Adrenal Insufficiency

• A diagnosis of adrenal insufficiency should be suspected in the presence of a number of non-specific symptoms:
  • fatigue, anorexia, weight loss, hypotension, hyponatremia and hyperkalemia

Salivary Adrenal Testing

- Cortisol and DHEA are the primary hormones produced by the adrenal glands.
- Dehydroepiandrosterone sulfate (DHEAS) is the sulfated version of DHEA.
- DHEA levels naturally peak in the early morning hours, however, DHEAS levels show no diurnal variation.
Hormone Metabolism

Cholesterol
  ↓ cholesterol desmolase
  Pregnenolone → Progesterone → corticosterone → Aldosterone
  ↓ 17α hydroxy Pregnenolone.
    ↓ 17α hydroxy Progesterone → 11-deoxy cortisol → Cortisol
      ↓ 5α reductase
DHEA → Androstenedione ← Testosterone → Dihydro Testosterone
  ↓ aromatase
    Estrone ← 17-β Estradiol → Estriol
Cortisol

- Cortisol is the most potent glucocorticoid produced by the human adrenal gland.
- Cortisol is synthesized from cholesterol.
- Its production is stimulated by pituitary adrenocorticotropic hormone (ACTH), which is regulated by corticotropin releasing factor (CRF).
- ACTH and CRF secretions are inhibited by high cortisol levels in a negative feedback loop.
- In plasma a majority of cortisol is bound with high affinity to corticosteroid binding globulin (CBG or transcotin).
Diurnal Cortisol Rhythm

- Cortisol production has an ACTH-dependent circadian rhythm with peak levels in the early morning and a nadir at night.
- The factor controlling this rhythm is not completely defined and can be disrupted by a number of physical and psychological conditions.
- ACTH and cortisol are secreted independent of circadian rhythm in response to physical and psychological stress.
Cortisol Effects

• Promotes the conservation of glucose, and inhibits glucose utilization
• Promotes hepatic protein synthesis and gluconeogenesis
• Stimulates the release of fatty acids from adipose tissue via lipase
• Anti-inflammatory - down-regulates phospholipase A2
• Immunosuppressive
Cortisol Levels

• Elevated cortisol levels and a lack of diurnal variation have been identified with Cushing's disease (ACTH hypersecretion) and adrenal tumors.

• Low cortisol levels are found in primary adrenal insufficiency (e.g. adrenal hypoplasia, Addison's disease) and ACTH deficiency.

• Due to the normal circadian variation in cortisol levels, distinguishing normal from abnormally low cortisol levels can be difficult; therefore, several daily collections are recommended.
High Cortisol

- Stress stimulates ACTH secretion, which is referred to as the “Fight or Flight” response.
- High levels of cortisol at night interfere with REM sleep.
- High cortisol is correlated with high protein diets, and an inverse relationship with high carbohydrate diets.
- Associated with calcium malabsorption and low bone mineral density.
- Prolonged stress may result in decreased AM and increased PM levels (a “cortisol flip”).
Low Cortisol

- Addison’s disease is a cortisol deficiency
- Low cortisol levels in the morning cause fatigue, and are associated with chronic fatigue syndrome
- Cortisol deficiency results in anorexia, weight loss, weakness, apathy, hypotension and an inability to withstand stress
- Cortisol deficiency associated with chronic illness, autoimmune and rheumatic disease
Cortisol Deficiency

- Vascular smooth muscle becomes unresponsive to NE and EPI (epinephrine used to be called adrenaline), eventually causing vascular collapse
- There is increased sensitivity to smells and taste
- Personality changes include irritability, apprehension, and an inability to concentrate
- An inability to excrete a water may cause water intoxication
Cushing’s Disease

- Cushing’s disease is caused by high cortisol levels in the blood
- Symptoms include: muscle weakness, obesity, weight gain, poor wound healing, easy bruising, renal calculi, Hirsutism, loss of libido and acne (androgens), psychiatric disturbances
Cushing’s Disease

Signs include: ecchymoses (skin atrophy with purple striae), moon faces, buffalo hump, trunkal obesity with skinny extremities, osteoporosis, peptic ulcer, diabetes (glucose intolerance), hypertension, and edema

