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Effects of Hypogonadism and Testosterone Administration on Depression Indices in HIV-Infected Men*

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ABSTRACT

Hypogonadism is prevalent among human immunodeficiency virus-infected men, in whom significantly reduced quality of life and mood disturbances have been reported. Previous studies have not investigated the relationship between depression score and gonadal function among such patients. We first compared depression scores in hypogonadal (n = 52) and eugonadal (n = 10) patients with acquired immunodeficiency syndrome (AIDS) wasting, matched for weight and disease status, and then investigated the effects of testosterone administration on depression score in a randomized, double-blind, placebo-controlled study among the group of hypogonadal men with AIDS wasting. The primary end point in all comparisons was the Beck Depression Inventory. Hypogonadal patients demonstrated significantly increased scores on the Beck inventory compared with eugonadal-, age-, weight-, and disease status-matched subjects (15.5 ± 1.1 *vs.* 10.6 ± 1.4 mean ± SEM, $P = 0.02$). Among the combined hypogonadal and eugonadal subjects, a significant inverse correlation was seen between the Beck score and both free ($r = -0.41$, $P < 0.01$) and total serum testosterone levels ($r = -0.43$, $P < 0.001$). The relationship between the Beck score and testosterone levels remained highly significant, controlling for weight, viral load, CD4 count, and antidepressant use ($P < 0.01$ for free testosterone, $P < 0.001$ for total testosterone). Furthermore, when subjects were divided into two groups, based on a Beck score greater than 18 or less than or equal to 18, serum total and free testosterone levels were significantly lower in the subjects with a Beck score greater than 18, whereas there were no differences in weight, viral load, CD4 count, or Karnofsky status. End of study data were available in 39 patients who completed the randomized, placebo-controlled study. Beck score decreased significantly only in the subjects receiving testosterone (-5.8 ± 1.3, $P < 0.001$), but not in subjects randomized to placebo (-2.7 ± 1.3, $P > 0.05$). In a regression analysis, the change in Beck score was related significantly to change in weight ($P < 0.01$). These data demonstrate increased depression score in association with hypogonadism in men with AIDS wasting, independent of weight, virologic status, and other disease factors. In such patients, administration of testosterone results in a significant improvement in depression inventory score. This effect may be a direct effect of testosterone or related to positive effects of testosterone on weight and/or other anthropometric indices. Additional studies are needed to assess the effects of testosterone on clinical depression indices in human immunodeficiency virus-infected patients. (*J Clin Endocrinol Metab* **85:** 60–65, 2000)

HYPOGONADISM is highly prevalent in men with acquired immunodeficiency syndrome (AIDS) (1), in whom significant mood disturbances have been reported (2). However, it remains unknown whether mood disturbances relate to androgen deficiency or to other potential causes, including immune dysfunction, severity of illness, and/or reduced performance and functional status in such patients. Recent data suggest an important, independent contribution of gonadal function to mood status and depression score in non-human immunodeficiency virus (HIV)-infected men. Increased depression scores have been demonstrated in hypogonadal non-HIV-infected men (3). In a recent study, Barret-Connor *et al.* (4) demonstrated a significant inverse association between bioavailable testosterone concentration and Beck depression score that remained significant after controlling for age, weight, and other factors. Furthermore, administration of physiologic testosterone replacement to hypogonadal non-HIV-infected men has been shown to improve mood, reduce sadness, and decrease anger (5). Despite the recent evidence of androgen effects on depression indices among non-HIV-infected hypogonadal men, relatively little is known regarding the effects of physiologic testosterone on depression indices in the large population of HIV-infected men with hypogonadism.

In this study, we investigate the relationship between depression score and testosterone concentration in HIV-infected men, comparing age- and weight-matched eugonadal and hypogonadal men with AIDS wasting. In addition, we compare changes in the Beck Depression Inventory among hypogonadal men with AIDS wasting randomized to receive testosterone or placebo. Our data suggest that Beck scores are significantly different between hypogonadal and eugonadal men with AIDS wasting. Of importance, administration of testosterone to such patients resulted in an improved depression score. These data suggest that among men with AIDS wasting, hypogonadism, independent of disease status and/or other factors, contributes to an increased depression score. Conversely, testosterone administration significantly lowers depression scores in hypogonadal men with AIDS wasting.

