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Serum Dihydrotestosterone and Testosterone Concentrations in Human Immunodeficiency Virus-Infected Men With and Without Weight Loss

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ABSTRACT: Weight loss is an important determinant of disease outcome in human immunodeficiency virus (HIV)-infected men. Others have suggested that a defect in dihydrotestosterone (DHT) generation contributes to weight loss in HIV-infected men. To determine whether DHT levels correlate with weight loss independently of changes in testosterone levels, we prospectively measured serum total- and free-testosterone and DHT levels in 148 consecutive HIV-infected men and 42 healthy men. Thirty-one percent of HIV-infected men had serum testosterone levels less than 275 ng/dL, the lower limit of the normal male range; of these, 81% had normal or low LH and FSH levels (hypogonadotropic), and 19% had elevated LH and FSH levels (hypergonadotropic). Overall, serum testosterone, free-testosterone, and DHT levels were lower in HIV-infected men than in healthy men, but serum DHT-to-testosterone ratios were not significantly different between the two groups. Serum total- and free-testosterone levels were lower in HIV-infected men who had lost 5 lb or more of weight in the preceding 12 months than in those who had not lost any weight. Serum DHT levels and DHT-to-testosterone ratios did not differ between those who had lost weight and those who had not. Serum testosterone and free-testosterone levels, but not DHT levels, correlated with weight change and with Karnofsky performance status. We also performed a retrospective analysis of data from a previous study in which HIV-infected men with serum testosterone levels less than 400 ng/dL had been treated with placebo or testosterone patches designed to nominally release 5 mg testosterone over 24 hours. Serum testosterone-to-DHT ratios did not change after testosterone treatment. Changes in fat-free mass were correlated with changes in both serum testosterone ($r = 0.42$, $P = 0.018$) and DHT ($r = 0.35$, $P = 0.049$) levels. Serum total- testosterone and DHT levels were highly correlated with one another, and when the change in serum testosterone was taken into account, serum DHT levels no longer showed a significant correlation with change in fat-free mass. We conclude that DHT levels are lower in HIV-infected men than in healthy men but that neither DHT levels nor DHT-to-testosterone ratios correlate with weight loss. During testosterone treatment, serum DHT levels increase proportionately, but the increments in serum testosterone correlate with the change in fat-free mass. Our data do not support the hypothesis that a defect in DHT generation contributes to weight loss in HIV-infected men independently of changes in testosterone levels; it is possible that such a defect might exist in HIV-infected men with more severe weight loss.

Key words: Testosterone, DHT, AIDS wasting, HIV-associated weight loss, 5-α-reductase.

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Muscle wasting during the course of human immunodeficiency virus (HIV) infection impairs mobility and quality of life, increases utilization of health care resources, and is associated with poor disease outcome (Chlebowski et al, 1989; Kotler et al, 1989; Hellerstein et al, 1990; Grunfeld and Feingold, 1992; Gunter et al, 1992; Linden et al, 1992; Nahlen et al, 1993; Sellmeyer and Grunfeld, 1996). Androgen deficiency may contribute to the multifactorial pathophysiology of the AIDS wasting syndrome (Coodley et al, 1994; Dobs et al, 1996; Grinspoon et al, 1996). There is a high prevalence of low testosterone levels in HIV-infected men (Dobs et al, 1988; Aron, 1989; Croxon et al, 1989; DePaepe et al, 1989; Meremich et al, 1990; Villete et al, 1990; Raffi et al, 1991; Salehian et al, 1999). Serum testosterone levels correlate inversely with weight loss (Coodley et al, 1994) and directly with exercise capacity in HIV-infected men (Grinspoon et al, 1996). Serum testosterone levels are lower in HIV-infected men who progress to AIDS than in those who do not (Salehian et al, 1999). Physiologic testosterone replacement increases lean body mass and muscle strength in healthy, hypogonadal men (Brodsky et al, 1996; Katznelson et al, 1996; Bhasin and Bremner, 1997; Bhasin et al, 1997). This has led to speculation that testos-

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terone replacement in HIV-infected men with weight loss might also produce meaningful increases in lean body mass and muscle function (Bhasin and Bremner, 1997; Cofrancesco et al, 1997; Bhasin et al, 1998; Grinspoon et al, 1998).