Epidemiology

- Female: male = 5:1, occurs during childbearing years
- Ectopic ACTH is more common in men, and usually occurs later in life.
Addison’s Disease

- Addison’s disease is primary adrenal insufficiency
- Signs include: fatigue, weakness, weight loss, dizziness, syncope, lightheadedness, fainting, mental changes (nervous irritability, depression, apprehension), increased skin pigmentation, headache, palpitation, craves sweets, alcohol intolerance, alternating diarrhea/constipation, premenstrual tension, scanty perspiration
- Symptoms include: postural hypotension, hypotension, dry and thin skin, sparse hair
- Associations: allergies, hay fever, skin dermatitis
Glucocorticoids

• Cause connective tissue dissolution
• Have an anti-vitamin D effect
• Cause proteolysis of muscle
• Inhibit lymphocytes and monocytes
• Increase acid and pepsin secretion
• Increase gluconeogenesis
DHEA

• DHEA (dehydroepiandrosterone) is synthesized primarily in the adrenal glands from the steroid precursor pregnenolone, which is synthesized from cholesterol.

• DHEA is the main precursor for estradiol and testosterone.

DHEAS

• DHEA is the most abundant circulating steroid in humans

• In the blood, most DHEA is sulfated (DHEA-S04) providing a storage depot for DHEA, thereby prolonging its half life and providing a steady state source of DHEA for conversion to estrogens and androgens in the adrenal glands, ovaries, and testes.
Functions of DHEA

DHEA has been associated with:

• The ability to stay thin and to make muscle
• Avoiding breast cancer (for women)
• Avoiding cardiovascular disease (for men)
• Improving memory and stress resistance
• Improving one's sense of "well-being"
Decreased DHEA

• Circulating levels are closely associated with aging, dropping nearly 5-fold from a peak at age 20-25 to a low at age 70-80.
• 17,20 desmolase, essential for synthesis of DHEA, is functionally reduced with aging.
• The zona reticularis of the adrenal gland, where DHEA is made, atrophies with age.
Diseases with Low DHEA

Various diseases have been associated with low circulating DHEA levels:

- Heart disease, cancer, diabetes, obesity, chronic fatigue syndrome, AIDS, Alzheimer’s disease, systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis
DHEA and Insulin/Cortisol

• Insulin both inhibits the synthesis of DHEA and accelerates the breakdown of DHEA.
• High levels of DHEA are anabolic, have an anti-glucocorticoid activity, and balance cortisol
DHEAS/Cortisol Ratio

- Cortisol is a mediator of stress-related negative effects on health
- The DHEAS/C ratio has been hypothesized as an index for the degree to which an individual is buffered against the negative effects of stress

Cortisol:DHEAS Ratio

- The cortisol:DHEAS ratio is positively associated with metabolic syndrome.

Increasing DHEA

• It has been suggested that measures which increase circulating DHEA levels such as exercise, proper diet, stress reduction, and/or supplementation can ameliorate some of the diseases associated with low DHEA levels, especially the generalized debilitation associated with aging.
DHEA Supplementation

- A single 50-mg dose of DHEA administered orally at 0700 hours restores the circadian rhythmicity of serum DHEA and almost completely normalizes the 24-hour profile of the cortisol/DHEA molar ratio in old subjects without affecting the cortisol circadian rhythm.

DHEA Cautions

• Use caution in patients at risk for developing hormone-dependent cancers: prostate cancer in men and reproductive cancers in women.

• Doses above 1500 mg/day have been known to result in insulin resistance in humans.
Salivary Adrenal Stress Tests

• Salivary tests of Cortisol and DHEA are commonly referred to as Adrenal Stress Tests
• Cortisol is usually measured 4 times during a 24-hour period
• DHEA or DHEA-S is usually measured once.
Chronic Fatigue Syndrome

• CFS is characterized by persistent or relapsing debilitating fatigue for at least 6 months in the absence of any other definable diagnosis.

• Symptoms of CFS may include depression, hypotension, weight loss, and inability to endure stress.

