

Testosterone: Support, don't Suppress

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There is a scene in the movie Grease in which the school secretary is promoting attendance at the pep rally over the public address speakers, ending her enthusiastic speech with the comment, "If you can't be an athlete, be an athletic supporter." That really has nothing to do with the topic but for the reason it makes men giggle. An athletic supporter, after all, is a jock strap. It supposedly supports the testicles like a secondary, fabric scrotum; if a cup is also used, it protects future fertility and reduces the risk of genital injury (ouch!).

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The concept of supporting the testicles and protecting future fertility can also be applied to pharmaceutical approaches used to restore or enhance testosterone levels. A little support is needed as American men have been experiencing a drop in testosterone for generations.¹ Further, the function of "the boys" is threatened by our environment: industrial and dietary estrogens, fast food restaurants making us fat, the cozy heat of climate control keeping our homes warmer, remote controls and automobiles reducing our activity, smoking bans and surgeon generals cutting down on smoking, and the clingy compression of tighty-whities.²

Of course, testosterone levels can be increased. The most common and reliable method used, particularly by athletes, is anabolic steroid therapy. Technically, only those steroids composed of testosterone esters actually increase testosterone levels, as other anabolic steroids contain testosterone-like drugs that are modified to increase potency or reduce side effects. One issue that is shared by all anabolic steroids is the subsequent suppression of natural testosterone production as androgen levels are maintained in the supraphysiologic (above normal) range.^{3,4} This suppression occurs because the body has a feedback mechanism that adjusts testosterone production to keep androgen levels in a defined range. When testosterone levels get low, regulatory glands in the brain — the hypothalamus and pituitary, send out hormonal signals that prompt the testicles to produce more testosterone. Conversely, when testosterone levels get too high, signals from the hypothalamus and pituitary drop way down and the testicles lower testosterone production. If testosterone (or other androgens) levels are elevated well above normal range and kept there for a long period of time, such as would occur during an anabolic steroid cycle, natural testosterone production is interrupted and the testicles go into a kind of hibernation.

This is the same concept behind birth control pills used by women, as high levels of estrogen and progesterone prevent the ovaries from being stimulated to release an egg, blunting natural estrogen and progesterone production at the same time. Understanding that elevated steroid hormone levels (testosterone or estrogen and progesterone) suppress both the endocrine (steroid hormone) and reproductive (sperm or egg production) functions at the same time clarifies why anabolic steroid use can cause sterility in many men until testicular function recovers off-cycle.

Unfortunately, to gain an anabolic advantage from anabolic steroids, it is necessary to dose the drugs into a range that is often suppressive to the testicles. In fact, for muscle growth, research has shown that in the range studied, there is a definite dose-response relationship – a term that suggests more is better.⁵⁻⁷ However, as most steroid users learn, more is not always better. As the anabolic steroid dose(s) go up, so too does the risk of adverse side effects, such as: gynecomastia, emotional instability, hair loss, acne, impotence and other issues.^{8,9} Most mature anabolic steroid users with experience in using the drugs tend to use very moderate doses, ranging from 400 to 800 mg weekly (testosterone equivalent).¹⁰ Certainly, this differs from the markedly higher doses used by competitive bodybuilders who are driven to maximize muscle growth; the majority of steroid users do not compete in bodybuilding or other sports according to data from a number of surveys.^{10,11} Interestingly, the choice of steroid also becomes less exotic as users mature; testosterone esters or nandrolone esters predominate, possibly due to the availability of these drugs through legitimate sources or the uncertainty that accompanies the use of the less familiar, more exotic steroids that can only be sourced through black market suppliers.

Anabolic responses can be generated through the use of very moderate doses. Research performed by Dr. Shalendar Bhasin and group demonstrated anabolic responses in young and older men using as little as 125 mg/week testosterone enanthate; greater results were noted with the groups taking 300 or 600 mg/week.⁵⁻⁷ A dose of 125 mg/week testosterone enanthate is slightly greater than the typical replacement dose (75 – 100 mg/week) and does not result in a supraphysiologic increase in blood testosterone level.¹² At these levels (125 – 600 mg/week), improvements in muscle mass and strength were noted with no significant side effects in subjects that were followed for six months. Interestingly, the lowest effective dose – 125 mg/week testosterone enanthate, provided significant benefits raising serum (blood) testosterone levels by approximately 16 nmol; the 300 and 600 mg/week dose groups’ testosterone levels were increased by 50 and 100 nmol, respectively.⁷ Nmole is the abbreviation for a measurement of how much of a chemical is in a solution (nanomolar). It is similar to the more familiar terms of concentration, such as grams per liter or milligrams per milliliter.