Testosterone is converted in the body to two metabolites, estradiol and dihydrotestosterone (DHT), that mediate androgen action in some tissues (Swerdloff and Wang, 1998). Testosterone effects on the prostate and the sebaceous gland in the skin require its conversion to DHT. The enzyme 5-α-reductase that converts testosterone to DHT is expressed in the muscle at low levels (Noormington and Russell, 1992; Russell and Wilson, 1994); however, we do not know whether reduction of testosterone to DHT by 5-α-reductase is obligatory for mediating its anabolic effects on the muscle.

Sattler et al (1998) reported on the basis of a retrospective analysis of HIV-infected men that serum DHT levels are lower and testosterone-to-DHT ratios higher in patients with the AIDS wasting syndrome and proposed that a defect in DHT generation may impair androgen action on the muscle and, therefore, contribute to muscle atrophy in these patients. The objective of the present study was to prospectively test this hypothesis in a larger, more representative sample of HIV-infected men. The hypothesis proposed by Sattler et al (1998) has therapeutic relevance because if 5-α reduction of testosterone were obligatory for mediating testosterone's anabolic effects on the muscle, then testosterone administration is unlikely to produce the desired increase in muscle mass in HIV-infected men. In that case, it would be more rational to administer DHT to achieve the anabolic effects in HIV-infected men.

We conducted two experiments to test this hypothesis. In the first experiment, we correlated serum testosterone and DHT levels with weight loss and HIV-disease markers in 148 consecutive HIV-infected men who attended our HIV clinic. In the second study, we administered replacement doses of testosterone to HIV-infected men with low testosterone levels (Bhasin et al, 1998), measured the relative increments in testosterone and DHT, and correlated these increments to changes in lean body mass. The Sattler hypothesis predicted that serum DHT but not testosterone would correlate with weight loss. In addition, it predicted that testosterone administration to HIV-infected men would be associated with a proportionately smaller increase in DHT levels than in testosterone levels. Furthermore, it predicted that the increments in DHT but not testosterone levels would correlate with increases in lean body mass.

Methods

Patients

The participants were 148 HIV-infected men, 18–66 years of age, who attended our HIV clinic. The patients were ambulatory and free of acute illness, fever, and diarrhea, defined as four or more stools each day with a recent increase in frequency of stools. Patients with cancer were included if they had stable disease and were not receiving chemotherapy or radiotherapy. CD4+ and CD8+ T lymphocyte counts, plasma HIV-RNA copy number, and anti-retroviral therapy were recorded. Patients receiving other anabolic agents such as Megace®, human growth hormone, insulin-like growth factor-1, marinol, and androgenic steroids were excluded. Patients receiving drugs that affect testosterone secretion or metabolism, such as ketoconazole or megesterol acetate, were also excluded.

We considered a 5-lb weight change over the preceding 6 months to be "significant weight change"; we felt that weight change greater than this amount was less likely to be due to measurement error in the clinic setting. However, all the HIV-infected patients who met this definition of significant weight change had experienced 5% or more weight loss.

Healthy Men

The control population consisted of 42 healthy men, 23–66 years of age. All subjects were free of disease; had normal testosterone, LH, and FSH levels; and were not on any medication.

Hormone Measurements

Serum total-testosterone levels were measured in a direct radioimmunoassay using iodinated testosterone as tracer (Bhasin et al, 1996; Sinha-Hikim et al, 1998). The sensitivity of the testosterone assay is 0.6 ng/dL, and the cross-reactivity of DHT in this assay is less than 1%. Free-testosterone levels were measured by an equilibrium dialysis method Sinha-Hikim et al, 1996). For the DHT assay, serum samples were extracted by a mixture of hexane and ethyl acetate and were subjected to celite chromatography. The fractions eluting with 5% ethyl acetate in isooctane (v/v) were dried, resuspended in the assay buffer, and assayed. The cross-reactivity of testosterone in the DHT assay was less than 1%. The sensitivity of the DHT assay was 2.5 ng/dL. Serum LH and FSH levels were measured by two-site, directed immunofluorometric assays (Bhasin et al, 1996). The cross-reactivity of other pituitary hormones and of free alpha subunit in the LH and FSH assays was less than 1%. The sensitivities of the LH and FSH assays were 0.05 and 0.1 U/L. Plasma HIV–RNA copy number was measured by reverse-transcription and polymerase chain reaction.