Researchers have proposed that CFS is actually a disease of the hypothalamic-pituitary-adrenal axis. CFS may be associated with excess cortisol secretion, or decreased cortisol in late stages when the adrenal glands become exhausted.

Insomnia

• Normal sleep rhythms are associated with increased melatonin and decreased cortisol and DHEA

• Rapid eye movement (REM) sleep occurs primarily when cortisol levels are decreasing

Menstrual Disorders

• A progesterone and estradiol deficiency can result from the accelerated conversion into cortisol.

• Excess cortisol signals the body to lower production (inhibition feedback), which may cause over-production of testosterone, progesterone and/or estrogen.


Alzheimer’s Disease

- DHEA levels were significantly lower in patients with early or late Alzheimer disease compared to normal controls.
- DHEA may protect against oxidative stress in the hippocampal region of the brain, a critical area for memory function often damaged by Alzheimer disease.

Nutritional Support

• In this section, we will review the nutritional support for the adrenal glands
Vitamin B5

• Vitamin B5 (Pantothenic Acid) is required for the formation of some steroids via the action of CoA

• Vitamin B5 is useful for adrenal insufficiency and stress

Vitamin C

- The adrenal gland is among the organs with the highest concentration of vitamin C in the body.
- The adrenal glands secrete vitamin C in response to stress.

Licorice

- Licorice supports the adrenal glands and was used for Addison’s disease.
- Liquorice is an adaptogen which helps regulate the hypothalamic-pituitary-adrenal axis.
- Licorice contains isoflavones (phytoestrogens).
Licorice and BP

• Large doses of glycyrrhizinic acid and glycyrrhetinic acid in liquorice extract can lead to hypokalemia and serious increases in blood pressure (apparent mineralocorticoid excess).

• As such, licorice is contraindicated in hypertension and pregnancy.
Ashwagandha

- Ashwagandha (Withania somnifera) is a tonic and adaptogen
- Alkaloids are sedative, reduce blood pressure and lower heart rate
- Withanolides are anti-inflammatory and inhibit growth of cancer cells
- Withanolides increase hemoglobin levels

Ginseng

- Siberian ginseng (Eluthrococcus senticosus) and Panax ginseng (ren shen) are adaptogens

- The adaptogenic properties of ginseng are believed to be due to its effects on hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotropicin and corticosteroids levels.

Blood Type O

• According to Dr. D’Adamo in “Eat Right for Your Blood Type”, people with blood type O use B vitamins for energy.

• Beef and liver, which they naturally crave, contain high amounts of niacin (vitamin B3).

• A high quality B complex with plenty of B5 may be beneficial.
Catecholamines

• The chromaffin cells of the adrenal medulla are the body's main source of catecholamine hormones adrenaline (epinephrine) and noradrenaline (norepinephrine).

• Catecholamines are part of the fight-or-flight response initiated by the sympathetic nervous system.
Biochemistry

Diagram showing the metabolic pathway from DL-Phenylalanine to inactive metabolites through Tyrosine, L-Dopa, Dopamine, and other intermediates. Key enzymes and co-factors involved in the pathway are labeled, including Phenylalanine hydroxylase, Tyrosine hydroxylase, P5P (B6), Dopamine β-hydroxylase, MAO, COMT, and vitamin C.
Tyrosine

• Notice the conversion of catecholamines  
  – Phenylalanine, Tyrosine, Dopamine  
  – Norepinephrine and Epinephrine (adrenaline)

• Those with phenylketonuria (PKU) don’t convert phenylalanine into tyrosine

Summary

- In this section we briefly reviewed diseases associated with imbalances in adrenal function
  - Addison’s and Cushing’s Disease
  - Chronic Fatigue Syndrome
  - Insomnia
  - Menstrual disorders
  - Alzheimer disease
Stress

• The adrenal gland presents a common link with several mechanisms of stress, including:
  – DHEA and Cortisol
  – Catecholamines (adrenalin/epinephrine)
  – Aldosterone (sodium and BP regulation)
  – Steroids (estrogen and testosterone)
Adrenal Support

• Nutritional support includes:
  – Vitamins B5 and C
  – Licorice (caution: may raise blood pressure)
  – Ashwagandha
  – Ginseng