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Role of testosterone in maintaining lean body mass and bone density in HIV-infected patients

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Low testosterone levels are common in both men and women with human immunodeficiency virus (HIV) infection and may contribute to loss of lean body mass and AIDS wasting. Causes of low testosterone levels are complex and may include chronic illness, HIV infection and its complications, medications used to treat HIV and opportunistic diseases, and normal aging-related declines. In the majority of studies addressing the use of testosterone treatment in HIV-infected patients, testosterone has been found to help prevent loss of lean body and muscle mass. Whether the combination of exercise and testosterone is more effective in preventing loss of lean body mass than either therapy alone is not yet clear and warrants further study. In addition to its effects on body composition, testosterone treatment results in improved mood and libido in HIV-infected women and increased bone mineral density in HIV-infected men. Testosterone may thus make a valuable contribution to the treatment of HIV-infected individuals.
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Introduction

One of the earliest observations in patients infected with human immunodeficiency virus (HIV) was that this disease was associated with a number of endocrinologic abnormalities, including hypogonadism. By the late 1980s, it became clear that hypogonadism was common in men with acquired immunodeficiency syndrome (AIDS).[1] Later studies found that low testosterone levels were correlated with loss of lean body and muscle mass, decreased CD4+ counts, and increased incidence of opportunistic infections and AIDS wasting syndrome.[2,3] Data from a nested case–control study of HIV-infected men with or without weight loss further suggested that a decline in testosterone levels was one of the early events, often preceding the diagnosis of wasting.[4] Abnormally low testosterone levels are also observed in HIV-infected women, particularly those in advanced stages of wasting.[5] These findings raised the possibility that testosterone replacement therapy can be useful in the treatment of AIDS-associated wasting.

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Decreased testosterone levels in HIV-infected men and women

In the early years following the identification of HIV as a clinical entity, approximately 40% of HIV-infected men suffered from hypogonadism, with testosterone levels decreasing with increasing disease severity.[1] Even with our improved understanding of how to care for patients with HIV, low testosterone levels remain a common problem in this population. With the use of more effective therapies to combat this, the prevalence of hypogonadism now appears to be reduced to around 20%.[6] Testosterone levels below the age-adjusted normal range have been observed in 33–66% of HIV-infected women.[5] Many studies suffer from inconsistencies in the methods used to measure serum testosterone levels. The presence of binding globulins necessitates the use of some measure of the free, unbound testosterone. In addition, the normal range of serum testosterone in women is not well established.

Multiple etiologies have been proposed for the decreased testosterone levels seen in HIV-infected patients (Table 1).[7,8] Chronic illness and weight loss tend to depress hypothalamic pituitary function, resulting in reduced testosterone. HIV infection or its complications may further contribute to hypogonadism. For instance, HIV can invade the testes, and toxoplasmosis may affect the pituitary gland.

Table 1 Mechanisms of decreased testosterone levels in HIV-infected patients[7,8]

Chronic illness/weight loss
Invasion of glands by HIV or other pathogens
Medications
Antiretroviral agents
Antifungal agents
Antiviral agents
Alkylating agents used to treat lymphomas and cancers
Megesterol, a commonly prescribed appetite stimulant
Age-related declines

Medications also play an important role in the low testosterone levels observed in HIV-infected patients. Certain antifungal drugs, such as ketoconazole and fluconazole, inhibit several enzymes in the steroidogenic pathway, whereas the appetite stimulant megesterol is a progestational agent that inhibits gonadotropins. Alkylating agents, which may be needed to treat carcinomas or lymphomas, can cause primary testicular damage.[7] Antiretroviral drugs may also contribute to decreased testosterone levels. In one study of HIV-infected men with wasting, 21% of those receiving highly active antiretroviral therapy were hypogonadal compared to 11% of those not receiving such therapy, even though the patients receiving antiretroviral therapy had a higher body mass index and CD4+ count.[6] Finally, as the HIV-infected population ages, age-related declines in testosterone may also become a factor.[9]

Low testosterone levels may have important consequences in HIV-infected patients. In men who are not infected with HIV, hypogonadism is associated with increased sexual dysfunction, depression, reduced muscle mass, and decreased bone density.[10] All of these may decrease the patient's quality of life. Perhaps the most important issue for women and men infected with HIV, however, is the association between decreased testosterone levels and loss of lean body and muscle mass, two features of AIDS wasting. Weight loss and loss of lean body mass are associated with increased mortality, reduced physical function, and reduced quality of life in patients with HIV infection.[11–13] By preventing or reducing HIV-associated wasting, testosterone could theoretically have a favorable impact on mortality in this patient population.

