for these debilitating conditions (Colao 2012; ClincalTrials.gov NCT01371526).

This protocol will provide an overview of adrenal function and examine the development and consequences of the two primary adrenal disorders – Addison's disease and Cushing's syndrome. Conventional strategies for managing adrenal disorders will be discussed, as well as emerging medical approaches and scientifically studied natural therapies.

3 Function of the Adrenal Glands

Each adrenal gland has an outer region, called the ***cortex***, and an inner region, called the ***medulla***. Each of these regions contains highly specialized cells that secrete distinct hormones to carry out different physiologic functions (PubMed Health 2011a).

- The **adrenal cortex** secretes 3 types of hormones: *glucocorticoids*, *mineralocorticoids*, and *androgens*.
    - ***Glucocorticoids*** (eg, *cortisol*) control inflammation and regulate the body's response to infections and stress. They also play a role in maintaining blood pressure, blood sugar, and cardiovascular function

(Charmandari 2010).
    - ***Mineralocorticoids*** (eg, *aldosterone*) regulate sodium and potassium levels in the body and thereby help maintain blood pressure and water balance, mainly via the kidneys (Farman 2001).
    - ***Adrenal androgens*** (eg, *dehydroepiandrosterone [DHEA]*) are precursors of the sex hormones testosterone and estrogen (Gurnell 2008). In addition, the adrenal glands also produce a small amount of testosterone (PubMed Health 2011a).

- The **adrenal medulla** produces the ***catecholamine hormones***, which comprise epinephrine (also known as adrenaline), norepinephrine (noradrenaline), and dopamine (PubMed Health 2011a). Norepinephrine and epinephrine are primarily responsible for the "fight or flight" response to stress or fear (Arun 2004).

  The "fight or flight" response manifests as increased heart rate and blood pressure, rapid breathing, and greater blood flow to muscles (Head 2009; Molina 2005). These physiologic responses arise via activation of the *sympathetic nervous system*. The sympathetic nervous system is a part of the involuntary nervous system, which controls processes such as breathing, heart rate, and metabolism (PubMed Health 2012; Molina 2005).

A precisely regulated relationship exists between the adrenal hormones and hormones secreted by the *hypothalamus* (a small region located at the center of the brain) and the pituitary gland (a pea-shaped structure located at the base of the brain). These 3 structures influence one another and collectively comprise the ***hypothalamic-pituitary-adrenal (HPA) axis*** (Bonfiglio 2011; Head 2009). The HPA axis is crucial to the regulation of a variety of physiologic functions including the body's response to stress. For example, one of the actions of the hypothalamus is to direct the pituitary gland to release ***adrenocorticotropic hormone (ACTH)***, which regulates the production and secretion of hormones from the adrenal cortex.

Under normal healthy conditions, the secretion of hypothalamic, pituitary, and adrenal cortex hormones is finely controlled by each of the other glands (Head 2009). For instance, increasing cortisol levels signal the pituitary to reduce ACTH secretion, which in turn decreases cortisol secretion (Head 2009; Bonfiglio 2011). Under chronic stress or disease conditions, however, this feedback system can become imbalanced (Anagnostis 2009; Foley 2010).

Impaired adrenal function

Impaired function of the adrenal glands may lead to either increased or decreased production of adrenal hormones. Cushing's syndrome and Addison's disease are conditions characterized by abnormal adrenal function.

Cushing's syndrome

In Cushing's syndrome, blood levels of cortisol remain high over an extended period of time and cause characteristic changes in the body (Pivonello 2008; Bertagna 2009). People with Cushing's typically have a rounded "moon" face, gain weight around the trunk, and have slender arms and legs. Their skin is often thin and can have a bruised appearance with stretch marks. Other features include muscle weakness, susceptibility to infection, elevated blood sugar levels (hyperglycemia), and weak bones (osteoporosis). These changes are often accompanied by mood disorders such as anxiety and depression. In children, excess cortisol can lead to stunted growth. Furthermore, men can exhibit reduced fertility and libido, while women can exhibit hirsutism (abnormal hair growth on face, neck, thighs, and chest) and menstrual disorders (Pozza 2012; Stratakis 2008). Excess secretion of adrenal androgens may also lead to virilization (presence of external male characteristics in females or in boys before puberty) (Stratakis 2008).

