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Effects of Testosterone Replacement in Hypogonadal Men*

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ABSTRACT

Treatment of hypogonadal men with testosterone has been shown to ameliorate the effects of testosterone deficiency on bone, muscle, erythropoiesis, and the prostate. Most previous studies, however, have employed somewhat pharmacological doses of testosterone esters, which could result in exaggerated effects, and/or have been of relatively short duration or employed previously treated men, which could result in dampened effects. The goal of this study was to determine the magnitude and time course of the effects of physiological testosterone replacement for 3 yr on bone density, muscle mass and strength, erythropoiesis, prostate volume, energy, sexual function, and lipids in previously untreated hypogonadal men.

We selected 18 men who were hypogonadal (mean serum testosterone ± SD, 78 ± 77 ng/dL; 2.7 ± 2.7 nmol/L) due to organic disease and had never previously been treated for hypogonadism. We treated them with testosterone transdermally for 3 yr. Sixteen men completed 12 months of the protocol, and 14 men completed 36 months. The mean serum testosterone concentration reached the normal range by 3 months of treatment and remained there for the duration of treatment. Bone mineral density of the lumbar spine (L2–L4) increased by 7.7 ± 7.6% ($P < 0.001$), and that of the femoral trochanter increased by 4.0 ± 5.4% ($P = 0.02$); both reached maximum values by 24 months. Fat-free mass increased 3.1 kg ($P = 0.004$), and fat-free mass of the arms and legs individually increased, principally within the first 6 months. The decrease in fat mass was not statistically significant. Strength of knee flexion and extension did not change. Hematocrit increased dramatically, from mildly anemic (38.0 ± 3.0%) to midnormal (43.1 ± 4.0%; $P = 0.002$) within 3 months, and remained at that level for the duration of treatment. Prostate volume also increased dramatically, from subnormal (12.0 ± 6.0 mL) before treatment to normal (22.4 ± 8.4 mL; $P = 0.004$), principally during the first 6 months. Self-reported sense of energy (49 ± 19% to 66 ± 24%; $P = 0.01$) and sexual function (24 ± 20% to 66 ± 24%; $P < 0.001$) also increased, principally within the first 3 months. Lipids did not change.

We conclude from this study that replacing testosterone in hypogonadal men increases bone mineral density of the spine and hip, fat-free mass, prostate volume, erythropoiesis, energy, and sexual function. The full effect of testosterone on bone mineral density took 24 months, but the full effects on the other tissues took only 3–6 months. These results provide the basis for monitoring the magnitude and the time course of the effects of testosterone replacement in hypogonadal men. (*J Clin Endocrinol Metab* **85:** 2670–2677, 2000)

TESTOSTERONE affects many organ systems. Some of the effects, such as on sexual differentiation, are time dependent and not reversible. Other effects, such as on muscle, bone, erythropoiesis, the prostate, energy, and sexual function, are reversible. Previous studies have shown that men who develop testosterone deficiency postpubertally have less muscle mass (1), lower bone mineral density (2–4), lower hematocrit and hemoglobin concentrations (5), smaller prostate glands (6), and diminished energy and sexual function (7) than normal men. Treatment of men who have testosterone deficiency has been demonstrated to reverse these deficiencies, specifically to increase muscle mass (1, 8–11), bone mineral density (1), hematocrit and hemoglobin (5), prostate gland size (6), and energy and sexual function (6, 7, 12, 13).

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Previous studies of the effects of testosterone treatment on men who have testosterone deficiency, however, have been limited by the method of administration of testosterone, the short duration of treatment, and the use of previously treated men. The method of administration of testosterone has usually been a long-acting ester of testosterone, such as the enanthate, in doses of 100 mg/week or 200 mg every 2 weeks. This method results in mean serum testosterone concentrations about 50–70% higher than the mean for normal young men and transiently 110–130% higher than the mean for normal young men (14), either of which could cause greater than normal effects. Conversely, most previous studies have been only weeks to months in duration, which could result in less than fully normal effects. Similarly, discontinuation of prior testosterone treatment only 8–10 weeks before making "pretreatment" measurements and resumption of the study testosterone preparation could result in a dampened effect of the study preparation.