Statistical Analysis

Continuous data are reported as mean ± SEM or median (25th and 75th percentiles), and categorical data are reported as frequency tabulations. All variables were examined to determine their distribution. Variables that did not meet the assumption of a normal distribution were analyzed by using nonparametric tests. *T*-tests for independent groups or the Mann-Whitney test were used to compare hormone levels between healthy men and HIV-infected men. Hormone levels in HIV-infected men who had lost weight and those who had not were compared by Student's *t*-test for unpaired samples or by the Mann-Whitney test. Serum testosterone and DHT levels were correlated with weight change in the preceding 12 months by Pearson correlation test.

Table 1. *Baseline characteristics of the participants**

Variable	Healthy men (n = 42)	HIV-infected men (n = 148)	HIV-infected men with weight loss (n = 25)	HIV-infected men without weight loss (n = 89)
Age (years)	31 ± 2 (20–66)	40 ± 1 (23–66)	43 ± 2 (26–61)	40 ± 2 (23–66)
Race				
Caucasian	27 [64%]	48 [32%]	8 [32%]	28 [31%]
Black	3 [7%]	39 [26%]	3 [12%]	28 [31%]
Hispanic	6 [14%]	56 [38%]	12 [48%]	30 [34%]
Other	6 [14%]	5 [3%]	2 [8%]	3 [3%]
Weight (kg)	79.3 ± 1.6 (60.0–109.0)	72.0 ± 3.0 (41.4–157.0)	64.3 ± 5.1 (41.4–84.7)	74.7 ± 1.8 (49.0–157.0)
HIV-RNA copy number (10^3 copies)/ml	NA	51.1 (0.0001–949.5)	54.2 (0.0001–258.0)	52.8 (0.0001–949.5)
CD4 T cell count/cmm	NA	180 ± 16 (0–822)	150 ± 40 (5–642)	188 ± 20 (0–822)
CD8 T cell count/cmm	NA	756 ± 44 (38–3,297)	625 ± 71 (38–1,760)	806 ± 64 (78–3,297)
Weight loss as a percentage of baseline weight	NA	0.5 ± 0.7†	11.3 ± 1.2 (5–29)	NA
Weight loss	NA			
≥5%		25 [22%]‡	25 [100%]	0
>10%		8 [7%]‡	8 [32%]	0
AIDS-defining illness	NA	89 [60%]	22 [88%]	46 [52%]

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NA, not applicable.
* Data are given as mean ± SEM (range), except for data on race, weight loss, and AIDS-defining illness, which are given as number [percentage].
† This represents the mean weight change in 114 patients for whom weights were available.
‡ Of 114 men for whom weight change data were available.

P values of less than 0.05 in two-tailed tests were considered statistically significant.

Results

Patients

The patients were 148 consecutive HIV-infected men who attended our HIV clinic (Table 1). They were 23–66 years of age and weighed 41.4–157.0 kg. Most HIV-infected men were receiving anti-retroviral therapy consistent with the prevalent practice. There was considerable heterogeneity in the HIV–RNA copy number and in CD4+ and CD8+ T cell counts in the HIV-infected men. The healthy men ranged in age from 20 to 66 years (Table 1).

Objective weight data were available in the clinic records of 114 patients. Of these, 25 (22%) had lost 5 lb or more of weight in the preceding 12 months. Seventeen out of 25 had experienced weight loss of 5–10%, five had lost 11–20%, and three had lost greater than 20%. Thus, weight loss in 7% of 114 men met or exceeded the original CDC (Centers for Disease Control) threshold for defining AIDS wasting.