Addison's disease

Addison's disease is an uncommon, debilitating disease that is rarely identified in its early stages. In Addison's disease, the function of the adrenal cortex progressively declines over time, resulting in glucocorticoid and mineralocorticoid deficiency, as well as reduced levels of DHEA and androgens (Nieman 2006; Ten 2001; Gebre-Medhin 2000; Luken 1999). The typical early symptoms of Addison's disease are weakness, low blood pressure upon standing, and fatigue. People with Addison's disease gradually develop an often heavy pigmentation of the skin (especially around bony prominences, skin folds, and on the back of arms and legs) and a bluish discoloration of the mucous membrane lining the mouth (Ten 2001). Cortisol and aldosterone deficiency together

cause changes in blood levels of sodium and potassium and a decrease in plasma volume, which can lead to extreme dehydration and shock (Padidela 2010). Trauma, surgery, and infections in people with reduced adrenal function may result in *adrenal crisis*, a life-threatening condition that can lead to extreme weakness, severe body pain, low blood pressure, and fever (Mattke 2002; Omori 2003).

Adrenal fatigue

Although not a diagnosis recognized by the conventional medical establishment, some innovative doctors characterize "adrenal fatigue" as a condition that shares some symptoms with Addison's disease, such as tiredness, depression, muscle pain, poor concentration, low blood sugar, craving for stimulants, and difficulty sleeping. However, in adrenal fatigue it is thought that the adrenal glands are unable to perform normally due to exposure to chronic stress. More information is available in Life Extension's **Stress Management** protocol (Ahn 2011).

4 Causes and Risk Factors

Addison's disease

Adrenal insufficiency, or decreased production of adrenal hormones, can occur for several reasons. ***Autoimmune Addison's disease***, in which the body's own immune system attacks the adrenal glands, is the most common cause (Betterle 2002; Ten 2001). In other cases, diseases such as tuberculosis, cancer, or adrenal hemorrhage can damage the adrenal glands, leading to reduced function or complete loss of function (Ten 2001; Betterle 2002). Sometimes, mutations in certain genes at birth or an inherent inability of the adrenal glands to respond to ***adrenocorticotropic hormone*** (ACTH)* can lead to the stunted growth of the glands, thereby causing them to secrete abnormally low levels of adrenal hormones (Ten 2001). In some severe cases, people with gene mutations can be deficient in all 3 types of adrenal cortex hormones—glucocorticoids, mineralocorticoids, and androgens (Ten 2001). Drugs that inhibit the synthesis of steroids in the adrenal cortex (eg, the antifungal drug ketoconazole) can also impair adrenal hormone production (Tabarin 1991; Loose 1983; Sarver 1997; Hahner 2010). Finally, since adrenal gland function is controlled by the hypothalamus and pituitary gland, decreased adrenal function can arise from conditions or events that affect these brain regions, such as pituitary or hypothalamic tumors, pituitary surgery or radiation treatment, or head trauma (Betterle 2002).

**Adrenocorticotropic hormone (ACTH)* is secreted from the pituitary gland and regulates the production and secretion of hormones from the adrenal cortex.

Cushing's syndrome

ACTH* signals the adrenal glands to produce cortisol, thus excess secretion of ACTH results in excessive elevation of cortisol levels. A common cause of elevated cortisol is the presence of a pituitary gland tumor that continually secretes ACTH (Yaneva 2010; Bertagna 2009). This is referred to as Cushing's *disease* and is considered distinct from Cushing's *syndrome*. In Cushing's syndrome, increased cortisol levels manifest after ACTH secretion from ectopic tumors (tumors in other organs, such as the lung) (Bertagna 2009). Since increased cortisol levels in these two conditions are a result of excess ACTH secretion, they are considered to be "ACTH-dependent." Cushing's syndrome can also occur due to the direct over-secretion of cortisol from adrenal gland tumors. This type of cortisol elevation is considered to be "ACTH-independent" (Stratakis 2008). Over-treatment with glucocorticoid medications is considered to be the most common cause of Cushing's syndrome (Tritos 2012).

