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ARTICLE

Effects of Androgen Administration in Men with the AIDS Wasting Syndrome

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Development of successful anabolic strategies to reverse the loss of lean body mass is of critical importance to increase survival in men with the AIDS wasting syndrome. Hypogonadism, an acquired endocrine deficiency state characterized by loss of testosterone, occurs in more than half of all men with advanced HIV disease. It is unknown whether testosterone deficiency contributes to the profound catabolic state and loss of lean body mass associated with the AIDS wasting syndrome.

Objective: To investigate the effects of physiologic testosterone administration on body composition, exercise functional capacity, and quality of life in androgen-deficient men with the AIDS wasting syndrome.

Design: Randomized, double-blind, placebo-controlled study.

Setting: University medical center.

Patients: 51 HIV-positive men (age 42 ± 8 years) with wasting (body weight $< 90\%$ of ideal body weight or weight loss $> 10\%$ of baseline weight) and a free testosterone level less than 42 pmol/L (normal range for men 18 to 49 years of age, 42 to 121 pmol/L [12.0 to 35.0 pg/mL]).

Intervention: Patients were randomly assigned to receive testosterone enanthate, 300 mg, or placebo intramuscularly every 3 weeks for 6 months.

Measurements: Change in fat-free mass was the primary end point. Secondary clinical end points were weight, lean body mass, muscle mass, exercise functional capacity, and change in perceived quality of life. Virologic variables were assessed by CD4 count and viral load.

Results: Compared with patients who received placebo, testosterone-treated patients gained fat-free mass (-0.6 kg and 2.0 kg; $P = 0.036$), lean body mass (0.0 kg and 1.9 kg; $P = 0.041$), and muscle mass (-0.8 kg and 2.4 kg; $P = 0.005$). The changes in weight, fat mass, total-body water content, and exercise functional capacity did not significantly differ between the groups. Patients who received testosterone reported benefit from the treatment ($P = 0.036$), feeling better ($P =$

0.033), improved quality of life ($P = 0.040$), and improved appearance ($P = 0.021$). Testosterone was well tolerated in all patients.

Conclusions: Physiologic testosterone administration increases lean body mass and improves quality of life among androgen-deficient men with the AIDS wasting syndrome.

The AIDS wasting syndrome is characterized by loss of lean body mass out of proportion to weight [1, 2]. The few effective treatments that have been identified are short-term pharmacologic agonists. Because loss of lean body mass is associated with decreased survival in men with the AIDS wasting syndrome [3], development of therapeutic strategies to increase lean body mass is of critical importance. Half of all men with AIDS are hypogonadal [4], and serum androgen levels correlate with lean body mass among hypogonadal men with the AIDS wasting syndrome [5]. Previous studies in non-HIV-infected hypogonadal men show that androgen administration has a significant anabolic effect on body composition [6-10].

We hypothesized that loss of the potent anabolic hormone testosterone in men with the AIDS wasting syndrome may contribute to the critical loss of lean body mass. Therefore, we investigated the effects of physiologic testosterone administration in men with the AIDS wasting syndrome.

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Methods

Patients

In 1995 and 1996, 51 HIV-positive men (42 ± 8 years of age) were recruited from the multidisciplinary HIV practice at the Massachusetts General Hospital and from newspaper, television, and radio advertisements. Weight, testosterone levels, and medication history were determined at a screening assessment. To be included in the study, patients had to have decreased free testosterone levels, defined as less than 42 pmol/L at screening (normal range for men 18 to 49 years of age, 42 to 121 pmol/L [12.0 to 35.0 pg/mL]), and wasting, defined as weight less than 90% of ideal body weight or involuntary weight loss greater than 10% of baseline weight [11]. The CD4 count was not an inclusion criterion. We excluded patients with severe diarrhea (>6 stools/d); hemoglobin value less than 5.0 mmol/L (<8 g/dL); platelet count less than 50 000 cells/mm³; creatinine concentration greater than 177 μmol/L (>2 mg/dL); new opportunistic infection within 6 weeks of screening; use of testosterone, anabolic steroids, growth hormone, ketoconazole, or systemic steroid therapy within 3 months before screening; or history of prostate cancer. In addition, patients receiving antiretroviral agents, including protease inhibitors, were required to be receiving a stable regimen for at least 6 weeks before study entry. Ten patients were receiving long-term, stable therapy with megestrol acetate for at least 8 weeks before study

entry and were equally distributed between the two treatment groups (5 in the testosterone group and 5 in the placebo group). All patients gave written consent, and the study was approved by the Human Studies Committee of the Massachusetts General Hospital.