The goal of the study described here was to administer testosterone to previously untreated hypogonadal men by a transdermal method that approximates the physiological

pattern of serum testosterone (15) and to continue the treatment for 3 yr, so that the magnitude and the time course of the effects of testosterone on bone, body composition, erythropoiesis, the prostate, lipids, energy, and sexual function could be observed.

Subjects and Methods

Subjects

We recruited men over 18 of age who were diagnosed with unequivocal hypogonadism, defined as a serum testosterone concentration less than 250 ng/dL (8.7 nmol/L) on 3 occasions in the morning. All subjects had previously completed puberty. None of the men had ever been treated for hypogonadism, which by history appeared to be of at least 1 yr, and in at least 2 cases to be more than 10 yr, in duration. Eight men had previously been diagnosed as hypoadrenal and were taking hydrocortisone; 9 men had previously been diagnosed as hypothyroid and were taking T_4. None of the men was taking GH. None of the subjects had a history of diseases known to affect bone mineral density, such as Cushing's disease or acromegaly. None of the subjects had ever taken a medication that affects bone mineral density, such as antiresorptive drugs or GH. None of the men had diseases that could be worsened by testosterone treatment, such as prostate cancer or severe benign prostatic hyperplasia. The committee on studies involving humans of the University of Pennsylvania approved the protocol, and each subject gave informed consent in writing. Eighteen men volunteered and enrolled. Sixteen had secondary hypogonadism (15 had pituitary adenoma; 1 had craniopharyngioma), and 2 had primary hypogonadism. Those who had secondary hypogonadism and were deficient in T_4 and/or cortisol continued to take replacement medications for the deficient hormones. One man who had had normal adrenal function at the beginning of the study developed adrenal insufficiency after 2 yr and began replacement hydrocortisone then.

Study design

Testosterone was administered for 36 months by scrotal patch (Testoderm, Alza Corp., Mountain View, CA). Each subject was asked to wear a patch at all times except when bathing, change the patch once a day, and shave the scrotum twice a week. Each subject began by wearing a 60-cm^2 testosterone patch, which delivers approximately 6 mg testosterone/24 h. One subject had serum testosterone concentrations consistently above 1000 ng/dL on this dose and subsequently wore only half a patch a day. Two subjects consistently had serum testosterone concentrations below 300 ng/dL on this dose and wore one and a half patches a day.

We asked men who were consuming less than four dairy servings a day or the equivalent before initiation of treatment to take one tablet a day of OsCal 500 + D (500 mg elemental calcium with 125 U vitamin D; SmithKline Beecham Laboratories, Philadelphia, PA) and an additional 400 U vitamin D, both of which we provided. On this basis, we provided OsCal to all but four men.

Assessment of bone mineral density and body composition

We measured bone mineral density and body composition before treatment and after 6, 12, 24, and 36 months of treatment by dual energy x-ray absorptiometry with a Lunar Corp. DPX scanner (Madison, WI) with acquisition software versions 3.1–3.61. Bone mineral density was measured in the lumbar spine (L2–L4) and three sites in the hip. Scanning a phantom every 2 weeks during the course of the study gave stable results. Body composition measurement employed body composition software version 1.3. All scans from the same subject were analyzed by a single operator (P.H.) at a single sitting.

Muscle strength

Strength of knee extension and flexion was measured by Biodex dynamometer. Before the measurements the subjects warmed up by using a stationary bicycle at low resistance for 5 min and then by two trials on the dynamometer using submaximal effort and two trials using maximal effort. With the instrument set for 60° angular velocity, the subject was asked to extend the knee with maximal effort and then flex passively and repeat this maneuver twice after 15–20 s of rest. The procedure was repeated three times with maximal effort flexing the knee and passive extension. The entire procedure was repeated with the instrument set for 180° of angular velocity. The maximum value for extension and flexion at 60° and 180° of angular velocity was used for analysis.

Hand grip strength was measured by a Jaymar dynamometer. Subjects were coached orally to exert maximum effort during three trials, each separated by a 2-min rest. The maximum result was used for analysis.