Studies of testosterone replacement in HIV-infected patients

In the last decade, several studies have addressed the effects of testosterone in HIV-infected patients. Although early trials focused primarily on testosterone replacement therapy in hypogonadal men, subsequent studies have also addressed the use of testosterone in women and eugonadal men with wasting. Some of the major conclusions from these studies are discussed in the following sections.

Effects on body composition and muscle mass

Perhaps the most intense area of research has involved the effects of testosterone on body composition and muscle mass in patients with HIV infection. AIDS wasting syndrome is a significant problem in this patient population, and therapies that help prevent declines in weight and muscle mass have the potential to make an important contribution to maintaining overall health, physical function, and quality of life. Several studies indicate that testosterone treatment helps prevent loss of lean body and muscle mass in HIV-infected patients.[14–19] In a study of 51 HIV-positive men with wasting and low testosterone levels, patients were randomized to placebo or testosterone enanthate at 300 mg intramuscularly (i.m.) every 3 weeks for 6 months. At the 6-month study end point, the testosterone-treated patients showed statistically significant increases in fat-free mass, lean body mass, and muscle mass compared to placebo patients (Figure 1). No changes were observed in weight or fat mass.[14] Following the 6-month double-blind portion of this study, all subjects received open-label testosterone for an additional 6 months. During this 6-month period, both groups gained lean body mass. At the end of 12 months, the original testosterone group had recorded a lean body mass gain of 3.7 kg, compared to 1.0 kg in the original placebo group.[15] These data indicate that improvements in body composition in response to injectable testosterone are sustained with continued therapy.

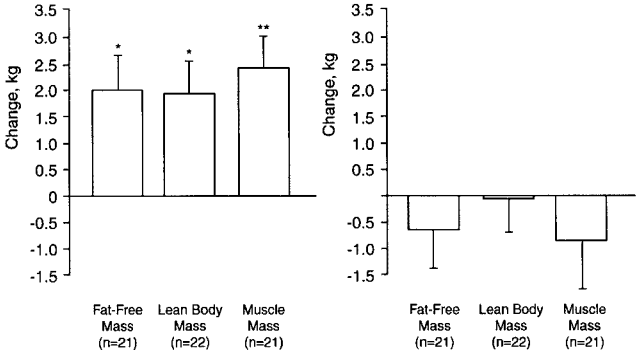

Figure 1 Mean changes ± s.e. for fat-free mass, lean body mass, and muscle mass in hypogonadal HIV-infected patients treated with testosterone (left) or placebo (right) for 6 months. The testosterone group received testosterone enanthate at 300 mg i.m. every 3 weeks. *$P<0.05$ for the change from baseline between the testosterone group and placebo group by analysis of covariance. **$P<0.01$ for the change from baseline between the testosterone group and placebo group by analysis of covariance. From Grinspoon *et al*,[14] reprinted with permission from *Annals of Internal Medicine*.

In contrast to these findings, a study of a transscrotal testosterone delivery system (6 mg/day) in hypogonadal HIV-infected males did not observe significant differences in mean weight change or body cell mass between the treatment and placebo groups at 12 weeks.[20] It is possible that this system of testosterone replacement does not achieve high enough testosterone levels to produce such changes. A recent meta-analysis of placebo-controlled trials that compared the effects of testosterone therapy with placebo in HIV patients with wasting supports the greater efficacy of i.m. testosterone formulations in this patient population. In six trials involving 324 randomized patients, the difference in lean body mass increase between testosterone and placebo groups was 0.51 kg ($P = 0.02$). However, when testosterone was administered by the i.m. route, a difference of 3.34 kg over placebo was observed ($P > 0.00001$; Figure 2).[21]

Exercise also improves body composition in HIV-infected men with wasting, and some studies have attempted to address whether testosterone and exercise might compliment each other in this setting.[17–19] In a four-arm study, 61 hypogonadal HIV-infected men with weight loss were randomized to treatment with placebo alone, testosterone alone (100 mg/week testosterone enanthate i.m.), placebo plus exercise, or testosterone plus exercise. At the 16-week study end point, testosterone alone or exercise alone were found to promote gains in body weight, muscle mass, muscle strength, and lean body mass. However, testosterone plus exercise did not result in significantly greater gains than either intervention alone.[17] Data from another study, involving 54 eugonadal men with AIDS wasting who were randomized to receive testosterone enanthate (200 mg/week i.m.) or placebo and then further randomized to resistance training or no training for 12 weeks, were suggestive of an additive effect of testosterone on muscle mass and muscle leanness. However, the study was not designed to detect differences between the combined therapy and monotherapy groups. Furthermore, testosterone doses