Protocol

Patients were randomly assigned to receive testosterone enanthate, 300 mg (Bio-Technology General Corp., Iselin, New Jersey), or placebo intramuscularly every 3 weeks by self-injection. Participants were stratified for weight less than or greater than 90% of ideal body weight and megestrol acetate use before randomization. Randomization was performed by the Massachusetts General Hospital Pharmacy by using a permuted block algorithm. The correspondence between patient code number and drug was generated by the study statistician; this list was available to the hospital pharmacist but not to the investigators or patients. The placebo contained sesame oil with chlorobutanol as a preservative and matched testosterone enanthate in color and consistency. The study drug was bottled by the Massachusetts General Hospital Pharmacy in containers labeled with the study name, expiration date, and patient code.

Before the first injection, participants returned within approximately 2 weeks of the screening visit for a 3-day baseline inpatient visit to the General Clinical Research Center at the Massachusetts General Hospital for hormonal, nutritional, immune function, and body composition analysis, which included assessment by dual-energy x-ray absorptiometry, bioimpedance analysis, potassium- ^{40}K isotope analysis, and measurement of urinary creatinine excretion. No patient experienced the onset of a new opportunistic infection, other complication, or substantial weight change between the screening and baseline visits. Patients were instructed on the proper technique for intramuscular injection; those who were unable to self-administer the study drug received injections every 3 weeks from the nursing staff of the General Clinical Research Center. Patients returned for an outpatient visit at 3 months for assessment of weight and determination of total-body potassium content and for a 3-day inpatient visit at 6 months; this visit was identical to the baseline evaluation. Patients also reported on response to therapy at the 6-month visit.

Baseline data from 26 patients have been reported elsewhere [5]. Subsequent study visits were timed to correspond to the midpoint between study drug injections. Study drug compliance was confirmed by history, medication diaries, outpatient injection records, empty vial counts, and serum testosterone levels. History of medication use was assessed at each visit. The change in fat-free mass assessed by dual-energy x-ray absorptiometry was the primary clinical end point; changes in weight, muscle mass, total body potassium content, and quality of life were secondary end points.

Body Composition Analysis

Body composition was determined by four methods: 1) dual-energy x-ray absorptiometry to assess fat and fat-free mass (Hologic-2000 densitometer, Hologic, Inc., Waltham, Massachusetts; precision error, 3% for fat and 1.5% for fat-free mass [12], 2) ^{40}K isotope analysis to assess total-body potassium content in a whole-body counter with sodium iodide detectors fixed above and below the patient at the xiphoid level (Canberra Nuclear, Meriden, Connecticut; precision error < 2.5% on the basis of repeated calibration with a known potassium chloride source [Appendix]), 3) urinary creatinine excretion averaged over 3 days (during which the patient received a meat-free diet) multiplied by a constant of 18 kg of muscle per gram of urinary creatinine and indexed for height to determine the percentage of predicted muscle mass [13, 14], and 4) bioimpedance analysis to determine total-body water content (Bioelectrical Impedance Analyzer Model BIA-101, RJL Systems, Clinton Turnpike, Michigan; correlation with deuterium oxide equivalent to $R = 0.99$ [15]). Lean body mass was derived from total-body potassium content by using the Equation of Forbes and Lewis of 68.1 mEq of potassium per kg of lean body mass [16].

Nutritional Assessment

Weight was measured on the first day of each visit after an overnight fast. The percentage of ideal body weight was calculated on the basis of standard height and weight tables [17]. Patients were instructed on completion of a 4-day food record, which was analyzed for total calorie, fat, protein, and carbohydrate content (Minnesota Nutrition Data Systems, version 8A/2.6, Minneapolis, Minnesota) by the Clinical Research Center dietitian. Patients received an isocaloric, meat-free, protein-substituted diet 3 days before and during the inpatient assessments at baseline and at 6 months, during which creatinine excretion and nitrogen balance were measured. Total urinary nitrogen excretion was measured by the Kjeldal technique from consecutive 24-hour collections averaged over 3 days. Nonurinary nitrogen losses were assumed to be constant at 4 g/d [13, 18, 19]. Nitrogen intake was derived from total protein intake divided by a constant of 6.25 g of protein per g of nitrogen [19]. Calorie and protein intake were monitored on a daily basis and were modified to match the reports in the outpatient food records immediately before these visits. Resting energy expenditure was measured by indirect calorimetry with a metabolic cart. Energy requirements were calculated by using the Harris-Benedict equation [20].

