Cortisone and Cortisol

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Cortisone is an inactive metabolite of cortisol. It is inter-converted to cortisol by 11-beta-hydroxysteroid dehydrogenase and is therefore considered cortisol “storage.” Cortisol is a major glucocorticoid that also has some mineralcorticoid activity. It is considered the body’s key stress hormone. 24 hour urinary free cortisol excretion rate in normal subjects ranges between 20 and 80 ug/d.

The 11-beta-hydroxysteroid dehydrogenase enzyme has bidirectional activity depending on the tissue. 11beta-HSD isoform type 2 uni-directionally inactivates cortisol, while type 1 isoform acts bi-directionally. This enzyme has a reductase activity in the liver, and a dehydrogenase activity in the kidney, which is why there are two isoenzymes for this enzyme.

Figure 1: Progesterone.jpg

_Tetrahydrocortisone, Tetrahydrocortisol and Allo-Tetrahydrocortisol_

Tetrahydrocortisone, Tetrahydrocortisol and Allo-Tetrahydrocortisol are terminal cortisol metabolites that reflect approximately 50% of daily cortisone synthesis. These will often reflect a chronic adrenal picture if levels are out of normal limits. The sum of these values should fall between 5000-7000 ug/24hr for normal daily output of cortisol. 5-alpha-reductase is the enzyme which converts cortisol to allo-tetrahydrocortisol.

_Tetrahydrocorticosterone and Allo-tetrahydrocorticosterone_

These are the terminal markers of corticosterone and sensitive markers of adrenal stress. "Acute" adrenal stress would produce elevated values. Adrenal fatigue would produce decreased values.

_Causes of Cortisol and Cortisone Imbalance in Men and Women_

- Increased Levels
  - Cushing's syndrome / disease
  - Ectopic ACTH production
  - unipolar depression
  - sleep deprivation
  - generalized anxiety order
  - post traumatic stress disorder
  - panic disorder, early stage
• exogenous cortisol
• licorice root supplementation
• Intensive physical exercise
• Acute ingestion of alcohol (cortisol only)

Decreased Levels
• Adrenal insufficiency - follow up with ACTH stimulation test or multi-point serum or saliva cortisol.
• Chronic fatigue syndrome
• fibromyalgia,
• rheumatoid arthritis

With urinary analysis, hypo-adrenal patients seem to show up with low terminal cortisol metabolites, and then if untreated, cortisol and cortisone also become suboptimal. Terminal metabolites are a measure of daily cortisol production, including what is metabolized. The sum of tetrahydrocortisol, allo-tetrahydrocortisol, and tetrahydrocortisone equals about 1/2 of the total daily production of cortisol. If they add up to 5000 micrograms (5 mg), then the body is making about 10 mg/day. The urinary cortisol values reflect the amount of circulating cortisol.

**Congenital Adrenal Hyperplasia**

Conversion of 17-OH Progesterone to 11-deoxycortisol is performed by the 21-hydroxylase enzyme. 11-deoxycortisol is then metabolized to cortisol. A deficiency in this enzyme is the most common form of congenital adrenal hyperplasia. An elevation in 17-alpha-hydroxyprogesterone is characteristic. Elevations in progesterone, 17-alpha-hydroxypregnenolone, pregnenolone, DHEA and DHEA-S, and plasma androstenedione and testosterone will also be noted when 21-hydroxylase is deficient. (Nimkarn, Lin-Su et al. 2009)

Non-classical congenital adrenal hyperplasia, also known as late-onset 21 OHD, have only mild to moderate enzyme deficiency and present postnatally with signs of hyper-androgenism.

Women may present with symptoms of androgen excess, including hirsutism, temporal baldness, and infertility. Menarche in females may be normal or delayed, and secondary amenorrhea is a frequent occurrence. Further virilization may include hirsutism, male habitus, deepening of the voice, or male-pattern alopecia (temporal recession). Polycystic ovarian syndrome may also be seen as a secondary complication in these patients.

Symptoms in adult males with NC-CAH may include short stature, acne, or oligozoospermia and diminished fertility. Severe cystic acne has been attributed to NC-CAH.

**Apparent Mineralocorticoid Excess (AME)**

AME is a result of the impairment of 11-beta-hydroxysteroid dehydrogenase enzyme activity. This enzyme inactivates cortisol in the kidney by converting it to cortisone. As a result, cortisol accumulates in the kidney, and cortisone concentrations decrease. Cortisol may reach as much as ten times the concentration of cortisone in the urine. The excess cortisol binds to
mineralocorticoid receptors in the distal tubule, which is normally the site of aldosterone binding. (Palermo, Quinkler et al. 2004)

Clinical symptoms of AME include hypertension, low plasma rennin-aldosterone levels, hypokalemia, normal plasma cortisol levels, and low plasma aldosterone levels.

Treatment may involve using a high-potency glucocorticoid to suppress endogenous production of cortisol. This may also bind to the mineralocorticoid receptor. Concentrations given are less than that of endogenous cortisol. Spironolactone may also be used, however, the anti-androgenic and progestational side effects limit long term use.

**Natural Therapies**

Natural ways to reduce cortisol include Phosphatidylserine, Ginkgo Biloba, Magnolia, Rhodiola.

- Phosphatidylserine (Monteleone, Beinat et al. 1990) (Monteleone, Maj et al. 1992)
- Ginkgo Biloba (Jezova, Duncko et al. 2002)
- Magnolia (Garrison and Chambliss 2006)
- Rhodiola (Panossian, Wikman et al. 2010) (Olsson, von Scheele et al. 2009)
- Vitamin C (Peters, Anderson et al. 2001) (Peters, Anderson et al. 2001) (Kodama, Kodama et al. 1994) (Liakakos, Doulas et al. 1975)
References