**Adrenocorticotropic hormone (ACTH)* is secreted from the pituitary gland and regulates the production and secretion of hormones from the adrenal cortex.

5 Diagnosis and Biomarkers of Adrenal Gland Dysfunction

Addison's disease

Addison's disease is typically diagnosed based on assessment of the clinical signs and symptoms described earlier. Laboratory tests are performed to assess electrolyte levels in the blood as well as serum levels of cortisol and ACTH; computed tomography (CT) scans of the adrenal or pituitary glands are sometimes performed as well

(Betterle 2002). Low serum cortisol with increased serum ACTH levels is indicative of Addison's disease (Al-Aridi 2011). Cortisol levels vary according to the time of the day (diurnal variation), with levels normally peaking no later than 8 AM (Lipworth 1999). Therefore, an 8 AM cortisol test is performed to check for cortisol levels in the blood, which are decreased (<3 µg/dL) in Addison's disease (PubMed 2011b; Lipworth 1999; Betterle 2002). Further, individuals with Addison's disease do not show an increase in serum cortisol level when given an injection of cosyntropin (a synthetic form of ACTH); this procedure is referred to as an ACTH stimulation test (Betterle 2002; Neary 2010).

On the other hand, people with Addison's disease specifically due to hypothalamic or pituitary disorders will show low levels of both ACTH *and* cortisol (Neary 2010). Upon fasting, these individuals often develop very low glucose levels in the blood (hypoglycemia), as their body is unable to produce glucose from stored fat and proteins (Betterle 2002).Abnormally low blood levels of levels of DHEA-sulfate (DHEA-S) along with decreased cortisol and aldosterone levels are indicative of *adrenal insufficiency*, warranting further testing of HPA axis function (Al-Aridi 2011).

Cushing's syndrome

The typical physical characteristics of Cushing's syndrome are diagnostic and are further confirmed by laboratory test results. People with Cushing's syndrome generally have grossly increased levels of free cortisol in their urine and, although cortisol levels normally show diurnal variation, this variation is not observed in Cushing's syndrome (Papanicolaou 1998). Measurement of ACTH levels can also help to distinguish between the 2 variants of Cushing's syndrome (ACTH-dependent and ACTH-independent) (Tritos 2012; Newell-Price 2007). Magnetic resonance imaging (MRI) and CT scans are useful for the diagnosis of pituitary and adrenal tumors (Arnaldi 2003; Tritos 2012).

6 Conventional Treatments

Addison's disease

The standard therapy for treating Addison's disease consists of replacing the deficient hormones (Ten 2001). ***Hydrocortisone***, which is a synthetic glucocorticoid, is one of the most common cortisol replacement therapies (Lennernas 2008). In acute illnesses, such as adrenal crisis, immediate administration of intravenous hydrocortisone and saline is needed to prevent potentially life-threatening complications (Kearney 2007).

Though effective, there are many challenges associated with using hydrocortisone. Since cortisol levels follow a diurnal variation, it is difficult to choose an optimal drug dosing regimen to simulate this natural *circadian rhythm* (Ten 2001; Grossman 2010). Furthermore, it is difficult to regulate levels of ACTH after administering hydrocortisone; ACTH levels can become very high because the hydrocortisone is released into the blood several hours after the morning dose (Ten 2001). Persistently high ACTH levels can lead to an increase in the size of the pituitary gland or even, in rare cases, to the development of a pituitary tumor (Himsworth 1978; Sugiyama 1996). Since the optimum glucocorticoid dose is difficult to determine, there is significant risk of overtreatment. Signs of overtreatment include dark pigmentation of the skin, weight gain, high blood pressure, high blood glucose, easy bruising, osteoporosis, and osteonecrosis (death of bone tissue) (Weinstein 2012; Ten 2001).