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Patients and Methods

Fifty-two men with AIDS wasting [weight <90% ideal body weight (IBW) or weight loss >10%] and a screening serum-free testosterone less than 12.0 pg/mL were enrolled in a randomized, placebo-controlled 6-month study of testosterone administration (300 mg im every 3 weeks) (6), as reported previously. Testosterone levels were drawn between 0800 and 0900 h as part of the baseline visit, before the initiation of the study, and approximately 2 weeks after screening. Baseline data were available in 51 patients. Baseline testosterone levels were compared with the end of study levels, which were drawn between 0800 and 0900 h 10 or11 days after the last testosterone injection. Ten age- and weight-matched men with AIDS wasting (weight <90% IBW or weight loss >10%) and screening free testosterone more than 12.0 pg/mL were recruited as a control group for baseline comparison only and did not receive testosterone (Table 1).

Gonadal function

Serum total and free testosterone were measured by a RIA kit (Diagnostics Products Corporation, Los Angeles, CA) with intra-assay coefficients of variation of 5–12% for total testosterone and 3.2–4.3% for free testosterone. The normal range of free testosterone at the Massachusetts General Hospital (12.0–35.0 pg/mL) was established with the Diagnostic Products Corporation assay based on a sample population of 101 healthy male volunteers. Estradiol was measured by a RIA kit (Diagostics Systems Laboratories, Inc., Webster, TX; sensitivity 5.0 pg/mL, intra-assay coefficients of variation 6.5–8.9%). Sex hormone-binding globulin (SHBG) was measured as described previously (6).

Beck Depression Inventory and medication history

The Beck Depression Inventory was administered to all patients (hypogonadal patients and eugonadal control subjects) at baseline and again after 6 months to the hypogonadal patients in the randomized study. The Beck Depression Inventory was administered on days 10 and 11 after the last study injection, commensurate with the final study visit. A Beck score of more than 18 was chosen based on the data from Beck *et al.* (7) to separate those patients with moderately to markedly increased depression scores from those with normal or only minimally elevated scores (Beck score ≤18). Antidepressant use was recorded for each patient and was categorized as current use or nonuse. Prior use of antidepressants was not recorded.

Anthropometric and functional indices

Weight and height were measured on all subjects and expressed as body mass index (BMI) as well as percent IBW based on Metropolitan Life Insurance Height and Weight Tables (8). Lean body mass was determined by dual energy X-ray absorptiometry (6). Karnofsky score was also determined for each patient to assess overall functional status (9).

Immune function

CD4 count (flow cytometry; Becton-Dickinson Immunocytochemistry Systems, San Jose, CA) and viral load (Amplicor HIV-1 Monitor Test; Roche Molecular Systems, Branchburg, NJ) were determined for each patient.

Statistical Analysis

The Shapiro-Wilk test was used to test for normality of the Beck score. Comparison of the Beck score in eugonadal men *vs.* hypogonadal men with AIDS wasting was made using the median rank test. Univariate and multivariate correlation analyses were performed among the entire group of subjects at baseline, before testosterone administration. In the multivariate analysis, the Beck score was considered the dependent variable, and testosterone, BMI, CD4, viral load, baseline use of antidepressants, and functional status were considered as independent variables. In addition, comparison was made between subjects with a Beck score more than 18 and those less than or equal to 18 at baseline by the median rank test.

Among those participating in the longitudinal study, the Beck score was compared between randomization groups by the median rank test. The change in the Beck score was determined within each group by paired *t* test. The change in antidepressant use was compared by χ^2 analysis between the treatment groups. In a stepwise regression analysis, the change in Beck score was again considered the dependent variable and changes in BMI, estradiol, lean body mass, antidepressant use, exercise history, and Karnofsky score were tested for inclusion in the model.

Results

Comparison of hypogonadal and eugonadal patients

The Beck score exhibited a normal gaussian distribution among the HIV-infected patients at baseline ($W = 0.96$, $P < W = 0.16$, where $P < 0.05$ indicates nonnormally distributed data). Although weight, CD4, viral load, and Karnofsky status were equivalent between the groups, the Beck score was significantly higher in the hypogonadal subjects compared with the eugonadal subjects (Table 1, Fig. 1). Baseline antidepressant use did not differ between the hypogonadal patients (11 of 51 patients) and eugonadal patients (5 of 10 patients) ($P = 0.11$). Antidepressant use in the hypogonadal men included amitryptiline (2), imipramine (1), doxepin (1), fluoxitene (2), nefazadone (3), and sertraline (2) at baseline. Antidepressant use in the eugonadal subjects included fluoxitene (1), amitryptiline (1), sertraline (1), doxepin (1), and desipramine (1).