Patient Reports of Response to Therapy

Each patient's perceived well-being was assessed at the end of the study by using nine linear analogue-scale questions on the overall treatment effect, change in quality of life, personal appearance, weight, and appetite (Table 1) [21]. A Karnofsky score was also determined at each visit.

View this table: [Table 1. Assessment of Patient Response to Therapy*](#)
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Exercise Functional Testing

Exercise history was assessed by a standardized questionnaire adapted from the study by Kohl and coworkers [22]. Exercise functional status was determined at the baseline and final visits by the physical therapy department of the Massachusetts General Hospital by using the 6-minute walk test, the timed sit-to-stand test, and the timed get-up-and-go test [23-25]. The distance covered in 6 minutes, the number of times the patient was able to move from a sitting to standing position in 10 seconds, and the time to cover a distance of 3 meters after standing from a seated position was recorded for each patient.

Biochemical and Immunologic Assays

Hematocrit and serum levels of follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin, and prolactin were measured at the baseline and final visits by using published methods [26]. Serum levels of total and free testosterone were measured by radioimmunoassay kit (Diagnostics Products Corp., Los Angeles, California) with intra-assay coefficients of variation of 5% to 12% for total testosterone and 3.2% to 4.3% for free testosterone. CD4 cell counts were measured by flow cytometry (Becton Dickinson Immunocytometry Systems, San Jose,

California). Viral burden was determined by using the Amplicor HIV-1 monitor test (Roche Molecular Systems, Branchburg, New Jersey).

Statistical Analysis

Sample size was based on the change in lean body mass in response to testosterone administration among adult men with acquired hypogonadism [8]. A change of $3.2\% \pm 4.0\%$ was expected over 6 months. With 20 patients in each group, the study had an 80% chance of seeing an effect of testosterone at a two-sided P value of 0.05 if the true difference in lean body mass was 3.2% between the groups. Because some drop-out was expected, enrollment was planned for 50 patients to ensure that 20 evaluable patients would remain in each randomization group. Baseline comparisons between groups were performed by using t -tests for continuous variables and the Fisher exact test for categorical variables. The treatment effect over 6 months was estimated by analysis of covariance with all observations available from each patient in an intention-to-treat analysis.

Forty-one patients completed the protocol (Figure 1). No follow-up data were available from eight patients. Partial follow-up data were available from two patients. In this model, we compared the change from baseline at 6 months in the two treatment groups while controlling for the baseline value. We used a t -test to compare patient reports of response to therapy at 6 months between the groups. Patients were classified according to whether they were receiving protease inhibitors at baseline, started receiving them during the study, or never received them. We used the Fisher exact test to compare the proportions in these three groups between the two treatment and to compare survival between groups. To ensure that the differences in the primary end points were not biased by mortality, we did a secondary analysis that combined mortality and body composition. In the combined analysis, we classified deaths as having an extreme decrease in mass, then used a Wilcoxon test to compare the groups. The change in body composition variables was compared between users and nonusers of protease inhibitors by using the Student t -test.

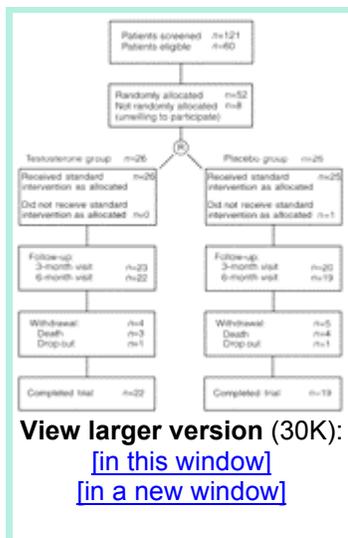


Figure 1. Flow of participants through the trial. R = randomization.