With regard to the replacement of aldosterone, ***fludrocortisone*** (also known as 9α-fluorohydrocortisone; a synthetic compound chemically similar to aldosterone with glucocorticoid and mineralocorticoid activity) can be orally administered. However, care needs to be taken to deliver an optimal dose because overtreatment can lead to hypertension (Ten 2001).

Cushing's syndrome

Surgery

Cushing's disease resulting from a pituitary tumor is treated by surgically removing the tumor (Biller 2008; Pozza 2012). However, only about 50% of people with large tumors benefit from surgery because the complete removal of the tumor is challenging. The tumors are also known to recur in up to 45% of people (Tritos 2012; Biller 2008; Pozza 2012). Moreover, repeat surgeries to the pituitary or adrenal gland are required in almost 25% of the people with a recurrence of Cushing's syndrome (Schteingart 2009; Tritos 2011).

In Cushing's syndrome where the cause is an ectopic tumor, removal of the tumor is required (Tritos 2012; Biller 2008). However, this is not always possible since: 1) identifying and locating the primary ACTH-secreting ectopic tumor may be difficult; 2) the tumor may have spread to different organs via the blood stream (metastasis); or 3) the tumor may be located at a site where surgery is difficult, eg, in the pancreas (Pozza 2012; Biller 2008; Tritos 2012).

Pharmaceutical treatment

Pharmacologic treatment of Cushing's syndrome includes the administration of drugs that prevent steroid production or that suppress the release of ACTH from pituitary or ectopic tumors (Tritos 2012). With the exception of mifepristone, which was approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of high blood sugar in people with Cushing's syndrome who are either not surgical candidates or who had failed surgery, none of the other medications are FDA approved for use in Cushing's syndrome as of the time of this writing (Tritos 2012). There are also limitations of these pharmacologic treatments. For instance, blocking steroid production has its own challenges—people on these medicines require frequent hospital visits and laboratory tests to ensure that the treatment does not result in adrenal insufficiency or adrenal crisis (Hahner 2010; Tritos 2012). If adrenal insufficiency is detected, glucocorticoids can be started; however, great care must be taken to ensure that this preventive measure does not worsen Cushing's syndrome (Tritos 2012).

The antifungal drug ***ketoconazole*** inhibits several steps in steroid synthesis within the adrenal cortex. It is also likely that ketoconazole directly inhibits ACTH secretion from the pituitary gland. It is one of the most widely used and effective medications for Cushing's syndrome (Tritos 2012). However, prolonged treatment with ketoconazole has been shown to cause adrenal crisis (Sarver 1997; Hahner 2010). Other side effects associated with ketoconazole are erectile dysfunction in men, low libido, and an increase in certain liver enzymes (Tritos 2012). This increase in liver enzymes occurs through injury to liver cells (García Rodriguez 1999). Moreover, ketoconazole is known to interact with and possibly interfere with actions of several other medications through the inhibition of the cytochrome P450 enzymes, which are critical for the metabolism of several drugs (Tritos 2012; Loose 1983).

Mitotane (*Lysodren*™) is used to treat people with tumors of the adrenal cortex. It prevents the production of steroids by interfering with enzymes involved in the conversion of cholesterol to various other steroid hormones. Though effective, mitotane has a late onset of action – it can take up to 2 weeks before showing beneficial effects. Mitotane has teratogenic effects (potential to cause birth defects) and can cause nervous system and gastrointestinal side effects (Tritos 2012).

7 Novel and Emerging Therapies

Given the side effects of currently available medications and the burden of repeated laboratory testing necessary to monitor hormone levels, scientists are trying to find novel treatment approaches for adrenal disorders that may be more effective and have an acceptable range of side effects (Pozza 2012).

