

# Testosterone and Fat Loss- Greater Benefits Than Realized

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Every time one joins a new gym, invariably the salesperson hands over an index card with columns of check boxes and tries to pigeonhole the new member by asking, "Do you want to gain muscle or lose fat?" Of course the correct answer is "both," as nearly everyone looking for an improved physique wants to trim fat and gain muscle.

## Melting Away Unwanted Pounds

As many drug-free bodybuilders have discovered, it's nearly impossible for a trained athlete to accomplish both at the same time. Certainly, poorly conditioned individuals may see a gain in lean mass while losing body fat when first beginning an exercise and diet program, but that's more a reflection of the dismal baseline conditioning of out-of-shape adults than any combined muscle-building/fat-burning effect. However, for bodybuilders, models and athletes with access to performance-enhancing drugs, dramatic changes are regularly and predictably seen, with slabs of thick muscle replacing the unwanted pounds of fat that seem to melt away. Among the various hormones and drugs used, most fall within a single category of being a muscle builder, fat burner or ancillary drug used to manage potential side effects. There are rare exceptions that cross over, such as clenbuterol and growth hormone, both of which build lean mass while reducing fat.<sup>1,2</sup> However, the most potent anabolic drugs, steroid hormones, seem to have only one function—muscle building. Yet, recent research suggests that a limited view of anabolic steroids is incorrect. In fact, a meta-analysis of the literature strongly suggests that anabolic steroids may directly aid in fat loss as well.

It's easy to understand why people would consider anabolic steroids to be one dimensional—use of the correct anabolic steroid(s) at the proper dose(s) leads to impressive and apparent muscle growth when combined with resistance training. At the same time, most users see a thinning of the skin, as subcutaneous fat diminishes, providing a leaner appearance. The fat loss occurring during steroid cycles is immediately attributed to the more intense exercise program, stricter diet and other drugs or supplements used during the cycle.

Would athletes be interested to know that some of the fat loss noticed during a cycle was directly related to anabolic steroid use? Could the general public benefit from supervised programs using the combination of anabolic steroids, along with diet and exercise to combat the national obesity pandemic? Of course.

## The Actions of Sex Steroids

Clearly, anabolic steroids have an indirect effect on fat loss. In other words, they affect other tissues in the body that then alter the energy balance such that fat loss occurs. Examples of this include gains in muscle mass increasing the basal metabolic rate as muscle is an active, calorie-burning tissue; or the increase in motivation to exercise that accompanies drug-aided success in the gym or on the playing field. A paper reviewing the literature on a possible steroid-fat loss connection was recently published in the journal, *Obesity Reviews*.<sup>3</sup> In this, the authors discussed in a detailed fashion many diverse investigations involving sex steroids and body fat. As has been noted, from the moment Adam awoke in the Garden of Eden, men's bodies differ from women's.<sup>4</sup> When fat gain occurs in young and middle-aged adults, men tend to deposit the fat intra-abdominally (think of the typical beer gut), while women tend to deposit fat in the gluteal-femoral region (buns and thighs). As most of the physical differences between men and women are due to the actions of sex steroids (estrogens, progesterone and androgens), it's been speculated that sex steroids may play a role in this difference as well. Not surprisingly, much of the research is dependent on animal studies. Unfortunately, the common laboratory animal species don't have physiologies identical to humans. This explains why many promising drugs developed in the lab aren't effective in human clinical trials. For example, a hormone produced by fat cells called leptin was developed for obesity treatment after it was discovered to have a potent fat loss effect in rats. Basically, when fat stores are high, leptin levels increase—reducing appetite and increasing the metabolic rate to burn calories faster. By supplying artificial leptin to obese rats, an amazing amount of fat was lost.<sup>5</sup> However, when artificial leptin was provided to obese humans, not only was it ineffective for the vast majority, but it was also

discovered that most obese people have naturally high levels of leptin.<sup>6</sup> Therefore, while a solution to any future rat obesity problem was discovered, it seems that humans are resistant to rather than deficient in leptin.

Other examples of differences between lab animals and humans have been documented, such as the questionable absence of  $\beta$ -2 adrenoreceptors in rats, confounding the use of animal data in predicting human response to drugs.<sup>3</sup> Even restricting a review to humans may not be specific enough, as it's been shown that men and women react differently to sex steroids. Much of this data comes from hormonal treatments given to transsexuals. Thus, it's important for the sake of clarity, to focus primarily on human data using male subjects.

### Genomic Effects

In the broadest sense, it can be stated that androgens are anti-adipogenic, while estrogens are pro-adipogenic.<sup>3</sup> In other words androgens (such as testosterone) reduce body fat stores and the development of new fat cells, while estrogens promote fat storage and development.

This isn't surprising, considering the clear differences between male and female bodies. Beyond recognizing this fact, it's important to understand why this difference exists if one is to try to manipulate body fat stores pharmaceutically. The classic understanding of steroid hormones is relatively straightforward. Essentially, a steroid crosses the cell membrane, links up with a receptor that's floating within the insides of a cell and the pair travels to the DNA. The steroid-receptor pair turns on certain genes, which create new proteins or alter cell function. But like all things in life, it's actually more complicated than that. Steroids do cross into the interior of a cell and associate with receptors in order to travel together as a pair to the DNA. However, there are many different co-modulators, molecules which change the effect of the steroid-receptor pair, either increasing or blocking the effect on the DNA. Receptors are also embedded in the cell membrane, which bind to steroids.<sup>7</sup> These membrane-bound receptors don't travel to the DNA after linking with steroids; rather, they alter the cell's sensitivity to other hormones. The scientific literature refers to the DNA-associated changes as genomic effects and the membrane-bound changes as non-genomic effects.