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Results

Clinical Characteristics

Clinical characteristics of the study sample are shown in [Table 2](#). Age, weight, body composition, Karnofsky score, virologic variables, and screening testosterone levels did not significantly differ between the testosterone and placebo groups. Except for serum albumin level, nutritional status was the same between the groups at baseline. All patients had a decreased serum level of free testosterone at screening and therefore met the entrance criterion for the study. Serum testosterone levels, repeatedly measured at baseline for subsequent comparison with end-of-study values, were not below the normal range in any patient. Testosterone levels were the same among patients who completed the study and were included in the treatment analysis ([Table 3](#)).

View this table: [Table 2. Clinical Characteristics of the Study Sample*](#)
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View this table: [Table 3. Clinical Response to Treatment*](#)
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Hormone Levels

Serum levels of total and free testosterone increased significantly, whereas serum levels of sex hormone-binding globulin and follicle-stimulating hormone decreased significantly in the testosterone group compared with the placebo group ([Table 3](#)).

Body Composition

Compared with patients who received placebo, testosterone-treated patients gained fat-free mass (change, -0.6 kg and 2.0 kg; $P = 0.036$), lean body mass (change, 0.0 kg and 1.9 kg; $P = 0.041$), and muscle mass (change, -0.8 kg and 2.4 kg; $P = 0.005$) (Figure 2, Table 3). The change in total-body potassium content from which lean body mass was derived was also significantly greater in the testosterone group ($P = 0.041$; data not shown). The changes in fat mass and total-body water content did not differ (Table 3). Among testosterone-treated patients, a highly significant correlation was found between the gain in fat-free mass as assessed by dual energy x-ray absorptiometry and the gains in lean body mass as assessed by the ^{40}K -isotope technique ($r = 0.65$; $P = 0.001$) and muscle mass as assessed by urinary creatinine excretion ($r = 0.56$; $P = 0.009$). Use of protease inhibitor was not associated with a gain in lean body mass in either treatment group. In the testosterone group, the 10 patients who were not taking protease inhibitors had a more significant gain in fat-free mass than the 11 patients who were taking these drugs (3.5 ± 2.8 kg and 0.6 ± 2.9 kg; $P = 0.034$).

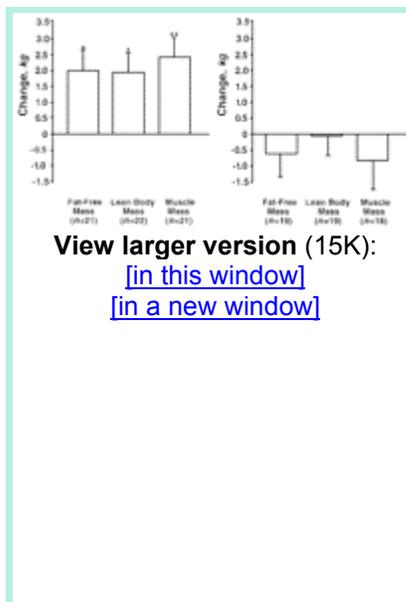


Figure 2. Mean change \pm SE for fat-free mass assessed by dual-energy x-ray absorptiometry, lean body mass determined from total-body potassium content, and muscle mass from urinary creatinine excretion in patients who received testosterone (left) and patients who received placebo (right) over 6 months. * $P < 0.05$ 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. n = number of patients for whom paired baseline and end-of-study data are available.

Nutritional Status

Patients who received testosterone gained an average of 1.9 kg more than patients who received placebo, but this difference was not statistically significant. Among the 21 testosterone-treated patients in whom paired measurements of dual-energy x-ray absorptiometry and weight were made, weight increased an average of 2.5 kg; this increase was similar to the increase in fat-free mass in this group (2.9 kg). Changes in other nutritional variables did not differ significantly between the groups (Table 3).

Patient Reports of Response to Therapy

Significant differences between the groups were noted in the responses to six of nine patient reports of response to therapy (Table 1). Testosterone-treated patients reported overall benefit from treatment ($P = 0.036$), feeling better ($P = 0.033$), improved quality of life ($P = 0.040$), and

improved appearance ($P = 0.021$) compared with patients who received placebo. The two groups had similar Karnofsky scores.

Exercise Functional Testing

Changes in exercise performance did not significantly differ between groups ([Table 3](#)).

Virologic and Hematologic Values

The changes in viral load, CD4 count, and hematocrit did not significantly differ between the groups ([Table 3](#)). Viral load decreased significantly in the testosterone group ($P = 0.027$) and the placebo group ($P = 0.031$) ([Table 3](#)). A similar proportion of patients in each group was receiving protease inhibitors at baseline (19% of patients who received testosterone and 16% of patients who received placebo) and started receiving these drugs during the study (27% of patients who received testosterone and 31% of patients who received placebo).