Stem cells

It is believed that the adrenal cortex contains dormant adrenal stem cells, which are specialized cells that can multiply and differentiate to replenish all cell types that make up the adrenal gland (Kim 2009). Further in-depth studies are needed to provide insights into the biology of these stem cells and to characterize their role in adrenal diseases before they can be utilized as a treatment option (Simon 2012).

At the time of this writing, one in-depth study is underway in the United Kingdom. Since cells of the adrenal cortex are sensitive to ACTH levels in the blood, investigators are exploring the possibility of stimulating adrenal cortex stem cells with ACTH, to push them to differentiate into steroid-producing cells. The assessment of serum cortisol levels after an ACTH stimulation test will be the main criterion to check if functioning adrenal cortical cells have been generated or not (ClincalTrials.gov NCT01371526). If successful, this trial could open the doors to a new treatment option for conditions, such as autoimmune Addison's disease, in which the adrenal glands do not secrete adequate amount of hormones but have not lost their ability to respond to ACTH stimulation.

Pasireotide (Signifor®)

A new drug called ***pasireotide*** has shown promising results in reducing cortisol levels in Cushing's disease. This drug is similar in structure and function to the naturally-occurring hormone somatostatin, which has been suggested as a therapeutic target for pituitary-dependent Cushing's disease, following a study revealing that adrenal cortex tumor cells have sites to which somatostatins can bind to prevent the release of ACTH (van der Hoek 2004). Results of a clinical trial examining the use of pasireotide in Cushing's disease were published in the *New England Journal of Medicine* in March 2012. The drug was administered for 12 months to 162 people with Cushing's disease who were divided into 2 groups receiving either 600 or 900 mcg of the drug by subcutaneous injection twice daily. In both groups, the levels of free cortisol in the urine decreased by approximately 50% by the second month of treatment and remained stable. The levels of cortisol in the serum and saliva also decreased. In addition, the overall symptoms of Cushing's disease diminished (Colao 2012).

8 Dietary and Lifestyle Management Strategies

The following dietary and lifestyle considerations may support healthy adrenal function (Miller 2007).

- **Avoiding simple carbohydrates.** Cortisol increases the levels of glucose in the blood and low glucose levels signal the adrenals to produce more cortisol (Anderson 2008). Low levels of glucose can occur when meals are skipped or taken at irregular intervals, or by eating foods rich in simple carbohydrates, since simple carbohydrates are metabolized and absorbed faster by the body. This quick absorption triggers a quick spike in blood glucose levels, which subsequently declines quickly as insulin levels rise. This can trigger the stress response mechanism and increase cortisol levels (Anderson 2008; Taubes 2001). Hence, eating meals at regular intervals and consuming foods rich in fiber, which slows carbohydrate absorption, may prevent the increase in cortisol levels caused by quickly absorbed carbohydrates.
  Proper glucose control is paramount not only for mitigating sugar-induced spikes in stress hormone levels, but for controlling and preventing a myriad of age-related diseases. Life Extension recommends a comprehensive approach to glucose control and weight management that takes several important, but often overlooked factors into account. A comprehensive, strategically developed approach to glucose and weight management is outlined in the Life Extension protocol on **Obesity**.
- **Dieting properly.** Chronic stress is associated with increased cortisol levels, which promote overeating and increases in abdominal fat (Gade 2010). Studies indicate that the brain limits weight gain above a set point, which is ultimately regulated by the levels of *leptin*, a hormone that regulates energy intake and expenditure. When one exceeds their set point, high leptin levels tell the hypothalamus that energy storage (ie, weight) is adequate and appetite is suppressed (Gade 2010). However, when dieting, the blood levels of leptin are decreased, which notifies the brain as to the presence of the decreased energy storage. The brain then reacts by increasing appetite and decreasing metabolism. Consequently, "yo-yo dieting" (an endless cycle of losing and gaining weight due to poor control of calorie intake) can disrupt the hormonal feedback to the brain and improperly disrupt appetite and metabolism (Gade 2010). On the other hand, well-planned diets that supply the body with all its essential nutrients can be useful for controlling weight, reducing stress, and improving performance. A clinical study evaluating the effect of calorie restriction for 1 month in otherwise healthy overweight women aged 20-36 found that, along with an average weight loss of almost 13 lbs, there was a significant decrease in blood pressure, heart rate, and cortisol concentration, improved hand-eye coordination, and no evidence of increased physiological or psychological stress (Buffenstein 2000).
- **Limiting stimulants.** Consumption of stimulants, such as energy drinks, has been linked to the perception of stress (Pettit 2011). Caffeine is known to exacerbate the stress response and to increase cortisol production. Therefore, caffeine should be consumed in moderation or avoided by people exposed to chronic stress or with impaired adrenal function (Anderson 2008). Nicotine exposure in habitual smokers also increases serum cortisol levels (Gilbert 2000).
- **Exercising.** Exercise stimulates the production of cortisol and other glucocorticoids from the adrenals (Anderson 2008). As such, people who exercise regularly, such as athletes undergoing endurance training, are continuously exposed to high levels of glucocorticoids. However, studies have shown that regular exercise can modulate the HPA axis whereby people undergoing regular exercise are less sensitive to the effects of elevated glucocorticoid secretion (Anderson 2008; Duclos 2003). In fact, a clinical study showed that physical conditioning, as performed by moderately- and highly-trained runners, was linked to a reduction in