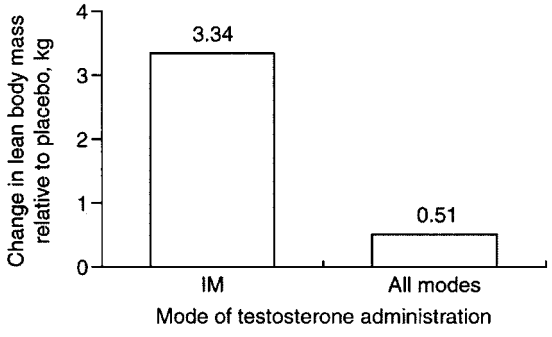

Figure 2 Effect of mode of testosterone administration on lean body mass in a meta-analysis of placebo-controlled clinical trials. For intramuscular (i.m.) testosterone studies, $n = 47$ for treatment group and 44 for placebo. For all modes, $n = 162$ for treatment group and 162 for placebo. Data from Kong and Edmonds.[21]

of twice the physiologic replacement dose were used in this study.[18,19] It thus remains unclear whether the combination of physiologic testosterone therapy and exercise is more effective in improving body composition than either exercise or testosterone alone.

Only one placebo-controlled study has addressed the benefits of testosterone therapy in HIV-infected women. This study assessed the use of transdermal testosterone patches in 53 women with AIDS wasting syndrome. Women were randomized to receive two placebo patches, one active/one placebo patch, or two active patches applied twice weekly to the abdomen for 12 weeks. The expected delivery rate of each active patch was 150 μg/day. Compared to the weight change observed in the group with two placebo patches (0.6 kg), significant increases in weight were observed in the group with one placebo/one active patch (1.9 kg), but not in the group with two active patches (0.9 kg). Fat-free mass increased to a slightly greater extent in the group with two active patches, but this difference was not statistically significant.[22] Further studies examining the most appropriate dosing in this patient population may thus be required.

Effects on sexual function and mood

Hypogonadal HIV-infected men have been found to be more depressed, as indicated by higher scores on the Beck Depression Inventory, than eugonadal HIV-infected men.[23] In addition, hypogonadal symptoms, such as decreased libido and depression, may be observed in eugonadal HIV-infected males. A small open-label study in which 23 eugonadal men with AIDS and hypogonadal symptoms received testosterone cypionate i.m. biweekly (initial dose of 200 mg, increasing to 400 mg at week 2) provided early evidence for the ability of testosterone to positively affect libido, mood, energy, and appetite.[24] Placebo-controlled trials have confirmed this finding. During a 6-week, placebo-controlled study involving 74 HIV-infected men with low testosterone levels and hypogonadal symptoms, testosterone injections (testosterone cypionate at an initial dose of 200 mg followed by 400 mg biweekly) for 12 weeks resulted in significant improvements in libido and energy, and a trend toward improved mood in subjects with an Axis I depressive disorder at baseline (Figure 3).[16] Data from two trials of longer duration (6 months) add further support to the effect of testosterone on mood. Compared to a placebo group ($n = 18$), significant decreases in Beck scores were documented in hypogonadal HIV-infected men receiving testosterone replacement therapy (300 mg testosterone enanthate i.m. every 3 weeks; $n = 21$) for 6 months.[23] Similarly, in a 6-month placebo-controlled study in which 51 HIV-positive men with low

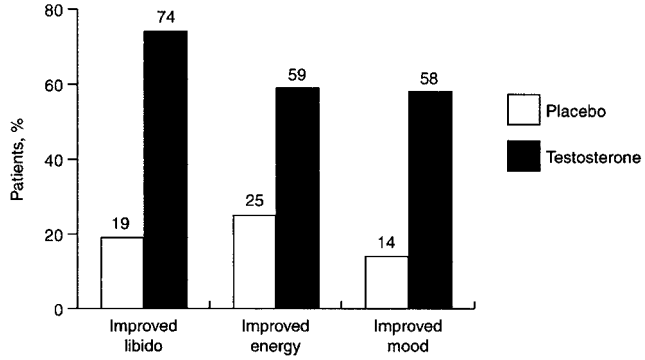

Figure 3 Effect of testosterone (testosterone cypionate at an initial dose of 200 mg followed by 400 mg biweekly; $n=38$) compared to placebo ($n=32$) on libido, energy, and mood in HIV-infected men with low testosterone levels and hypogonadal symptoms at the 6-week trial end point. Evaluations of improved energy involved 62 completers with fatigue at baseline (testosterone, $n=34$; placebo, $n=28$). Evaluations of improved mood involved 26 completers with an Axis I depressive disorder at baseline (testosterone, $n=19$; placebo, $n=7$). Data from Rabkin *et al.*[16]

testosterone levels were randomized to placebo or testosterone enanthate 300 mg i.m. every 3 weeks, self-reports indicated that testosterone-treated patients felt significantly better and perceived significant improvements in quality of life relative to patients on placebo.[14] It should be noted that some of these studies use supraphysiologic concentrations of testosterone. Most would, nonetheless, support testosterone's beneficial effects on mood and libido in both hypogonadal and eugonadal HIV-infected men.