Forty-six out of 89 men without weight loss had suffered from one or more AIDS-defining illnesses (Table 1); of the 25 men with weight loss, 22 had suffered an AIDS-defining illness. Thirty-three out of 89 men without weight loss and 13 out of 25 men with weight loss had experienced an opportunistic infection.

The survey was conducted in 1996, before the advent of highly active anti-retroviral therapy. Seventy-five out of 89 men without weight loss were receiving anti-retroviral therapy; only two patients in this group were on protease inhibitors. Of the 25 men with weight loss, 24 were on anti-retroviral therapy; none were on protease inhibitors.

Hormone Levels

Serum testosterone levels (median [25th, 75th percentiles]) were lower in HIV-infected men than in healthy controls (401 [227, 560] vs. 563 [422, 767] ng/dL; HIV-infected men vs. controls, $P < 0.0011$; Fig. 1, panel A, left column). Serum total-testosterone levels (median [25th, 75th percentiles]) were lower in HIV-infected men who had lost weight than in those who had not (241 [144–393] vs. 428 [285–627] ng/dL; $P < 0.001$; Fig. 1, panel A, right column). Forty-seven (32%) HIV-infected men had serum testosterone levels in the hypogonadal range, defined as serum testosterone level less than 275 ng/dL; of these, 9 (19%) had elevated LH and/or FSH levels (hypergonadotropic), and 38 (81%) had either low or normal LH and FSH levels (hypogonadotropic).

Serum free-testosterone levels (median [25th, 75th percentiles]) were significantly lower in HIV-infected men than in healthy controls (58 [40, 70] vs. 83 [66, 92], $P < 0.001$; Fig. 1, panel B, left column). Serum free-testosterone levels were lower in HIV-infected men who had lost weight than in those who had not (40 [30, 55] vs. 60 [48, 70] pg/mL; median [25th, 75th percentiles] $P < 0.001$; Fig. 1, panel B, right column).

Serum DHT levels (median [25th, 75th percentiles]) were lower in HIV-infected men as compared with those