adrenal-pituitary activation (Luger 1987). Interestingly, another study evaluating the effect of exercise intensity on the HPA axis in moderately-trained men showed that low-intensity exercise resulted in a reduction of circulating cortisol levels (Hill 2008). These studies suggest that low- to moderate-intensity exercise could be beneficial in Cushing's syndrome.

- **Maintaining a positive outlook and good self esteem.** Low self esteem and loneliness are known to increase cortisol levels, while maintaining a positive outlook on life and a good social support system is associated with lower stress hormone levels (McEwen 2006).
- **Sleep.** Along with chronic stress, sleep deprivation is a common cause of high cortisol levels (Reini 2010). Disturbed sleep, overactivity of the HPA axis, and metabolic disturbances are often observed in people with Cushing's syndrome, insomnia, and depression (Balbo 2010). High glucocorticoid concentrations in Cushing's syndrome have a deleterious effect on sleep (Balbo 2010). Sleep deprivation can have a direct effect on the HPA axis and may be an important risk factor leading to stress-related disorders. Some studies have shown that lack of sleep in healthy people can lead to mild increases in cortisol levels, and that restful sleep can slightly decrease the cortisol levels (Meerlo 2008). Thus changing one's lifestyle to get adequate sleep at regular intervals may help prevent HPA axis disturbances and stress-related disorders.

9 Nutrients

Given the crucial role of the adrenal glands in maintaining normal body function and the extended (often life-long) treatment needed for adrenal disorders, there is a pressing need for alternative strategies that can help people cope with the debilitating effects of Cushing's syndrome, Addison's disease, and related conditions. Research has shown that several natural compounds have an impact on adrenal physiology (Anderson 2008). In this section, several nutritional interventions that may play a supportive role in the treatment of adrenal disorders will be reviewed. Additional discussion about natural compounds that may support adrenal health (eg, in "adrenal fatigue") is available in the **Stress Management** protocol.

Nutritional interventions in Cushing's syndrome

Melatonin

Melatonin is a hormone secreted by the pineal gland in the brain during the night. It plays a role in inducing sleep and regulating the circadian rhythm (Dominguez-Rodriguez 2012; Cajochen 2003). Cushing's syndrome has been associated with low melatonin levels and disruption of its circadian secretion (Soszynski 1989; Tomova 2008). A study assessing the effects of melatonin on adrenal hormone production in healthy men found that melatonin reduced cortisol secretion in response to an ACTH stimulation test, but did not affect the levels of other steroid hormones. This suggests that melatonin may have a direct action on the adrenal glands (Campino 2008).

