

The Testosterone:Cortisol Connection

Written by Dan Gwartney, MD

Testosterone

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In the humorous parody periodical, Mad Magazine, a recurring feature is “SPY vs. SPY.” Two spies, identical except for their coloring (one is black and the other is white), attempt to thwart each other by devising all sorts of creative and hilarious booby traps. Of course, readers over the decades have never seen these two actually accomplish any worthwhile spying as the efforts serve merely to cancel each other out. Despite the extreme measures taken, neither spy gains an advantage in the man-to-man battle.

The Battle Within

A similar battle rages every day within the human body. Two nearly identical molecules are pitted against each other in a seemingly futile war to shift the balance of power from one side to the other. In fact, a stalemate is maintained unless something occurs in the environment to create an advantage for either side. The two molecules are testosterone and cortisol. Testosterone, an intimately familiar hormone to all bodybuilders, is considered an anabolic steroid due to its positive effects on muscle and sex-related glands. Cortisol is often referred to as a catabolic steroid as it has the reverse effect when present in excess; high cortisol levels lead to a breakdown of muscle, loss of lean mass and strength. Though they appear to be complete opposites, the two molecules are very similar in physical structure and are linked in a reciprocal fashion; meaning when one is up (elevated), the other is often down. It's the hormonal equivalent of Superman and Bizarro, an arch-nemesis to the cartoon superhero who was the exact opposite, despite having nearly identical super powers. The relationship between testosterone and cortisol is important to clinicians and critical to athletes. Exercise, when performed at a suitable intensity and volume, can increase the anabolic stimulus, resulting in stronger and larger muscles.¹ However, as many have discovered the hard way, exercising to excess can result in a weakened, catabolic state known as the overtraining syndrome.²⁻⁴ Numerous examples exist in the scientific literature, confirming that moderate-volume, high-intensity training can increase testosterone, growth hormone, IGF-1 and other anabolic signals, resulting in improved exercise performance.^{4,5} Other studies show how high-volume, high-intensity exercise leads to increased inflammatory and catabolic hormones levels.⁶ Persisting in the overtrained state often leads to impaired long-term performance, muscle loss and decreased mental function.⁷

The Anabolic-to-Catabolic Balance

Fortunately, the body appears to be able to recover from excess exercise with rest. One study examining rugby players over the course of a tournament found that though testosterone lowered and cortisol rose by the end of the tournament, a compensatory anabolic state occurred during the following days of rest, returning to normal after five days. The researchers concluded that intense competition should be followed by a minimum of one week's rest to avoid overtaxing the body's ability to recover from extreme exertion.⁸ In a hospital setting, it's been documented that stressed individuals have a greater reaction to ACTH (the pituitary hormone responsible for stimulating cortisol secretion) than normal persons.⁹ Prolonged illness or chronic poor health results in high levels of catabolic hormones and low levels of anabolic

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hormones, including a low testosterone-to-cortisol ratio, with an accompanying loss of muscle.¹⁰ Even more data has been collected relating to this issue in the field of aging. As people grow older, testosterone levels fall and cortisol levels rise, creating a hormonal environment that doesn't support the muscle mass attained during young adult years.¹¹ Clearly, paying attention to the anabolic-to-catabolic balance is vital over the long term. The most often cited measure of this balance is the testosterone-to-cortisol ratio. Bodybuilders are quite adept at increasing testosterone levels. This is easily achieved through the use of exogenous anabolic steroids, resulting in impressive gains in muscle mass and strength. However, during intense training, especially under the hypocaloric conditions encountered as bodybuilders are cutting up for a competition, stress levels rise and catabolic conditions set in. Pounds of hard-earned muscle can disappear in a matter of days, leaving one with a depleted appearance. To avoid this, some bodybuilders try to control cortisol levels pharmaceutically.