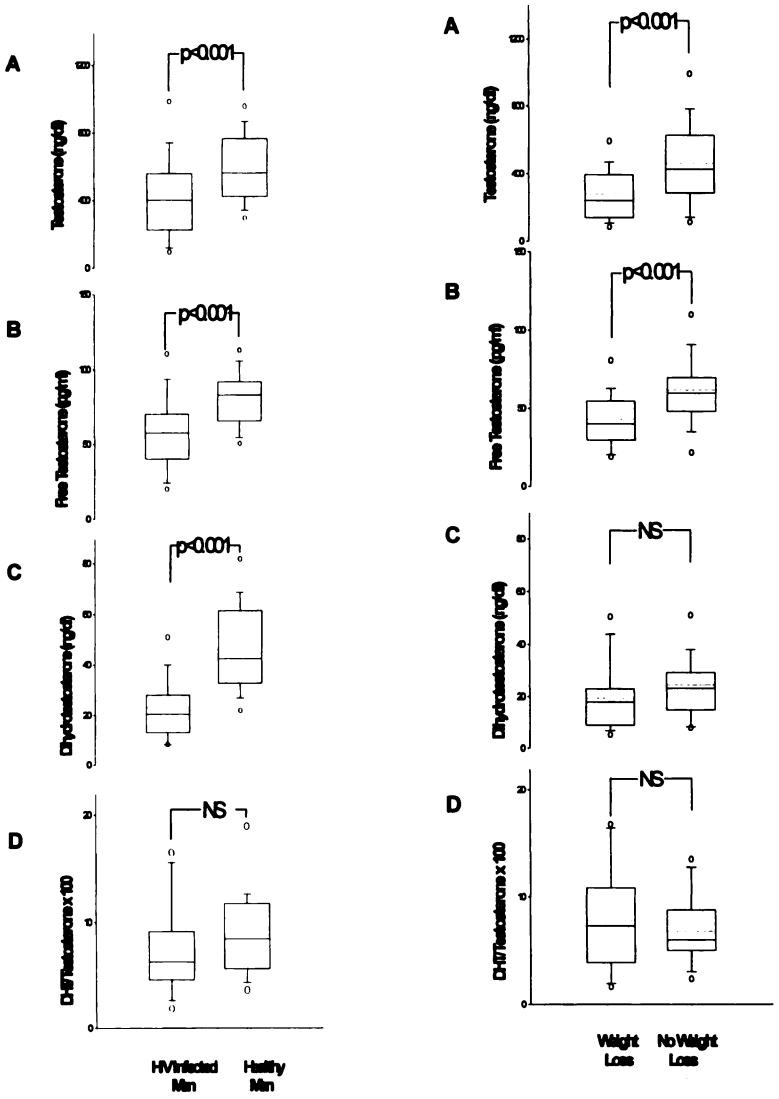

FIG. 1. Left column: serum testosterone **(panel A)**, free-testosterone **(panel B)**, and DHT **(panel C)** levels and DHT-to-testosterone ratio **(panel D)** in HIV-infected (n = 148) and healthy (n = 42) men. The box represents the 25th and 75th percentile values, the horizontal line inside the box represents the median value, the dotted line inside the box represents the mean, and the vertical bars represent the standard errors. The open circles outside the box denote the 10th and 90th percentile values. Because serum hormone levels were not normally distributed, the levels in healthy and HIV-infected men were compared by using the nonparametric Mann-Whitney test. To convert the numbers to SI units, multiply testosterone levels in ng/dL by 0.034 to obtain concentrations in nmol/L, free-testosterone levels in pg/mL by 0.34 to obtain concentrations in pmol/L, and DHT levels in ng/dL by 0.034 to obtain concentrations in nmol/L. DHT-to-testosterone ratio was calculated by dividing serum DHT levels by serum testosterone levels and expressing the result as a percentage. P values for the comparison of HIV-infected and healthy men are shown above each panel. Right column: serum testosterone **(panel A)**, free-testosterone **(panel B)**, and DHT **(panel C)** levels and DHT-to-testosterone ratio in HIV-infected men who had experienced more than a 5-lb weight loss and those who had experienced no weight loss or had lost less than 5 lb. Accurate information about weight change was available for 114 HIV-infected men; of these, 25 had experienced weight loss of 5 lb or more. Eighty-nine HIV-infected men had experienced no weight loss. DHT-to-testosterone ratio was calculated by dividing serum DHT levels by serum testosterone levels and expressing the result as a percentage. P values for the comparison of HIV-infected men with weight loss with those without weight loss are shown above each panel.

of healthy men (21 [13, 28] vs. 40 [31, 60] ng/dL; $P < 0.001$; Fig. 1, panel C, left column). However, serum DHT-to-testosterone ratios were not significantly different between HIV-infected men and healthy controls (6% [5%, 9%] vs. 8% [5%, 12%], median [25th, 75th percentile]; $P = 0.24$; Fig. 1, panel D, left column). Serum DHT levels were not significantly different between those who had lost weight and those who had not (18 [9, 23] vs. 23 [15, 29] ng/dL, $P = 0.125$; Fig. 1, panel C, right column). Serum DHT-to-testosterone ratios were not significantly different between HIV-infected men with weight loss and those without weight loss (Fig. 1, panel D, right column).

We also compared the hormone levels in HIV-infected men with greater than 10% weight loss (the threshold used in the original CDC definition of AIDS wasting syndrome) with those in HIV-infected men with no weight

loss or with less than 10% weight loss. Serum testosterone (165 [113, 295] vs. 403 [254, 563] ng/dL; $P = 0.009$) and free-testosterone levels (35 [24, 50] vs. 60 [41, 7]; $P = 0.021$) were significantly lower in HIV-infected men with 10% or more weight loss compared with levels in those without weight loss or with less than 10% weight loss. However, serum DHT levels were not significantly different between these two groups of HIV-infected men (19 [9, 24] vs. 21 [13, 29] ng/dL; P = NS [nonsignificant]). Serum DHT-to-testosterone ratios were higher in men with >10% weight loss than in those without weight loss or with less than 10% weight loss (8.2 [7.3, 11.4] vs. 5.7 [4.6, 8.5], median [25th, 75th percentile values]; $P = 0.161$). Because fewer men had lost 10% or greater weight, the power of this analysis at alpha = 0.05 was less than the desired power of 0.8.