Vitamin D & Calcium

Vitamin D supports calcium absorption and its deficiency can contribute to osteoporosis. In Cushing's syndrome, high cortisol levels lead to osteoporosis (Tritos 2012). Similarly, long-term glucocorticoid treatment can also result in osteoporosis. Vitamin D supplementation is considered to be an important step for preventing osteoporosis due to glucocorticoid treatment (Davidson 2012). A group of researchers analyzed studies conducted over 33 years and concluded that vitamin D and calcium supplements should be given to people receiving long-term corticosteroids (Amin 1999). A second analysis of studies conducted between 1970 and 2011 showed that adults who received glucocorticoid treatment had less than optimal levels of vitamin D, which were inadequate for the prevention of osteoporosis (Davidson 2012). Thus, vitamin D supplements may be useful in people with Cushing's syndrome who have high cortisol levels, as well as in Addison's disease where long-term hormone replacement is necessary.

Potassium

Potassium levels are known to be low in individuals with Cushing's syndrome, and low potassium levels are a significant determinant of cardiovascular complications in this population (PubMed Health 2011c; Takagi 2009). Hence, potassium supplements could be useful in people with Cushing's syndrome. However, people on ketoconazole treatment for Cushing's syndrome should avoid potassium supplements since ketoconazole treatment can also increase potassium levels (Sonino 1991).

Additional support for Cushing's disease

The following interventions may provide support for Cushing's disease, though more studies are needed to confirm their efficacy in humans.

- *Vitamin A*
  Laboratory and animal studies have shown that retinoic acid (a form of vitamin A) decreases ACTH synthesis and decreases proliferation (or multiplication) and survival of pituitary tumor cells (Pozza 2012; Paez-Pereda 2011). It also decreased proliferation and corticosterone production in adrenal cortex cells (Paez-Pereda 2001). In one study, animals with Cushing's disease were given either ketoconazole or retinoic acid. After 90 and 180 days of treatment there was a significant decrease in ACTH levels in the retinoic acid treated animals compared to no change in the ketocanozole group. The retinoic acid treated animals also showed improvements in clinical signs and survival time, and a significant reduction in pituitary tumor size (Castillo 2006).

- *Curcumin*
  Curcumin, one of the active constituents of *Curcuma longa* (a spice commonly used in South Asian cooking), has been widely studied for its therapeutic properties. ACTH-secreting pituitary tumors are one of the most common causes of Cushing's disease (Yaneva 2010). Using pituitary tumor cells from mice, a laboratory study showed that curcumin suppresses ACTH secretion, stops tumor cell growth and proliferation, and induces the death of tumor cells (Bangaru 2010).

Nutritional interventions in Addison's disease

Licorice

Licorice (*Glycyrrhiza glabra*) has been used for hundreds, if not thousands of years in both Eastern and Western cultures to treat myriad illnesses and to increase physical endurance (Davis 1991). Licorice may also protect against DNA damage induced by carcinogens (cancer-causing compounds) and induce the death of cancer cells (Wang 2001). It was used for the treatment of stomach and duodenal ulcers until the advent of modern anti-ulcer medicines. It was in the context of its use as an anti-ulcer compound that the mineralocorticoid-like actions of licorice were noticed. People taking licorice extracts for extended periods of time showed sodium and water retention and increased excretion of potassium (Davis 1991). This effect was also observed in animal experiments (Souness 1989). Further research showed that licorice appeared to be successful in reversing the effects of Addison's disease (Davis 1991). With advances in scientific research in the 1980s, it was found that a chemical compound, called glycyrrhetinic acid, present in licorice causes changes in adrenal steroid metabolism, resulting in increased levels of corticosterone in animals and cortisol in humans (Davis 1991).