In association with the anabolic benefits, even at these moderate doses, subjects often experience testicular atrophy and a reduction in sperm production, if not complete sterility.⁴ In part, this is due to the negative feedback mentioned earlier, but it is also due to low testosterone levels in the testicles themselves. The testicles normally maintain a very high internal testosterone concentration to promote sperm maturity, approximately 100 times that of the serum.¹³ During an anabolic steroid cycle, testicular testosterone levels fall, as the hormone is no longer being produced locally and matches the concentrations present in the blood. Even though a cycle may provide 4 to 20 times the level of circulating (blood) testosterone, the testicles would be in a relative internal testosterone deficit. So, sperm production is hampered by both a lack of pituitary hormones from the brain due to negative feedback, and low testosterone concentration within the testicular tissue.

There are options for increasing serum testosterone levels in a manner that will not cause testicular atrophy and should maintain sperm production. These options are utilized by some anti-aging centers and are banned by the World Anti-Doping Agency (WADA), the agency that governs sports doping for the Olympics and other groups.^{14,15}

These options include using agents known to increase testosterone output either by increasing the stimulatory signal to

the testicles or reducing the negative feedback at the hypothalamus and pituitary glands. The origins of these drugs stem primarily from fertility medicine, chemotherapy for certain female cancers or prostate enlargement.

There are three basic groups of drugs that increase testosterone production: gonadotropins, anti-estrogens and 5- α reductase inhibitors. While there is a limit to the overall increase in testosterone, the effect is significant enough to promote muscular development and provide an athletic advantage.¹⁵

Gonadotropins are drugs that mimic the signal produced by the pituitary gland to stimulate the testicles to produce testosterone. This class is represented by human chorionic gonadotropin (hCG). hCG is familiar to many bodybuilders as it is commonly used to accelerate testicular function recovery post-cycle.¹⁶ However, the stimulatory effect of hCG not only affects suppressed testicles; it also increases production in normally functioning testicles, resulting in elevated or even supraphysiologic testosterone concentrations. hCG has been documented to increase testosterone in normal men by 10 – 30 nmol and it is possible that slightly greater increases may be possible.¹⁷⁻¹⁹ This would result in high-normal to mildly supraphysiologic testosterone levels, roughly equivalent to 200 mg/week of testosterone enanthate. While this is not an exaggerated increase, it is sufficient to provide an anabolic effect. Because this effect is dependent upon having at least one functioning testicle, these drugs are only banned in men. In fact, it is not even tested for in women because the presence of hCG is the basis for pregnancy testing. WADA and other groups believe that a female athlete's right to privacy would be violated by testing and that such testing is unnecessary as there is no evidence of obtaining a performance advantage in the absence of having testicles.¹⁵ Interestingly, hCG is produced in minute amounts in men and women naturally, and in higher levels by certain tumors.

Pharmaceutical hCG is obtained from two sources; it can be isolated from the urine of pregnant women or produced by recombinant technology – similar to the production of human growth hormone.²⁰ hCG is normally produced in trace amounts in humans, except for during the state of pregnancy. The fetus (unborn baby) is attached to the wall of the mother's uterus by a flat, plate-like appearing gland called the placenta; sometimes it is referred to as the afterbirth as it is expelled immediately after the baby is born. The placenta is extremely vascular; meaning a highly concentrated network of blood vessels is present in the tissue. It serves several functions, including bringing nourishment to the fetus from the mother's blood, eliminating fetal waste into the mother's blood, protecting the fetus from exposure to many but not all drugs and infectious agents (viruses, bacteria, etc) and lastly producing many hormones that support the state of pregnancy. Among the hormones produced, the most prominent is hCG.²¹ hCG is a glycoprotein hormone and is easily detectable in the urine, making it the basis for home pregnancy test.

In men, the testicles are directly stimulated to produce testosterone by a hormone released from the pituitary gland called luteinizing hormone (LH). hCG is structurally very similar to LH with a few differences that make it more stable and longer-acting.²² This is critical as during pregnancy the placenta must maintain the uterus for nine months between menstrual periods, instead of the usual 28 days.

LH is released in a roller-coaster pattern of spikes and valleys and its effect is short-lived, causing testosterone to be released in several bursts throughout the day.²³ hCG's effect is longer acting, allowing it to be dosed just once a day or even every other day. When hCG is given to a man with normally functioning testicles, the longer acting signal results in dose-dependent elevations in testosterone concentrations; meaning that higher doses result in greater elevations in testosterone, to a point.