Assays related to testosterone and bone metabolism

Blood for determination of the serum testosterone concentration was drawn in the morning three times before beginning treatment and once at 3, 6, 9, 12, and then every 4 months during treatment. Blood for determination of the serum bone-specific alkaline phosphatase concentration was collected twice before treatment and at 3, 6, 9, and 12 months of treatment. Urine was collected for 24 h once before treatment and after 3, 6, and 12 months of treatment for creatinine and N-telopeptide determinations. All samples were frozen at −70 C until the end of the study. Serum testosterone was measured by RIA using a kit from Diagnostic Systems Laboratories, Inc. (Webster, TX). Serum bone-specific alkaline phosphatase was measured by immunoradiometric assay using a kit (Tandem R Ostase) from Beckman Coulter, Inc. (Columbia, MD). Urinary N-telopeptide was measured by enzyme-linked immunoabsorbant assay using a kit (Osteomark) from Ostex International, Inc. (Seattle, WA). Intraassay coefficients of variation for all of the assays were less than 5%, and interassay coefficients of variation were less than 10%. For each assay, all samples from each subject were measured in the same assay run.

Erythropoiesis

Erythropoiesis was assessed by measurement of hemoglobin and hematocrit before treatment, every 3 months during the first year of treatment, and every 4 months thereafter.

Prostate parameters

We tested each man for several prostate parameters periodically. Prostate volume was estimated by ultrasound at 0, 6, 12, 24, and 36 months. The volume was estimated by halving the product of the three measured dimensions of the prostate. The serum prostate-specific antigen concentration was measured in blood drawn at 0, 3, 6, and 12 monthsand then every 4 months for 36 months. We also tested for prostate cancer by manual examination. Urinary obstruction was evaluated by Boyarsky Symptom Score (16), urine flow rate (17) by a Urodyn 1000 urine flow meter (Medtronic-Dantec Corp., Allendale, NJ), and residual urine in the bladder after voiding by a hand-held ultrasound instrument, BladderScan BVI 2000 (Diagnostic Ultrasound Corp., Redmond, WA).

Energy and sexual function

Energy and sexual function were assessed by a 100-mm visual analog questionnaire. It was administered before treatment, every 3 months during the first year, and every 4 months during the second and third years. The questionnaire consisted of eight questions, four about general sense of energy and four about sexual function. Scores for each question were 0–100, with 0 indicating least possible energy or sexual function and 100 indicating the most. For each test, scores for the four energy questions were averaged, and scores for the four sexual function questions were averaged.

Lipid analyses

Lipid parameters [total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides] were measured fasting every 3 months during the first year and every 4 months thereafter. Total and HDL cholesterol and triglycerides were determined by enzymatic-colorimetric assays in the William Pep-

per Laboratory of the Hospital of the University of Pennsylvania, and LDL cholesterol was calculated by the Friedewald equation.

Statistical analyses

The principal test was the paired *t* test, comparing the change from 0 to 36 months. The results were confirmed using the Wilcoxon matched pairs signed rank test and repeated measures ANOVA. Because the results of all three analyses were similar, only the results of the paired *t* test are reported, except where indicated. All analyses were performed using SAS version 6.12 (SAS Institute, Inc., Cary, NC). All *P* values reported are two sided; a significance level of less than 0.05 was considered statistically significant.

Results

Of the 18 men who enrolled in the study, 2 discontinued before the 12 month measurements, 1 because of an exacerbation of Haley-Haley disease and 1 for personal reasons. All analyses were performed on the remaining 16 men, whose ages ranged from 22–78 yr (median, 51 yr). Of these, 1 died suddenly after 16 months, and 1 discontinued after 24 months; 14 completed the entire 36 months of the protocol.

Serum testosterone

The mean serum testosterone concentration increased from 78 ± 77 (±SD) ng/dL (2.7 ± 2.7 nmol/L) before treatment to 407 ± 153 ng/dL (14.1 ± 5.6 nmol/L; $P < 0.001$) at 6 months and remained at approximately the same level for the remainder of the 36 months of treatment (Fig. 1). Fourteen of the 16 men had average serum testosterone concentrations within the normal range (300–1000 ng/dL; 10.4–34.7 nmol/L) during the 36 months of the study, and 2 had average values below 300 ng/dL (10.4 nmol/L).