Testosterone's Effect on Cortisol

Before getting into more specific drugs that lower cortisol and its catabolic effects, it's important to realize that the drug-enhanced athlete often doesn't need to be overly concerned about cortisol, as long as he's not overtraining with high volume exercise. Exercise, fitness, and many of the drugs used to build mass also have a fortunate consequence of lowering cortisol levels. Exercise builds muscle and improves the condition of the body. One component of the effects of exercise is an improvement in insulin sensitivity; a measure of how well the body handles sugar. Though the relationship between the two is unclear, it's been shown that for males, a decrease in testosterone is experienced with a coinciding rise in cortisol. This pattern of low testosterone and high cortisol is associated with insulin resistance.¹² It's unclear whether the insulin resistance causes the shift to a catabolic balance or if a catabolic hormonal environment inhibits insulin's actions. Regardless, the beneficial effects of exercise on insulin sensitivity appear to favor an anabolic balance. Obesity is often related to a low testosterone:cortisol ratio. The hypothalamic-pituitary-adrenal axis is overactive in obese men and elevated cortisol levels are seen in people with central obesity (predominantly abdominal fat).¹³ It's known that central obesity is predictive of other metabolic diseases and an altered testosterone:cortisol ratio is prevalent in people with type 2 diabetes, hypertension and cardiovascular disease.¹⁴ Testosterone, and likely other androgens, has a suppressive effect on the adrenal glands— the source of cortisol. Cortisol is produced and secreted under the influence of the hypothalamic-pituitary-adrenal gland axis. The hypothalamus (a region in the brain) sends a chemical messenger called CRH to the pituitary (a gland located near the base of the brain) to release another hormone called ACTH. ACTH travels through the bloodstream to the adrenal glands, stimulating the production and secretion of cortisol. Testosterone inhibits the adrenal glands' response to ACTH, resulting in lower cortisol output.¹⁵ Interestingly, human chorionic gonadotropin (hCG) stimulates the release of both testosterone and cortisol, though the impact on testosterone persists for a longer period.¹⁶

Drugs Affecting Cortisol Levels

Another anabolic hormone frequently used is growth hormone (GH). GH is well known for its fat reducing properties, in addition to increasing lean mass. GH promotes tissue growth primarily through the actions of IGF-1, but its fat burning properties appear to be more direct. One function of GH that may explain this is its effect on an enzyme called 11 β -hydroxysteroid dehydrogenase (11 β -HSD). This enzyme has two forms, type 1 and 2, which are involved in

The Testosterone:Cortisol Connection

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cortisol metabolism. Type 1 11β -HSD reactivates cortisol from its inactive form—cortisone. GH inactivates type 1 11β -HSD, preventing cortisol from being reactivated from the inactive form, cortisone. This effect occurs at very low dosages (0.17 milligrams per day) and isn't dependent on changes in fat mass, IGF-1 or insulin sensitivity.^{17,18} It appears that two of the most potent anabolics, testosterone and GH, derive some of their ability to shift metabolism to an anabolic balance from their abilities to lower the catabolic signal of cortisol. One class of drugs used by bodybuilders to cut up is associated with muscle wasting if used to excess, these being thyroid hormone drugs. Thyroid hormone appears to activate the hypothalamic-pituitary-adrenal axis, resulting in greater cortisol output.¹⁹ Elevated cortisol levels can certainly result in muscle wasting and a loss of strength, symptoms of thyroid hormone excess. Aside from drugs with incidental effects on cortisol levels, there are drugs with more specific actions against cortisol. The most well known and commonly used of this group is aminoglutethimide (Cytadren®).²⁰ Aminoglutethimide is a drug affecting the production of many steroids by blocking the actions of several enzymes involved in steroid synthesis.^{21,22} Bodybuilders typically only take aminoglutethimide for short periods, during the most catabolic period of pre-competition training as it may cause a number of side effects, including anorexia, nausea, vomiting, weakness and electrolyte imbalances.²³ Aminoglutethimide is taken during this catabolic phase due to its presumed ability to lower cortisol, resulting in less muscle loss and lower fluid retention. However, much of the physique-enhancing effect of the drug may be due to another property of the drug used clinically, that being aromatase inhibition.²⁴ Aromatase is an enzyme complex that converts androgens into estrogens, promoting fat and water retention. By lowering aromatase, and thus estrogens, many bodybuilders walk on stage harder and leaner, attributing the look to lower cortisol. In fact, aminoglutethimide is more efficient at lowering aromatase activity and estrogen levels than affecting cortisol. It appears that the body is able to compensate for partial suppression by low doses of aminoglutethimide by increasing ACTH stimulation of cortisol secretion.²¹ The aromatase inhibition occurs at lower doses, possibly as low as 125 milligrams per day, whereas a minimum of 750 milligrams per day is required to lower cortisol levels.²⁵ This combination of aromatase inhibition and cortisol suppression is seen with other drugs, but these drugs have lost favor as more potent and specific aromatase inhibitors have been developed which don't affect cortisol levels.²⁶