There are some points that should be considered by those interested in using hCG for enhancing testosterone production. First, it typically is packaged as a dry powder that needs to be mixed with sterile water, though there are pre-mixed options available. Second, hCG needs to be protected from heat and not exposed to direct sunlight. This is especially important after the powder has been dissolved, as proteins are not stable and become biologically inactive if exposed to heat or left in solution for a long period. Most users follow the recommendation to refrigerate hCG all the time, just like growth hormone. Many users substitute bacteriostatic water for the packaged sterile water to prolong storage. Third, hCG needs to be injected. As it is equally effective injected into the muscle, a vein or under the skin, most people take the path of least resistance and inject the drug subcutaneously; insulin syringes are often used.¹⁹ Fourth, the drug does not last in the system long. It is much more stable than LH, but as it rapidly enters the bloodstream, hCG needs to be injected daily or every other day. Protein hormones such as hCG, growth hormone and insulin can not be esterified like steroids to allow weekly injections, making the protein-based drugs less convenient. Fifth, hCG can max out natural testosterone production, but does not offer any testosterone increase beyond that point. The maximum response has not been clearly defined but it would appear that hCG is able to double testosterone production. It is possible that greater increases may be possible, but certainly not the ultra-high levels seen with anabolic steroid use. Sixth, as testosterone increases; so too does estrogen. The body produces and handles testosterone exactly as it would naturally, just more so. The positive to this is that the T-E ratio (testosterone to epitestosterone) is "normal"; which would allow an athlete to use this drug to increase testosterone concentration without failing a drug test based upon T-E ratio.¹⁵ This may be a moot point in many cases as hCG is easily detected as well.²⁴ Gynecomastia is often reported during hCG use for post-cycle recovery because of the associated estrogen increase.²⁵ Lastly, hCG is dependent upon testicular function. Older men may not receive as much benefit from hCG as middle-aged and young adult men would.²⁶

Another category of drug used to increase testosterone is anti-estrogens. This awkward term refers to drugs that block the estrogen receptor or inhibit estrogen production by blocking the aromatase enzyme that converts androgens to estrogens. Classically, bodybuilders use a drug called tamoxifen (Nolvadex) to block the actions of estrogens at their receptor.²⁷ Nolvadex is not a pure estrogen blocker, and some breakthrough is often experienced with gynecomastia and water retention being the main complaints. Tamoxifen was developed for use in breast cancer patients to reduce the hormonally stimulated growth of tumors in the breast. A similar drug, Clomiphene (Clomid) is used in fertility clinics to enhance a woman's ability to stimulate the ovaries to produce eggs by increasing the signal from the hypothalamus and pituitary. Aromatase inhibitors (Arimidex, Femara) are becoming popular options for both breast cancer treatment and infertility as they block the formation of estrogen, rather than attempting to block its signal.²⁸

Focusing on estrogen seems antithetical (opposite thinking) when one is attempting to increase testosterone. To understand the role estrogen plays in testosterone production, it is important to understand that testosterone is a pro-hormone, in addition to being a hormone.²⁹ Testosterone can act directly with androgen receptors (making it a hormone) or be further metabolized into estradiol or dihydrotestosterone (DHT) which then act with steroid receptors, typifying testosterone as a pro-hormone. Estrogen interacts with a different receptor (the estrogen receptor) than testosterone or DHT (the androgen receptor). The signal from estrogen is often stronger than the signal provided by testosterone, explaining why estrogenic side effects are so common even when the testosterone concentration is so much greater in the blood. Further, many tissues (breast, fat, etc) contain high levels of the aromatase enzyme, increasing the potential for testosterone to be converted to estrogen and act directly on the site.

The relative strength of the estrogen signal is easily demonstrated when one considers the effect of estrogens versus androgens on bone growth. Children get taller because their bone growth plates are not closed. However, during puberty, these growth plates fuse under the influence of sex steroids (estrogens and androgens) until they are closed and no further height increase is possible. There are receptors for both estrogens and androgens in bone, but growth plate closure is dictated by estrogen's action.³⁰ This is why females stop growing at an earlier age and generally are not as tall as men.