Serum total-testosterone levels were significantly correlated with percentage weight change in the preceding 12 months ($r = -0.23$; $P = 0.012$; Fig. 2A) and with Karnofsky performance scores ($r = 0.219$; $P = 0.0096$). There was a good correlation between total- and free-testosterone levels ($r = 0.65$; $P < 0.0001$). Free-testosterone levels also correlated with percentage weight change ($r = -0.186$; $P = 0.048$, Fig. 2B) and with Karnofsky performance scores ($r = 0.248$; $P = 0.0037$). DHT levels were significantly correlated with total-testosterone ($r = 0.482$; $P < 0.0001$) and free-testosterone ($r = 0.457$, $P < 0.0001$) levels. Serum DHT levels did not significantly correlate with percentage weight change ($r = -0.123$; $P = 0.391$; Fig. 2C) or with Karnofsky performance scores ($r = 0.102$; $P = 0.452$).

Testosterone Replacement in HIV-Infected Men with Low Testosterone Levels

This was a retrospective analysis of data from a previous study (Bhasin et al, 1998) in which we administered a physiologic replacement dose of testosterone by means of a nongenital patch, Androderm®, to HIV-infected men with low testosterone levels. The details of this study have been published (Bhasin et al, 1998).

Participants in this study were HIV-infected men, 18–60 years of age, with serum testosterone less than 400 ng/dl. They were free of acute illness and were not on anabolic agents or drugs that alter testosterone secretion or metabolism. Forty-one patients were randomly assigned to one of two treatment groups: group I received two placebo patches, and group II received two testosterone patches designed to nominally deliver 5 mg testosterone over 24 hours. The two groups were similar with respect to weight, height, weight change, CD4/CD8 counts, plasma HIV-RNA copy number, and baseline testosterone levels (see Bhasin et al, 1998 for baseline characteristics of the subjects).

Serum testosterone levels did not change in the placebo group (211 + 20 vs. 218 + 25 ng/dL, baseline vs. week 12) but increased from 258 ± 50 ng/dl to 367 ± 35 ng/dl during Androderm® treatment. Serum DHT levels did not change in the placebo group but increased in the testosterone-treated men in proportion to the increase in se-