The mean serum-free testosterone concentration was significantly reduced at baseline in the hypogonadal (free testosterone < 12.0 pg/mL at screening) compared with the eugonadal HIV-infected subjects (free testosterone > 12.0 pg/mL at screening) (12.5 ± 0.9 *vs.* 22.1 ± 1.5 pg/mL, $P <$ 0.001). The free testosterone level was not below 12.0 pg/mL on repeat testing at baseline in all hypogonadal patients.

TABLE 1. Comparison of hypogonadal and eugonadal subjects

	Hypogonadal (n = 51)	Eugonadal (n = 10)	*P* value	Normal range
Age (yr)	41.6 ± 1.1	41.3 ± 2.9	0.86	NA
IBW (%)	93.7 ± 1.7	92.4 ± 3.1	0.19	NA
BMI (kg/m^2)	21.5 ± 0.4	20.9 ± 0.8	0.52	NA
Viral load (copies)	191,151 ± 36,483	111,920 ± 37,766	0.72	Undetectable
CD4 (cells/mm^3)	175 ± 30	205 ± 91	0.49	>800
Beck score	15.5 ± 1.1	10.6 ± 1.4	0.02	<10
Karnofsky score	82 ± 2	88 ± 4	0.17	100
Total testosterone (ng/dL)	427 ± 34	738 ± 74	<0.01	270–1070
Free testosterone (pg/mL)	12.5 ± 0.9	22.1 ± 1.5	<0.001	12.0–35.0
Estradiol (pg/mL)	12.0 ± 1.1	14.2 ± 2.6	0.46	5.6–50.1
SHBG (nmol/L)	34.0 ± 3.5	44.0 ± 7.9	0.11	6.0–44.0

NA, Not applicable.

SHBG levels did not differ between the groups (Table 1) and correlated with total (r = 0.47, $P < 0.001$), but not free testosterone (r = −0.09, $P = 0.49$).

Comparison by Beck score

Subjects were divided into two groups, those with a Beck score more than 18 and those with scores less than or equal to 18. Total and free testosterone levels were significantly lower among subjects with a Beck score more than 18, whereas no differences in weight, CD4, viral load, Karnofsky score, or SHBG were seen (Table 2). For example, 57% of men with a Beck score more than 18 (moderate to severe depression) *vs.* 24% of men with a Beck score less than or equal to 18 (no or minimal depression) were hypogonadal by free testosterone level ($P = 0.01$) by χ^2 analysis. Forty percent of HIV-infected patients with a Beck score more than 18 were receiving antidepressant medications, whereas as 26% of patients with a Beck score less than 18 were receiving antidepressant medications; however, this difference was not significant.

Multivariate regression analyses

The Beck score correlated with total (r = −0.43, $P < 0.001$) and free testosterone (r = −0.41, $P < 0.01$) but not estradiol levels (r = −0.15, $P = 0.24$). In a multivariate regression analysis with the Beck score as the dependent variable and BMI, viral load, CD4, baseline antidepressant use, age, and Karnofsky score as the independent variables, the serum-free testosterone level remained significant ($P < 0.01$). The only other significant variable in the model was Karnofsky score ($P = 0.03$). The overall R^2 for the model was 0.30. Using a similar model, total testosterone also remained significant ($P < 0.001$). Again, the only other significant variable in the model was Karnofsky score ($P = 0.03$, overall $R^2 = 0.35$).

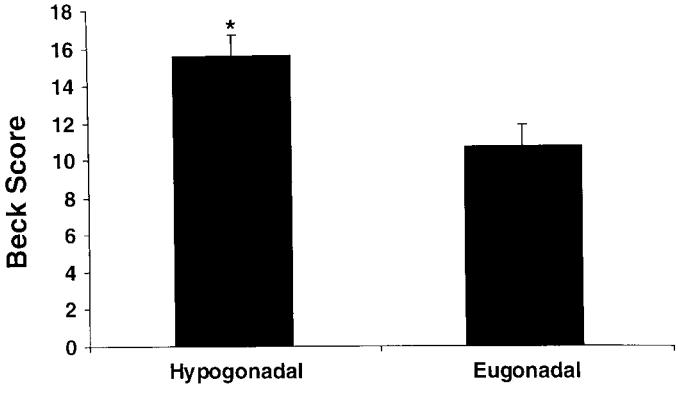

FIG. 1. Comparison of Beck score in hypogonadal (N = 51) and eugonadal (N = 10) HIV-infected patients. * $P = 0.02$ by the Median Rank Test.