Effects on bone

Compared to healthy, non-HIV-infected subjects, HIV-infected men with wasting have reduced bone mineral density (BMD). In a study of eugonadal HIV-infected men with wasting, 33% were found to have osteopenia as assessed by total hip BMD.[25] The effects of testosterone on osteopenia were examined in a study of 54 eugonadal HIV-infected men with wasting. Treatment with testosterone enanthate (200 mg/week i.m. for 3 months) resulted in significant increases in lumbar spine and total hip BMD relative to the placebo group. In contrast, resistance training did not increase BMD.[25] These findings should provoke further investigation into the long-term use of testosterone to prevent fractures in HIV-infected individuals.

Potential side effects

The long-term side effects of testosterone therapy in HIV-positive or, for that matter, in HIV-negative individuals are not clear. Testosterone treatment in hypogonadal men does result in a slight increase in prostate size and in serum prostate-specific antigen (PSA). However, these changes are usually mild and, in short-term studies, have not been associated with an increased risk of developing prostate cancer. Long-term safety studies are needed. A second potential risk of testosterone treatment is increased hematocrit. Although this is likely to be beneficial in HIV-infected men, hemoglobin concentrations need to be monitored to prevent polycythemia. In general, all men should have a serum PSA test, digital rectal exam, and a complete blood count (CBC) before and during treatment.

Future questions and challenges

Data on the use of testosterone in HIV-infected patients are encouraging. In this patient population, testosterone therapy appears to be associated with improvements in body composition, mood, and bone density. Several questions still surround the best use of such therapy, however. These include: What is the serum level of testosterone required to treat and prevent some of the androgen-dependent end-organ effects of HIV? What is the role of supraphysiological dosing? Should such dosing be short-term only, or will long-term usage be required to maintain mood and body composition changes? Will testosterone therapy contribute to or counteract metabolic abnormalities associated with highly active antiretroviral therapy (HAART), such as lipodystrophy? What is the role of testosterone therapy in women? Hopefully future studies will address such questions, allowing improved utilization of testosterone in the treatment of HIV-infected patients.

Discussion

Dr Lisa Tenover: Have there been any studies concerning when, in the course of AIDS wasting, testosterone is most effective? In other words, should you try to look for hypogonadism early, even before the patient has a lot of wasting, or does wasting already need to have occurred before testosterone shows an effect?

Dr Adrian Dobs: There is a drop in testosterone that occurs very early on in the weight-loss period. The usual definition of wasting is a decrease of 10% in body weight. However, it turns out that there could be a drop in testosterone with as little as 5% wasting. And generally the trend has been to address the wasting at 5% and not wait for the 10% drop. I think that testosterone levels should be

measured in HIV-infected men who have lost any degree of weight.

Dr Glenn R. Cunningham: Some patients with HIV seem to have really 'bulked up' in response to testosterone therapy. Do you have any comments on this phenomenon?

Dr Dobs: People who 'bulk up' while on testosterone therapy are using supraphysiological doses of testosterone. Their testosterone levels are extremely high, and at that dose the bulking up certainly occurs. Nobody would recommend that from a medical point of view. Part of the controversy with testosterone replacement therapy in HIV-infected men has been that many HIV-infected patients are over-replaced. I think this is a problem we see in the sports arena as well as in certain subsets of the HIV-infected populations. And that is really an abuse of anabolic hormones and testosterone. However, I think we can assume that this is a small subset of the HIV-infected population. At this point, testosterone replacement therapy should be reserved for HIV-infected men who exhibit documented hypogonadism.

Dr Tenover: Have any of the studies of testosterone replacement in HIV-infected subjects been followed long enough to see if this therapy has any effect on mortality?

Dr Dobs: None of them has really been long enough. One might assume that increasing lean body mass might improve mortality. However, I think we have to be realistic: the thing that has really affected AIDS mortality is HAART. Testosterone therapy helps improve quality of life in men being treated with HAART, so it is very important.

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