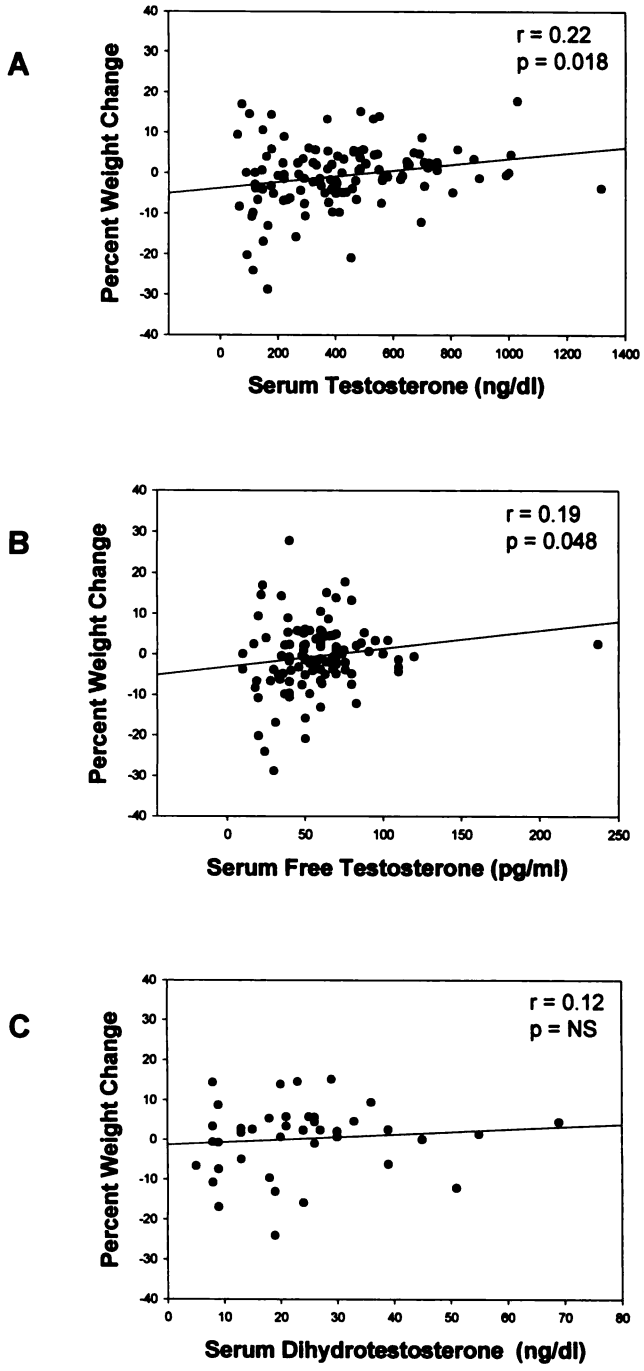

FIG. 2. Correlation of serum testosterone levels **(panel A)**, free-testosterone levels **(panel B)**, and DHT levels **(panel C)** with percentage weight change in the preceding 1 year in HIV-infected men. Positive numbers reflect weight gain and negative numbers, weight loss. r = Pearson correlation coefficient.

rum testosterone levels (baseline vs. week 12 DHT levels, 21.9 + 3.1 vs. 32.5 + 2.6 ng/dL). Serum DHT-to-testosterone ratio did not change after treatment (baseline vs. week 12 testosterone-to-DHT ratio, 9.0% [6.5%, 11%] vs. 9.5% [6.0%, 11.0%]; P = NS) and was similar to that previously reported in healthy hypogonadal men treated with the Androderm® patch (Meikle et al, 1992).

Lean body mass, measured by dual energy x-ray absorptiometry (DEXA) scan, did not change in the placebo group but increased by a mean of 1.345 kg in the testosterone-treated men (Bhasin et al, 1998). The change in fat-free mass during treatment (placebo or testosterone) correlated with the increase in serum testosterone levels (r = 0.42; P = 0.018). The change in serum DHT levels during testosterone treatment was also correlated with the change in fat-free mass (r = 0.35, P = 0.049). Serum DHT levels were significantly correlated with serum testosterone levels (r = 0.65; $P < 0.0005$). Partial correlation revealed that when change in serum testosterone levels during Androderm® treatment was taken into account, serum DHT levels did not significantly correlate with change in fat-free mass (r = 0.11; P = 0.337).

Discussion

These data confirm previous observations that serum DHT levels are lower in HIV-infected men than in healthy men (Sattler et al, 1998). However, total-testosterone levels are also lower in HIV-infected men, and DHT-to-testosterone ratios are not significantly different between HIV-infected men and healthy men. Serum testosterone, but not DHT, levels correlate with weight loss in HIV-infected men. The retrospective analysis of data from our intervention study demonstrates that the mean percentage increment in DHT levels in HIV-infected men treated with the Androderm® patch is similar to that reported previously in healthy, hypogonadal men treated with the same nongenital patch (Meikle et al, 1992). Serum DHT-to-testosterone ratios do not change during transdermal testosterone administration. Gains in lean body mass during testosterone treatment are correlated with changes in serum testosterone and DHT levels. However, serum DHT levels are highly correlated to serum testosterone levels, and partial correlation analysis reveals that when change in testosterone levels is taken into account, the change in DHT levels no longer correlates significantly with change in fat-free mass during Androderm® treatment. Therefore, our data do not support the hypothesis that a defect in DHT generation contributes to wasting in HIV-infected men. We cannot exclude the possibility that a subset of HIV-infected men with more severe wasting might have a defect in their ability to convert testosterone to DHT.

