

Is it Time to Test the Effect of Weight Loss on Testosterone?

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Testosterone is a sex-steroid hormone, synthesized in the testes, with biologic effects on numerous tissues. Low circulating concentrations, seen with testicular or hypothalamic–pituitary defects, are often associated with decreased sexual function, muscle mass, and poor quality of life, along with a risk of osteoporosis. Primary testicular failure can be due to testicular trauma, chemotherapy, radiation therapy, or chromosomal abnormalities, although secondary causes, also termed centrally mediated hypogonadism, are associated with pituitary tumors or hypothalamic disease. In addition to these well-known etiologies, there is an increasing appreciation that hypogonadism can be the result of aging, medications, and chronic diseases.

A physiological decrease in testosterone concentrations has been well documented after the fourth or fifth decade of life and has been postulated to result from a decline in both testicular and hypothalamic–pituitary function. In scenarios in which the patient has a clear pathophysiologic mechanism for the hypogonadism, treatment with testosterone is nearly always recommended to alleviate symptoms of hypogonadism and maintain secondary sexual characteristics (1).

Possible Risks of Testosterone Therapy

Men on replacement therapy should be monitored for polycythemia, falls in serum high-density lipoprotein, worsening of sleep apnea, and increase in prostate-specific antigen concentrations (2, 3). Because long-term evidence of safety with supplementation is yet to be established, testosterone therapy is not routinely recommended in older men or in men with an unclear underlying etiology for their low testosterone concentrations. Because low serum testosterone is commonly observed in chronic illness, there may be less invasive ways to naturally increase serum concentrations. This circumstance creates an opportunity to explore other intervention options that could favorably increase the

endogenous testosterone production in the absence of potential side effects.

Laboratory Analyses in Obesity

The interpretation of laboratory tests can be confusing in men as they age and become more obese because both factors modulate sex by hormone-binding globulin (SHBG)³ concentrations. Obese men have been noted to have lower total testosterone (TT) concentrations, primarily due to decreased SHBG, and this effect worsens over time. However, aging increases SHBG. Thus, the TT could falsely appear normal in older men, although the negative effect of body mass index (BMI) on SHBG has been noted to be of greater significance than the positive effect of age on SHBG (4). This finding may explain the low TT seen in older obese men. Because the variation in SHBG can influence testosterone concentration, measurement of free or “bioavailable” testosterone can serve as a better marker. Current Endocrine Society practice guidelines recommend evaluation of SHBG concentrations in addition to TT to estimate for free testosterone.

Association of Testosterone to Obesity

The 2 most common comorbid conditions associated with low serum testosterone are obesity and type 2 diabetes. Multiple cross-sectional data from studies like European Male Aging Study and that by Rohrmann et al. have revealed the association between increased BMI and low serum testosterone (5, 6).

Rohrmann et al. observed an association between measures of body fatness and sex steroids. The 3 measures of adiposity included BMI, waist circumference, and percentage body fat. They observed a decrease in free testosterone (FT) and SHBG concentrations with increasing body fatness, and the extent of the decline was similar across all 3 measures (6).

Another cross-sectional study including elderly men compared the TT and FT concentrations between healthy, overweight, and obese men. Testosterone was found to be

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³ Nonstandard abbreviations: SHBG, sex hormone-binding globulin; TT, total testosterone; BMI, body mass index; FT, free testosterone.

significantly lower in the obese population than the nonobese (7). Of course, association does not always mean causation, but a recent bidirectional Mendelian randomization analysis supports the hypothesis that obesity has a causal relationship with low testosterone. However, the reverse causality was not established (8).

Mechanisms of Hypogonadism in Obesity

The primary mechanism explaining the low testosterone in obesity is believed to be mediated at the hypothalamus–pituitary level, leading to a hypogonadotropic–hypogonadic state. This central inhibition has been attributed to multiple mediators including the role of insulin resistance, inflammatory mediators, and leptin in addition to the negative feedback regulation by increased estrogen.

Obesity induces a proinflammatory state leading to increased concentrations of cytokines, such as interleukin-6 and tumor necrosis factor, which primarily are believed to blunt the hypothalamic axis (5). A few studies, however, also postulate direct inhibition of testicular function via modulation of Leydig cell steroidogenesis (9, 10).

Another suggested mechanism is aromatization of testosterone by P450 aromatase expressed in the peripheral adipose tissue, leading to a significant increase in the amount of estradiol, which can then suppress the hypothalamic–pituitary–gonadal axis via feedback inhibition (11). However, no study has demonstrated increased estradiol concentrations in such individuals.