Licorice is also known to regulate the HPA axis. Healthy male and female volunteers who consumed a licorice-containing confectionary showed increased levels of DHEA and testosterone in the saliva (Al-Dujaili 2011). Thus, licorice may also be useful for androgen deficiency in adrenal disorders. In one study, people with Addison's disease on cortisone replacement therapy who were given licorice were found to have increased cortisol tissue levels (Methlie 2011).

Dehydroepiandrosterone (DHEA)

Individuals with Addison's disease, in addition to cortisol insufficiency, have been reported in some studies to have low DHEA levels, which researchers speculate may contribute to decreased quality of life. A small clinical study of DHEA supplementation among Addison's patients revealed an immunomodulatory role for the hormone in this population, whereby supplementation appeared to improve regulation of inflammation and immune response (Coles 2005). In another clinical trial, men and women aged 25-69 with Addison's disease were given DHEA daily for 12 weeks. Their DHEA levels increased from below normal to a normal range for healthy young people (Hunt 2000). In a year-long study, 106 people with Addison's disease were given 50 mg of DHEA daily or no supplement. The group receiving DHEA showed increased levels of circulating DHEA-S and androstenedione, a reversal of bone density loss at the neck of the femur (thigh bone), and improved emotional health (Gurnell 2008). DHEA supplementation may also counter some consequences of adrenal insufficiency that arise secondarily to impaired pituitary gland function (Zang 2008).

There are several variables that can influence DHEA levels among individuals with adrenal dysfunction, whether due to Addison's or Cushing's, and DHEA supplementation may not be ideal for everyone with impaired adrenal function. Therefore, a diligent approach entails testing blood levels of DHEA-S, a major metabolite of DHEA, to determine if DHEA concentrations are outside the optimal range and initiating supplementation if an insufficiency or deficiency is observed. Life Extension suggests an optimal DHEA-S level of 350 – 490 µg/dL in men and 275 – 400 µg/dL in women.

Pantothenic acid (vitamin B5)

Pantothenic acid (vitamin B5) plays a role in the synthesis and maintenance of co-enzyme A (CoA), a crucial cofactor for many biological enzymatic reactions and a primary component of lipid and carbohydrate metabolism (Horvath 2009). Pantothenic acid is thought to be needed to maintain normal adrenal structure and function, as the administration of pantothenic acid to deficient animals improves adrenal function (Kelly 1999). Adrenal gland cells from rodents treated with pantothenic acid produced higher levels of corticosterone and progesterone than adrenal cells from rats that did not receive treatment (Jaroenporn 2008).

Prolonged stress from physical, mental, or environmental causes has deleterious effects on the body, including increased levels of cortisol, reduced immune function, and a disruption of the gastrointestinal microflora (beneficial bacteria) (Kelly 1999). Pantothenic acid administered to human subjects with various diseases better controlled the increase in cortisol metabolites in the urine following ACTH stimulation. This suggests pantothenic acid can modulate cortisol secretion in response to stress (Kelly 1999).

Coenzyme Q10 (CoQ10)

Coenzyme Q10, comes in the form of ubiquinone or ubiquinol, is essential for cellular energy production. It has antioxidant properties and protects cell membranes from damage. It is also commonly taken as an anti-aging supplement and to increase endurance in athletes (Mancini 2011; Lopez-Lluch 2010). When coenzyme Q10 is utilized as an antioxidant within the body, its availability for energy production may decrease (Mancini 2011). This is the rationale behind the dietary replenishment of coenzyme Q10 in many disease conditions. Preliminary data suggest that adrenal hormone secretion is related to coenzyme Q10 levels. Analysis of coenzyme Q10 levels in people with irregular pituitary-adrenal axis function showed that coenzyme Q10 levels are considerably lower in people with isolated decreases in adrenal function compared to people with adrenal hyperplasia or multiple pituitary deficiencies (Mancini 2005). The ubiquinol form of coenzyme Q10 has been shown to absorb better into the bloodstream than ubiquinone.

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