Cortisol Suppression

In the clinical world, there are several other options for suppressing high cortisol levels, such as is seen in the disease Cushing's syndrome. All of these drugs act by blocking enzymes involved in the production of steroid hormones, with some being more potent and selective, whereas others are weak or non-specific: trilostane is a weak option; aminoglutethimide is effective, but requires high dosages with frequent side effects; metyrapone inhibits 11β -HSD recycling, but carries many side effects; ketoconazole is a potent inhibitor, but suppresses androgen production, more so than cortisol, and causes liver toxicity; etomidate is the most potent agent, but requires intravenous injections.^{27,28} Some other interesting drugs that may affect cortisol's effects exist, but there's no experience base from which to judge their actions. RU-486, known as the morning after pill because it's used to prevent pregnancies after unprotected sex, decreases cortisol receptor activity.²⁹ Cortisol is metabolized in the body by a variety of enzymes, but two are of interest. 11β -HSD, which recycles cortisol from its inactive metabolite cortisone, is easily suppressed by a component found in licorice root extract.³⁰ Oral use of licorice root may result in a loss of potassium and high blood pressure if overconsumed,

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but one study has shown that topical use of licorice extract may stimulate loss of subcutaneous fat.³¹ Another metabolic path of cortisol is 5 α - and 5 β -reduction. 5 α -reduction is the process responsible for converting testosterone to the more potent androgen DHT. Though 5 α -reduction is associated with lower cortisol levels, it's unclear whether the 5 α -reduced metabolite is more potent, such as in the case with the androgenic effects of testosterone. It's been shown that high levels of the 5 α - and 5 β -reduced metabolites are associated with obesity and insulin resistance.^{32,33} Clearly, there are many physical consequences when cortisol levels are high, especially in the setting of low testosterone. Secondly, there also appears to be negative mental effects to having high cortisol levels. Severe depression is associated with high cortisol levels.³⁴ Several reports describe beneficial responses to cortisol suppression therapy in depressed individuals.^{35,36} Many of these individuals appear to be more sensitive to the hypothalamic hormone, resulting in higher ACTH levels.³⁷ Treating high cortisol levels improves signs of depression in approximately 70 percent of Cushing's syndrome patients and depressed patients.³⁸ Even for those not affected by depression, high cortisol levels interfere with information processing, making it more difficult to think or make decisions.³⁹ This cortisol–depression connection may explain the high incidence of depression that occurs after the completion of a cycle, if testosterone levels fall too rapidly.

The Battle All Bodybuilders Face

The anabolic:catabolic balance is the battle all bodybuilders face in their pursuit of developing lean, muscular physiques. It's important to consider the testosterone:cortisol ratio, as an imbalance quickly shifts the metabolism to favor one side and over the long term can dictate the amount and quality of muscle mass one attains. Cortisol is controlled somewhat by androgens and growth hormone, but there are also several drugs that lower the hormone. These drugs are not specific and can carry significant side effects if used for long periods. Much of the effect of the more commonly used aminoglutethimide may be ascribed to aromatase inhibition rather than cortisol suppression. For the drug-using bodybuilder, the anabolic effect of androgens and growth hormone, along with the aromatase suppression of more specific drugs such as Arimidex® or Femara® should provide the same protection with a much lower risk of side effects. It should be noted that a shift in balance favoring cortisol can be expected once a cycle ends, which may induce depression in some individuals. There's certainly a need to control cortisol levels, but rather than resorting to dangerous, non-specific drugs, monitoring training volume and avoiding prolonged stress is a safer alternative.

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The Testosterone:Cortisol Connection

Written by By Dan Gwartney, MD

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