The same phenomenon is seen at the hypothalamus, the regulatory gland in the brain. The hypothalamus does not appear to measure testosterone directly, rather its metabolites — estradiol and DHT. By blocking the interaction of estradiol with hypothalamic estrogen receptors (Clomid and Nolvadex do this) or preventing the formation of estrogen in the blood or at the site of the hypothalamus (aromatase inhibitors do this), the negative feedback is not as strong and

higher testosterone levels are tolerated. Several studies have now shown an increase in blood testosterone levels in normal men, young and old, with the use of aromatase inhibitors.³¹⁻³⁴ This increase is milder than what is reported with hCG, ranging from 5 – 20 nmol, roughly equivalent to 125 mg/week testosterone enanthate, a very mild dose for athletes and bodybuilders.^{33,34} Nonetheless, anabolic benefits may be seen in many individuals, particularly those with higher estrogen levels such as the obese, older males or those using hCG.³⁵

As with hCG, there are advantages and disadvantages to using anti-estrogens. First, there are limits to the testosterone increase that will be experienced. Anti-estrogens merely “ease off the brakes” rather than “pushing on the gas” when it comes to testosterone production. The increases are substantial, but one would not expect dramatically supraphysiologic testosterone levels using anti-estrogen drugs. Second, estrogen plays a beneficial role in men as well as women. Estrogen maintains bone density and appears to improve the lipid profile relative to cardiovascular risk (cholesterol and triglyceride levels). It is also believed that estrogen may play a role in preventing hair loss, so it is possible that baldness could be accelerated. Third, there are some men born without aromatase and though they have relatively high testosterone, they don’t appear to thrive.³⁶ Given these cautions, anti-estrogens certainly could aid in preventing estrogen excess, but it is difficult to recommend their use to suppress estrogen below normal male ranges.³⁷ Anti-estrogens may be best used in conjunction with other therapies or in conditions that might increase estrogen (use of hCG, aromatizable steroids, obesity, etc). Comfort may be taken in noting that the men who experienced increases in testosterone using certain aromatase inhibitors maintain physiologic estrogen levels. Also, Nolvadex offer some estrogenic effects and is used long term in some situations, so complete estrogen loss is unlikely; improvements in blood lipids (cholesterol and triglycerides) have been reported with Nolvadex use in women.³⁸ Again, the anabolic benefit would depend upon testicular function, so any benefit would be limited to men with fully functioning testicles.

5-a reductase is an enzyme that converts testosterone into the more androgenic DHT, increasing the steroid’s effect on sex glands, skin and hair. Prostate enlargement and hair loss are directly related to DHT; these conditions are treated with drugs that block the actions of 5-a reductase, such as finasteride (Propecia, Proscar) and dutasteride (Avodart).^{39,40} Another site where the 5-a reductase is present in high concentration is in the brain. DHT is believed to be responsible for many of the psychotropic properties of testosterone (aggression, focus, libido). Additionally, DHT, like estrogen, is involved in testosterone feedback regulation. By blocking 5-a reductase at the hypothalamus, there would be less negative feedback, allowing testosterone levels to be maintained at a higher level. Generally, 5-a reductase inhibition leads to a 15 – 20% increase in serum testosterone or roughly 3 nmol.⁴¹ This slight increase is unlikely to result in an anabolic effect. In fact, 5-a reductase inhibition may be ergolytic, as many patients using the drugs for hair loss or prostatic hypertrophy report sexual dysfunction, loss of aggression/focus and gynecomastia. Reducing DHT (by approximately 90%) affects the androgenic : estrogenic balance, increasing the risk for feminizing side effects.^{41,42}

The minimal increase in testosterone and associated side effects make the use of 5-a reductase inhibitors an inappropriate choice for an anabolic advantage, with the possible exception of using such drugs concurrently with an anti-estrogen. Even then, adverse side effects may arise that would negate any benefit.

Anabolic steroids are not the only means of increasing serum testosterone. hCG, anti-estrogens and 5-a reductase inhibitors have all been reported to increase testosterone; some into the supraphysiologic range. While the combined effects of two or more of these class of drugs have not been reported in the literature, anecdotal reports and their use in anti-aging regimens suggest that the combination of hCG and aromatase inhibitors are being used successfully by practitioners. It is important for those who are considering the use of these drugs to realize they will have a mild to moderate effect on testosterone and muscle growth. Further, the doses of all drugs should be moderated to avoid fluctuations in estrogen or DHT. Proper dosing will require blood tests and monitoring.

These methods are less effective methods at raising testosterone levels or promoting muscle growth than the use of anabolic steroids provide, but they are options that make use of natural testosterone production by maximizing stimulation and minimizing feedback inhibition. hCG and anti-estrogens are effective enough to warrant their placement on the banned substance list by WADA; they are also commonly used in many clinical situations. The long term safety and effectiveness of these agents, particularly in men with impaired testicular function remain unknown. As there are centers offering the use of these agents, soliciting the direction of an experienced physician may be crucial to maximizing benefits while avoiding any potential pitfalls or side effects.

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