The enzyme 5-α-reductase that converts testosterone to DHT exists in two isoforms and is expressed widely in mammalian tissues (Russell and Wilson, 1994). Studies of patients with 5-α-reductase deficiency suggest that both isoforms contribute to circulating DHT levels (Imperato-McGinley et al, 1979; Imperato-McGinley et al, 1991); 46, XY male pseudohermaphrodites with inactivating mutations of the type 2 enzyme have lower but detectable serum DHT levels. Androgen effects on the prostate and the skin require the conversion of testosterone to DHT (Swerdloff and Wang, 1998).

The enzyme 5-α-reductase is expressed in the skeletal muscle (Noormington and Russell, 1992). However, we do not know whether 5-α-reduction of testosterone to DHT is obligatory for mediating its anabolic effects on the muscle. Two previously published observations are notable in this regard. First, 46, XY male pseudohermaphrodites with congenital, type I 5-α-reductase deficiency have normal muscle mass at puberty (Imperato-McGinley et al, 1979). Second, men treated with 5-α-reductase inhibitor, finasteride, do not experience muscle loss. These data suggest that conversion of testosterone to DHT is not essential for mediating its effects on the muscle.

Circulating levels of insulin-like growth factor-1 (IGF-1) are lower in HIV-infected men than in healthy men (Grinspoon et al, 1996). Because IGF-1 is a regulator of 5-α-reductase activity (Horton et al, 1993), Sattler et al (1998) speculate that lower IGF-1 concentrations in HIV-infected men are associated with a decreased conversion rate of testosterone to DHT. Our data suggest that DHT levels are decreased in proportion to the decrease in serum testosterone levels and that this is likely the result of decreased testosterone production. Our study differs from that reported previously by Sattler et al (1998) in several important ways. First, the patients included in the previous study (Sattler et al, 1998) had greater weight loss and presumably more advanced disease than those in the present study. We recruited a larger sample of consecutive patients who attended our HIV clinic. Therefore, we had a more representative cross-section of the HIV-infected men. Only 25% of the 114 HIV-infected men in our study for whom reliable weight change information was available had experienced weight loss of 5 lb or greater. It is possible that HIV-infected men with more advanced disease and severe weight loss may have a defect in 5-α-reductase activity as proposed by Sattler et al (1998); however, our data indicate that this defect is not universal among HIV-infected men.

Several ongoing studies are examining the effects of DHT administration in older men (Wang et al, 1998) and in HIV-infected men with the AIDS wasting syndrome. Although DHT may have anabolic effects of its own, DHT administration may not provide specific advantages over testosterone supplementation. The exogenous DHT

will likely lower endogenous testosterone production by inhibiting LH and FSH secretion. Because circulating estradiol in men is derived in part from peripheral aromatization of testosterone, exogenous DHT administration will result in lower estradiol levels. There is agreement that testosterone effects on bone resorption are partly mediated through testosterone's conversion to estradiol (MacGillivray et al, 1998). Because DHT does not undergo aromatization, there is concern that the resulting estradiol deficiency may produce osteoporosis in patients treated with DHT. However, androgen receptors have been demonstrated on the osteoblast cells (Colvard et al, 1989; Orwoll et al, 1991), and it is possible that DHT may have direct effects on bone formation.

There has also been concern about the long-term effects of exogenous DHT administration on the prostate (Vermeulen and Deslypere, 1985). However, earlier studies using the DHT gel reported a decrease, rather than an increase, in prostate size in older men (Schaison et al, 1991), leading to speculation that exogenous DHT, by suppressing circulating testosterone, may lower intraprostatic DHT concentrations. In one such study (Schaison et al, 1991), administration of 2.5% hydro-alcoholic gel to men 55–70 years of age for 1.8 years was associated with a 15% decrease in prostate size.

In summary, our data do not provide evidence of a universal defect in DHT generation in men with HIV-associated weight loss. Given that reduction by 5-α-reductase of testosterone is not obligatory for mediating its anabolic effects on the muscle and given the uncertainty about DHT effects on the bone and the prostate, the advantages of using DHT for androgen replacement or for its putative anabolic effects in HIV-infected men remain to be demonstrated.

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