Compliance, Side Effects, and Adverse Events

All patients claimed compliance with the study; this was confirmed by medication diary, injection records, and empty vial count. Seven patients died of AIDS-related complications before completing the study (three in the testosterone group and four in the placebo group). No difference in survival was noted between the groups. Results of the secondary analyses that combined mortality with fat-free mass, muscle mass, and body cell mass were similar to the results of primary analyses of these variables alone ($P = 0.04$, 0.03 , and 0.07 for fat-free mass, muscle mass, and lean body mass, respectively). Testosterone was well tolerated in all patients.

Two patients (one in each group) dropped out of the study for personal reasons. One additional patient was withdrawn from the study at baseline before initiation of therapy because of gastrointestinal bleeding. No patient withdrew from the study because of a drug-related side effect. Prostate enlargement or new nodules were not detected in any patient.

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Discussion

The development of successful anabolic strategies to increase lean body mass is critical in men with the AIDS wasting syndrome, in whom the decrease in lean body mass is associated with decreased survival [3]. Previous short-term pharmacologic therapies have had limited efficacy in increasing lean body mass. Hypogonadism, an acquired endocrine deficiency state, was

recognized recently to be highly prevalent among men with the AIDS wasting syndrome and results in loss of the potent endogenous anabolic factor testosterone.

We assessed the effects of testosterone administration in men with the AIDS wasting syndrome and decreased free testosterone levels. Because of the known variability in free testosterone levels and regression toward the mean, some patients had a level within the normal range on baseline retesting. Thus, some patients may have had only relative androgen deficiency. Data obtained from our sample of HIV-infected men show that testosterone administration substantially increases lean body mass and improves patient well-being.

The anabolic effect of testosterone was shown by the significant increase in fat-free mass in patients in the testosterone group compared with patients in the placebo group. Testosterone treatment also increased total-body potassium content, a sensitive index of lean body mass that is lost out of proportion to fat mass and weight among men with the AIDS wasting syndrome [1, 2]. At baseline, patients weighed, on average, 94% of ideal body weight but had only 75% of predicted muscle mass, suggesting a great need for anabolic therapy in this population. Of note, the gain in lean body mass was not attributable to protease inhibitor use or to a difference in disease status between the groups.

A limitation of our study was that we were not able to collect follow-up data on eight patients because of death (seven patients) or discontinuation at baseline related to underlying morbidity (one patient). However, partial data on two additional patients were available and were included in the intention-to-treat analysis.

Patients who received testosterone gained 1.9 kg in body weight compared with patients who received placebo, but this change was not statistically significant. The changes in total-body water and fat content also did not differ significantly between the treatment groups. The absence of any treatment effect on water or fat content suggests that the effect of testosterone is primarily anabolic. The more substantial effect of testosterone on lean body mass than on weight is consistent with the known anabolic effects of testosterone in androgen-deficient men [8, 27]. The mechanism of androgen effects on fat-free mass and muscle mass in this population is not known. In the two groups, caloric intake did not increase and nitrogen balance did not differ. Physiologic androgen replacement has been shown to directly affect muscle protein synthesis in some studies of non-HIV-infected hypogonadal men [7, 10]; further studies are therefore needed to determine the mechanism of androgen action in this population. Although we found no effect of testosterone on exercise functional capacity, we did not strictly control for exercise, and patients with advanced HIV disease may not have been able to attain their maximum performance on effort-dependent testing.

The mechanisms of androgen deficiency in HIV-infected men are not known but may relate to decreased gonadotropin production caused by severe illness [28, 29]; undernutrition [30]; or the effect of medications, such as megestrol acetate [31]. Gonadotropin levels were elevated in 25% of patients, consistent with primary gonadal failure; the remaining patients had normal or low gonadotropin levels. Prolactin levels were elevated in 16% of patients at baseline and may have contributed to hypogonadism in some patients. None of the patients had clinical evidence of hemochromatosis or other diseases that might result in hypogonadotropic hypogonadism. Pituitary imaging was not performed unless it was clinically indicated for symptoms of mass effect. No differential effect of androgen replacement was found in men with primary or secondary hypogonadism.