Effects of testosterone administration

Fifty-two hypogonadal subjects were randomized to receive testosterone therapy (300 mg im) or placebo administration every 3 weeks for 6 months. Thirty-nine patients completed the study (6). Three deaths occurred in the testosterone group, and four deaths occurred in the placebo group. Four withdrawals occurred in the testosterone group, and five withdrawals occurred in the placebo group. No patient dropped out or was discontinued for adverse effects related to testosterone. In a prior analysis, we have demonstrated no significant differences in the dropout or death rates between the groups (6). In addition, one additional patient in the testosterone group and one in the placebo group did not fill out the questionnaire, bringing the total number of patients evaluable for change in Beck score to 21 in the testosterone group and 18 in the placebo group. All available baseline and end of study information were used in the analysis. Total (482 ± 52 *vs.* 416 ± 56 ng/dL, $P = 0.40$, testosterone- *vs.* placebo-treated) and free testosterone (14.0 ± 1.3 *vs.* 12.1 ± 1.4 pg/mL, $P = 0.32$) levels were not different at baseline among the patients who completed the study (n = 39).

The Beck score was not different between the treatment groups at baseline [14.8 ± 1.5 *vs.* 16.3 ± 1.6 ($P = 0.85$) for all patients; 15.0 ± 1.5 *vs.* 13.4 ± 1.6 ($P = 0.48$) for patients who completed the study, n = 39] (testosterone- *vs.* placebo-treated, respectively). The Beck score decreased by 5.8 ± 1.3 points to 9.2 ± 1.4 in the testosterone-treated subjects ($P < 0.001$) but did not change significantly, decreasing 2.7 ± 1.3 points to 10.8 ± 1.6 ($P > 0.05$) in the placebo-treated patients (Fig. 2). The corresponding end of study free testosterone levels were 33.9 ± 4.3 *vs.* 14.4 ± 1.4 pg/mL (normal range, 12.0–35.0 pg/mL) in the testosterone- and placebo-treated groups, respectively. The change in Beck score was highly related to the change in weight among the 39 subjects in the randomized study (r = 0.65, $P < 0.0001$). A positive correlation between change in weight and Beck score was seen among the testosterone- (r = 0.49, $P < 0.05$) and placebo-treated patients (r = 0.78, $P < 0.001$), but weight gain was greater in the testosterone-treated subjects ($P < 0.05$). Estra-

TABLE 2. Comparison of subjects by Beck score

	Beck score ≤18 (n = 38)	Beck score >18 (n = 21)	*P* value	Normal range
Age (yr)	41.7 ± 1.4	41.8 ± 1.7	0.71	NA
IBW (%)	95.5 ± 2.0	90.6 ± 2.4	0.21	NA
BMI (kg/m^2)	21.7 ± 0.5	20.8 ± 0.6	0.48	NA
Viral load (copies)	193,070 ± 40,847	171,830 ± 54,585	0.42	Undetectable
CD4 (cells/mm^3)	195 ± 38	155 ± 46	0.48	>800
Beck score	10.1 ± 0.6	23 ± 0.9	<0.0001	>10
Karnofsky score	87 ± 2	77 ± 4	0.58	100
Total testosterone (ng/dL)	560 ± 39	340 ± 52	0.03	270–1070
Free testosterone (pg/mL)	16.5 ± 1.0	10.1 ± 1.4	<0.01	12.0–35.0
SHBG (nmol/L)	35.9 ± 4.1	35.6 ± 5.6	0.60	6.0–44.0

NA, Not applicable.

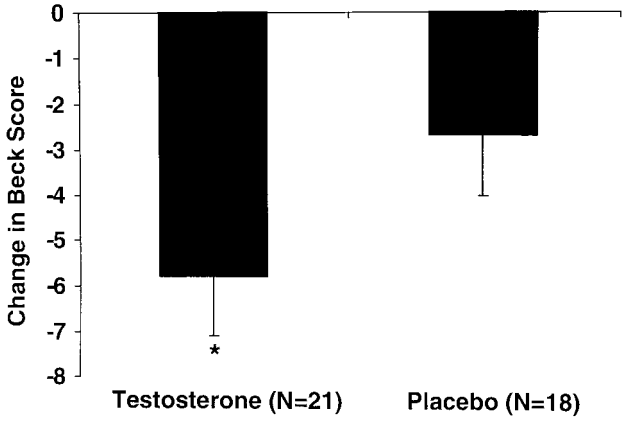

FIG. 2. Change in Beck score among hypogonadal subjects by testosterone treatment groups. N refers to subjects who completed the study in each group and were available for analysis. $P < 0.001$ in the testosterone treated group and $P > 0.05$ in the placebo-treated group by paired t-test.