Another postulated link between obesity and hypogonadism is the role of adipokines. Leptin has been noted to have a stimulatory effect on gonadotropin-releasing hormone production in rodents (12). Obesity, however, is believed to induce a leptin-resistant state leading to high circulating concentrations. High leptin concentrations are therefore correlated with increased adiposity and low testosterone (13, 14).

Effects of Exercise and Weight Change on Testosterone

The effects of exercise and weight loss on testosterone concentrations are limited and sometimes controversial. Corona et al performed a metaanalysis on 24 trials that studied the effect of body weight loss on sex hormones concentrations (11). Out of the 24 trials, 22 studied the effect of diet or surgery, and 2 compared both. Analysis revealed a positive correlation of weight loss, either through diet modification or bariatric surgery, with increase in serum testosterone. This increase was proportional to the degree of weight loss achieved. Both a low-calorie diet and bariatric surgery were associated with an increase in plasma TT. However, in comparison, bariatric surgery was associated with a higher mean percentage

weight loss of $32\% \pm 4\%$ as compared to $9.8\% \pm 4.5\%$ for low-calorie diet, and a more significant increase of testosterone than in the diet-only group. Regression analysis revealed that more weight loss was associated with greater androgen increase (11). The Diabetes Prevention Program was a randomized clinical trial studying the effect of lifestyle intervention or pharmacological therapy (metformin) in delaying the onset of diabetes in individuals with impaired glucose tolerance. A secondary analysis performed on this trial showed an association of decreased adiposity, either visceral or subcutaneous, with an increase in testosterone concentrations (15). One study (16) looked at the combination of exercise with testosterone replacement against testosterone replacement alone. Fifty patients with erectile dysfunction, low testosterone, and a sedentary lifestyle were followed for 20 weeks. At 12 weeks, symptomatic improvement with an increase in testosterone concentrations was noted in both groups. However, symptoms were better in the exercise plus replacement group. Treatment was stopped after 20 weeks with resultant worsening of symptoms in the replacement alone group. Furthermore, improvement in symptoms was maintained in the combination group with continued exercise even after cessation of therapy (16). This study, however, has its limitation given the lack of a control group. Another study (17) evaluated the effect of low- vs. high-volume moderate-intensity exercise in 70 obese sedentary men with erectile dysfunction as primary outcome. Men 30–65 years of age were followed for 24 weeks after being randomized to either low-volume (<150 minutes/week) or high-volume (>200 minutes/week) moderate-intensity exercise, with serum testosterone and SHBG measured at 0, 12, and 24 weeks. At the end of this 24-week study, the high-volume exercise group had statistically significant improvements in sexual function and testosterone concentrations compared to the low-volume group (17).

A parameter of significance is the relationship of type of exercise, resistance vs aerobic, with concentrations of testosterone. Acute increases in testosterone can be induced by resistance exercises; however, aging results in a reduced testosterone response to resistance exercise.

On the opposite spectrum, highly trained endurance athletes have been found to have lower testosterone concentrations than control participants, suggesting that extreme exercise, reduced weight, and low-fat mass causes hypogonadism (18). This finding is similar to the hypogonadism observed in young women with anorexia nervosa, who develop amenorrhea. Some uncertainty in this area therefore exists. Considering the studies linking the relationship of adiposity and testosterone concentrations, it is plausible that aerobic exercise, which reduces fat and improves cardiorespiratory fitness, would perhaps be more beneficial than strengthening exercises (19).

Conclusion

Normal concentrations of testosterone are generally a marker of good health. Low serum TT and FT have been associated with increasing BMI and abdominal adiposity. Many of these men suffer from the nonspecific signs and symptoms of hypogonadism, such as fatigue and sexual dysfunction. This is exactly the population that may benefit from noninvasive treatments to increase serum testosterone, by reducing weight and abdominal adiposity rather than administering testosterone therapies. Obesity has several pathophysiologic mechanisms to explain the fall in testosterone. Direct treatment of obesity may have direct cardiovascular disease benefit and indirect improvement in testosterone concentrations. In such individuals, physiologic ways to increase testosterone are deemed appropriate because testosterone treatment may be associated with risk and with increased need for monitoring. Although some controversy still exists between exercise and testosterone concentrations, most available evidence does support a rise in serum testosterone with greater degree of weight loss, although this change is most impressive after bariatric surgery.

The direction of future investigation should include large, randomized control trials of longer duration to

characterize the benefits of weight loss and exercise on serum testosterone and the signs and symptoms often associated with male hypogonadism. This direction may provide a more physiologic approach to increase serum testosterone concentrations, with the added benefit of reducing weight and improving muscle mass and bone density. The time is right to recommend studies to document the degree of weight loss needed to significantly increase serum testosterone concentrations. The intent would be to improve the symptoms of hypogonadism and provide a safe and effective modality for long-term benefit on overall health.

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