In order to assign any effect in fat cells to steroids, it was first necessary to prove that fat cells contained steroid receptors. This has been proven for androgens, estrogens and progesterone.<sup>8,9</sup> Interestingly, different areas of fat have different concentrations of sex steroid receptors. Androgen receptors are highest in intra-abdominal fat, while estrogen and progesterone receptors are highest in gluteal fat regions.<sup>10,11</sup> The steroid receptors are sensitive to steroid levels and increase in number when steroid levels rise.<sup>9,10</sup> This is very interesting as it explains why greater effects are seen in supraphysiologic anabolic steroid cycles and why aging men seem to have such difficulty keeping fat off. In the first case, fat cells are more sensitive to androgens when exposed to higher levels. In the second, not only do steroid levels fall, but the aged male is less sensitive to the hormones. The fat loss effects of androgens appear to involve both genomic and non-genomic processes. Classic steroid receptors allow steroids to affect the formation of new proteins, such as enzymes and hormones. Lipoprotein lipase and leptin are two examples of genomic control of fat balance by steroids. Lipoprotein lipase (LPL) is an enzyme released by fat cells that breaks down triglycerides (fats) circulating in the blood, so it can absorb the free fatty acids and glycerol components of these triglycerides.<sup>12</sup> It's been theorized that by decreasing LPL, lesser amounts of free fatty acids would be available to be absorbed by the fat cell, preventing a gain in fat stores. Studies involving other hormone seem to support this, as LPL rises with cortisol and insulin—two hormones known to increase fat stores; and is lowered by growth hormone—a fat-reducing hormone.<sup>13</sup> In women, this may be true, as estrogens given as hormone replacement to menopausal women reduce LPL levels and fat loss has been documented. Androgens (testosterone) actually increase LPL levels in women.<sup>14</sup> In men, testosterone has the opposite effect, reducing LPL levels.<sup>15</sup> This effect was not seen with the more potent androgen, DHT, leading researchers to investigate the possible role of aromatization. Aromatization is the enzymatic process by which testosterone is converted into estrogens. Aromatase is present in human fat cells.<sup>16</sup> It was discovered that the LPL-lowering effect of testosterone isn't present when aromatase is blocked. Given that DHT doesn't consistently affect LPL and that the LPL-lowering effect isn't seen when an aromatase inhibitor is present, it's evident that the LPL-lowering effect of testosterone is due in part to its ability to act as an estrogen precursor.<sup>17</sup> It isn't understood why this discrepancy exists between males and females, but it demonstrates the need to consider gender when studying steroid effects.

## cAMP and Phosphoinositide

As was mentioned earlier, leptin is a hormone produced by fat cells. Theoretically, when leptin levels are high, the body receives signals to eat less and the metabolic rate is increased to facilitate calorie burning and weight loss. Yet, women have naturally higher levels of leptin and testosterone has been shown to lower leptin production.<sup>4</sup> The basic understanding of leptin would lead one to believe that women would then be leaner and more capable of maintaining lower body fat content. Again, there's a yet-to-be understood disparity, proving that fat loss and weight maintenance remain a mystery at the bio-molecular level.

Genomic effects, such as LPL and leptin require the affected cells to create new proteins and the effects are generally not seen for days to weeks. Non-genomic effects are much more rapid, showing an effect in minutes to hours.<sup>18</sup> Non-genomic effects of steroids occur when receptors embedded in the cell membrane interact with steroids circulating in the blood. When this occurs, other nearby receptors or proteins are altered, so that the cell becomes more responsive to non-steroid hormones. Two examples to demonstrate the non-genomic effects of steroids include cAMP and phosphoinositide. Cyclic-AMP, known as cAMP, is a secondary messenger in cells that carry the signal from membrane receptors to functions inside the cell. Epinephrine, the fight-or-flight hormone that makes the heart race when scared or excited, causes a potent fat release from fat cells that's dependent on cAMP. When fat cells are pre-exposed to estrogens, the fat release effect of epinephrine is lessened.<sup>19</sup> In part, this may be due to an estrogen-stimulated increase in  $\beta$ -2-adrenoreceptors; a subclass of receptors that block lipolysis (fat release). Testosterone increases cAMP-dependent lipolysis, an effect clearly demonstrated in female-to-male transsexuals.<sup>20</sup>

Phosphoinositides are also secondary messengers. Fat cells exposed to insulin store fat more easily and precursor cells mature into full-grown fat cells, due to the signal generated by phosphoinositides. For what they're worth, rat studies have shown that estrogens increase phosphoinositides, promoting fat cell growth; androgens have the opposite effect.<sup>21</sup>

## Greater Benefits Than Realized

The field of study remains wide open, but the interesting studies noted above strongly support the idea of anabolic steroids having direct effects on fat loss. Considering the diverse effects of testosterone and the obvious differences between men and women, it's not surprising to learn of this potential. The greatest clinical promise for these findings lies with the aging population, as they suffer from age-related declines in many hormones.<sup>22</sup> It's likely that pharmaceutical companies will attempt to develop specific steroids or steroid-like molecules to take advantage of the fat reducing effects noted. By increasing the rate at which fat is released from fat cells, preventing the development of new fat cells and increasing the metabolic rate through the growth of muscle and lean mass, anabolic steroids may offer even greater benefits than have been realized to date.

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