diol levels increased in the testosterone-treated patients compared with the placebo-treated patients (+4.2 *vs.* −0.7 pg/mL, $P = 0.04$), but were not correlated with the change in Beck score. Antidepressant use did not differ between treatment groups either at baseline (6 of 21 testosterone-treated *vs.* 2 of 18 placebo-treated patients, $P = 0.25$) or end of study (5 of 21 *vs.* 3 of 18, $P = 0.70$) among the patients completing the study (n = 39). Furthermore, antidepressant use did not change significantly between the groups during the study (one patient in the placebo-treated group began sertraline, and one patient in the testosterone group discontinued doxepin, $P = 0.16$). In a regression analysis, controlling for change in weight, lean body mass by dual energy X-ray absorptiometry, free testosterone, antidepressant use, estradiol levels, and Karnofsky score, only the change in weight remained significant ($P < 0.01$). No differences in death, opportunistic infections, or protease inhibitor use were observed between the treatment groups (6).

Discussion

In this study, we compare depression scores among age- and weight-matched hypogonadal and eugonadal men with AIDS wasting. The Beck depression score was significantly greater in the hypogonadal patients, and the relationship between testosterone and Beck score remained highly significant after controlling for weight, immune function, age, antidepressant use, and performance status in a multivariate regression analysis. Importantly, the Beck score decreased significantly among the hypogonadal men randomized to receive testosterone, but not among patients receiving placebo. These data suggest an important relationship between gonadal function and depression score among men with AIDS wasting and demonstrate a benefit of testosterone administration to reduce depression score in hypogonadal men with AIDS wasting.

Hypogonadism is highly prevalent among men with AIDS. In early studies, 50% of men with AIDS demonstrated hypogonadism (1, 10). In recent studies conducted after the introduction of more effective antiviral therapy, a lower but still significant percentage (17%) of HIV-infected men demonstrate hypogonadism (11). An increased prevalence of hypogonadism (25%) is observed among HIV-infected men with wasting, despite newer antiviral regimens (11). In the majority of cases (75%), hypogonadism is related to inadequate gonadotropin secretion among HIV-infected men, which may result from illness *per se*, weight loss, or other factors (12). In this study, hypogonadism was defined based on a screening free testosterone level below the established normal range for the assay. We used an analog assay to measure free testosterone. In prior studies, Winter *et al.* (13) have shown that SHBG levels may correlate with the free testosterone by the analog-free testosterone assay, suggesting that determination of free testosterone by this methodology may be influenced by changes in SHBG. To the contrary, we found no relationship between serum-free testosterone and SHBG, suggesting no such effect in our patients. However, additional studies are needed to determine the relationship between true bioavailable testosterone and depression indices among HIV-infected patients.

Rabkin *et al.* (2) have previously investigated mood dysfunction among relatively androgen-deficient men with HIV disease (testosterone <400 ng/dL, CD4 count <400 cells/mm^3). Sixty-five percent of relatively androgen-deficient HIV-infected men reported mood disturbances by the Hamilton Depression Rating Scale. However, depression rating and mood score were not directly compared between eugonadal and hypogonadal HIV-infected men in prior studies, nor were the potentially confounding effects of disease status, weight, and other variables assessed in determining the relative role of gonadal function in depression status.

We demonstrate a significantly greater Beck score among hypogonadal compared to age, weight, and disease status-matched eugonadal HIV-infected men. Viral load and CD4 count, as well as Karnofsky score, were not significantly different between the groups, suggesting that disease status was equivalent between the groups. Furthermore, the inverse association between Beck score and serum testosterone concentration remained significant in a multivariate analysis, accounting for potential confounding variables including immune parameters, weight, performance status, and antidepressant use. The relationship between depression score and testosterone concentration demonstrated in this study of HIV-infected men with wasting is similar to that demonstrated by Barrett-Connor *et al.* (4) in non-HIV-infected men, in which the Beck Depression Inventory was also used as a primary end point. However, the depression scores in both groups of HIV-infected patients were generally higher than that of otherwise healthy, relatively older men reported by Barrett-Connor *et al.* (4).