An important result of this study is that patients reported benefit from testosterone administration. Previous studies documented reduced quality of life among symptomatic patients with AIDS, including decreased physical function, role function, social function, and mental health perception and increased pain [32]. Rabkin and Rabkin [33] showed that 80% of hypogonadal men reported decreased energy. We chose to measure patients' perceived benefits in response to treatment by

using a standardized questionnaire ([Table 1](#)) that assessed appetite, image, weight, overall well-being, quality of life, and benefit of therapy. This instrument has been used previously to assess treatment effects in men with the AIDS wasting syndrome [\[21\]](#). Patients who received testosterone reported an overall benefit from therapy and improvements in overall well-being, quality of life, and concern about weight and appearance compared with patients who received placebo. Positive trends toward improvement in appetite and enjoyment of eating were also noted but were not statistically significant. These data suggest a true benefit with respect to quality of life in testosterone-treated patients. However, further studies that use newly developed questionnaires with more firmly established psychometric properties are needed to more thoroughly investigate the effects of testosterone on quality of life in this population.

Few therapies have proven successful in the treatment of the AIDS wasting syndrome. These therapies have used primarily pharmacologic methods to influence body composition and appetite. In randomized, controlled studies, therapy with growth hormone or megestrol acetate had substantial effects on nutritional and body composition values. However, the rationale for the use of these agents differs greatly from that for the use of testosterone in our study. Megestrol acetate is used primarily as an appetite stimulant to increase caloric intake and weight but not lean body mass [\[21, 34\]](#). Growth hormone administration at pharmacologic doses is also anabolic and increases fat-free mass as well as weight but has not been shown to improve quality of life [\[35\]](#). Other anabolic agents, including the synthetic oral androgens, are currently being studied but may be associated with increased risk for liver toxicity.

The anabolic effects of testosterone were achieved without reported side effects in any patient. Testosterone was given at a dosage of 300 mg intramuscularly every 3 weeks, a standard replacement dosage for androgen-deficient men [\[36\]](#). Although pharmacologic levels may have been reached immediately after administration in some of the study patients, the mean testosterone level of the treated patients, measured on day 10 of the 21-day injection cycle, was in the normal reference range. This suggests that the observed results were consistent with physiologic androgen administration and not with sustained pharmacologic therapy.

Our study does not investigate testosterone administration for women with the AIDS wasting syndrome. Women constitute an increasing percentage of HIV-infected patients [\[37\]](#) in whom testosterone levels are decreased, and these levels have been shown to correlate with indices of muscle mass [\[38\]](#). Transdermal delivery of testosterone to women with AIDS wasting was recently shown to be safe and was not associated with side effects during short-term administration [\[39\]](#). Determination of the clinical efficacy of testosterone administration in women with the AIDS wasting syndrome is therefore an important area of future research.

Our data suggest that men with the AIDS wasting syndrome may benefit from screening for androgen deficiency, and, if they are androgen deficient, should receive testosterone replacement to increase lean body mass and improve their sense of well-being. For patients with low-to-normal free testosterone levels, repeated testing may provide sufficient evidence for androgen deficiency to justify treatment. We cannot generalize our results to patients with borderline low levels of free testosterone because all patients in our study had a low free testosterone level on screening. Further studies are needed to address the critical issue of whether testosterone administration is effective in men with persistently borderline or normal serum androgen levels and in women.

Appendix: Potassium-40 Counting

The total ^{40}K count was corrected for simultaneous radon measurement before unblinding by using regression equations developed independently for the upper and lower sodium iodide detectors from 68 consecutive analyses performed over 72 hours on a calibrated standard. For the upper detector, the change in ^{40}K attributable to radon was calculated as follows:

$$\text{Change } ^{40}\text{K counts} = (0.282 \times \text{radon count at 1765 keV}) + 0.001 \quad (r^2 = 0.49; P < 0.001)$$

For the lower detector, the change in ^{40}K attributable to radon was calculated as follows:

$$\text{Change } ^{40}\text{K counts} = (0.285 \times \text{radon count at 1765 keV}) + 0.001 \quad (r^2 = 0.75; P < 0.001)$$

The ^{40}K count at each detector for each scan was summed to obtain the total ^{40}K count. Total-body potassium content was derived from a constant of 95 g of potassium per 13 800 counts of potassium determined in a calibrated phantom.

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