In addition, we divided the patients based on a Beck score less than or equal to 18 or more than 18, indicative of moderate to severe depression, and compared clinical end points in the two groups (9). Significantly lower testosterone concentrations were seen among men with a Beck score more than 18 compared with patients with a score less than or equal to18. For example, 57% of men with a Beck score more than 18 (moderate to severe depression) *vs.* 24% of men with a Beck score less than or equal to 18 (no or minimal depression) were hypogonadal by free testosterone level ($P = 0.01$

by χ^2 analysis). In contrast, no differences in immune parameters, weight, or performance status were seen in the comparison by Beck score and again the differences in testosterone concentration remained significant in a multivariate regression analysis controlling for these factors.

The Beck score decreased significantly in response to testosterone administration in this 6-month randomized study. Antidepressant use did not change significantly, although one of the testosterone-treated patients was able to discontinue antidepressant therapy, whereas a placebo-treated patient required initiation of antidepressant use during the study. Mood was shown to improve in a prior open label study of testosterone administration in relatively androgen-deficient men with HIV infection (2, 14). However, testosterone administration (400 mg every 2 weeks) in prior studies was supraphysiological and approximately twice the recommended dosing for hypogonadal men. Therefore, this is the first randomized, placebo-controlled study of the effects of physiologic testosterone replacement on depression indices in hypogonadal men with AIDS wasting.

Potential mechanisms to explain the observation of improved depression score in response to androgen therapy include a direct effect of androgen therapy on higher mood centers, systemic or localized conversion to estrogen (15), or improvement in weight, muscle mass or functional status, which could indirectly improve mood. Testosterone levels often peak in the supraphysiological range after im injection and may fall to subtherapeutic levels before the subsequent dose. We chose to measure end of study testosterone levels 10 or 11 days after the last injection in all patients, at the midpoint of the dosing cycle. Although the free testosterone level was significantly increased in the testosterone- *vs.* placebo-treated patients, the testosterone level in the actively treated patients was, on average, in the normal range. The Beck inventory was administered simultaneously with the assessment of the end of treatment testosterone level. It is possible that the score may vary acutely with testosterone levels within a dosing cycle, but this was not assessed in our patients.

No differences in opportunistic infection rate or protease inhibitor use were observed between the groups to account for the changes in depression score. Although estradiol levels increased in the response to testosterone administration, the change in Beck score did not correlate with estrogen. In contrast, Beck score was significantly associated with change in weight in response to testosterone administration. In a stepwise regression analysis including change in testosterone and estrogen concentrations, antidepressant use, lean body mass, weight, and Karnofsky status, the change in weight was the most significant single predictor of change in Beck score, accounting for 35% of the variation in Beck score. These data suggest that the effects of testosterone administration on depression indices in HIV-infected patients may be indirect and a result of increased weight in such patients. In contrast, endogenous testosterone concentration was highly predictive of depression score, independent of weight in the cross-sectional comparison of weight-matched eugonadal and hypogonadal men.

Although we did not perform a structured interview to assess for clinical depression in our subjects, previous studies of the Beck show that it is a useful and reliable index of depression status. The Beck Depression Inventory covers six of nine criterion for depression by the Diagnostic and Statistical Manual of Mental Disorders IIIR (16). The Beck score has been shown to correlate well with clinical depression rating in numerous studies, with correlation coefficient values ranging from 0.55–0.96, with a mean of 0.72 (7). Although this relationship has not been tested specifically in HIV-infected men, these data nonetheless suggest that the Beck score is a valid, well-standardized tool to assess depression score. In particular, the use of each patient as his own control in the randomized portion of the study minimizes potential variability associated with Beck scores. However, additional studies of the clinical effects of testosterone on depression and other psychiatric end points in hypogonadal men with AIDS are needed to better define the effects of testosterone on clinical depression status in such patients.

In this study, we demonstrate that the Beck score is significantly increased in hypogonadal men compared with eugonadal age- and weight-matched HIV-infected men with wasting. In response to physiologic testosterone administration, the Beck score improved significantly in the hypogonadal men, although this effect seemed to result primarily from changes in weight. Our data suggest that gonadal function is related to depression status in HIV-infected men and that a positive effect on depression score is yet another benefit to physiologic testosterone replacement in hypogonadal men with AIDS wasting. Additional studies are needed to investigate the effects of physiologic testosterone replacement on clinical depression indices in this population. In addition, more studies are needed to determine the effects of testosterone replacement on depression indices in HIV-infected men without wasting and to determine the potential effects of testosterone administration in depressed, but eugonadal, HIV-infected men.

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