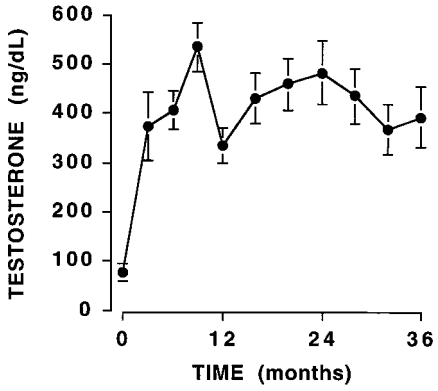

FIG. 1. Mean (±SE) serum testosterone concentrations in 16 men with previously untreated hypogonadism who were replaced with testosterone transdermally for 36 months. To convert testosterone values to nanomoles per L, multiply by 0.03467.

Bone mineral density and markers of bone metabolism

Bone mineral density of the lumbar spine increased by 7.7 ± 7.6% (mean ± SD; $P < 0.001$) during the 36 months of treatment, and that of the trochanter also increased (4.0 ± 5.4%; $P = 0.02$). The increases in bone mineral density of the femoral neck and Ward's triangle were not statistically significant by paired *t* test (Table 1), but were significant by repeated measures ANOVA ($P = 0.001$ and $P < 0.02$, respectively). The increases continued for 24 months, but not thereafter (Fig. 2). The urinary excretion of N-telopeptide and the serum concentration of bone-specific alkaline phosphatase decreased from pretreatment to 12 months (Table 1), suggesting a decrease in bone turnover during treatment.

Body composition

Fat-free body mass increased significantly from before treatment to 36 months of treatment (Table 2); most of the increase occurred within the first 6 months (Fig. 3). Although fat mass tended to decrease during the course of treatment, the decrease was not of statistical significance (Table 2).

Analysis of regional body composition showed that fat-free mass increased in the arms and legs during treatment, but not in the trunk (Table 2). Fat mass tended to decrease in all three sites during treatment, but the decreases were not of statistical significance (Table 2).

Muscle strength

Strength of knee extension and flexion at 60 and 180°/s angular velocity did not change significantly during the course of treatment, nor did handgrip strength (Table 3).

Erythrocytosis

Mean hematocrit and hemoglobin both increased dramatically from slightly subnormal to midnormal during treatment (Fig. 4). Most of both increases occurred within the first

TABLE 1. Parameters of bone mineral density and turnover in previously untreated hypogonadal men before and after testosterone replacement

Parameter	Measurement		Change	*P*
	Pretreatment	End of Treatment		
Bone mineral density, L2–L4 (g/cm^2)	1.146 ± 0.243	1.219 ± 0.238	0.078 ± 0.068	<0.001[a]
Bone mineral density, femoral neck (g/cm^2)	0.963 ± 0.156	0.978 ± 0.178	0.023 ± 0.046	0.09[a]
Bone mineral density, Ward's triangle (g/cm^2)	0.782 ± 0.199	0.784 ± 0.208	0.022 ± 0.052	0.14[a]
Bone mineral density, trochanter (g/cm^2)	0.877 ± 0.179	0.910 ± 0.184	0.032 ± 0.046	0.02[a]
Bone-specific alkaline phosphatase (ng/mL)	14.7 ± 6.3	11.5 ± 6.1	−2.9 ± 3.0	0.002
Urine N-telopeptide (nmol/mmol creatinine)	159 ± 102	98 ± 76	−65 ± 90	0.05

Values are the mean ± SD. End of treatment is 36 months for bone mineral density and 12 months for bone-specific alkaline phosphatase and N-telopeptide. Change is from pretreatment to the end of treatment. The number of subjects is 16 for pretreatment and 14 for end of treatment and for change. *P* values are paired *t* test results for the change from pretreatment to the end of treatment.

[a] *P* values by repeated measures analysis of variance: $P < 0.001$ for L2–L4, $P < 0.001$ for the trochanter, $P = 0.001$ for the femoral neck, and $P = 0.02$ for Ward's triangle.

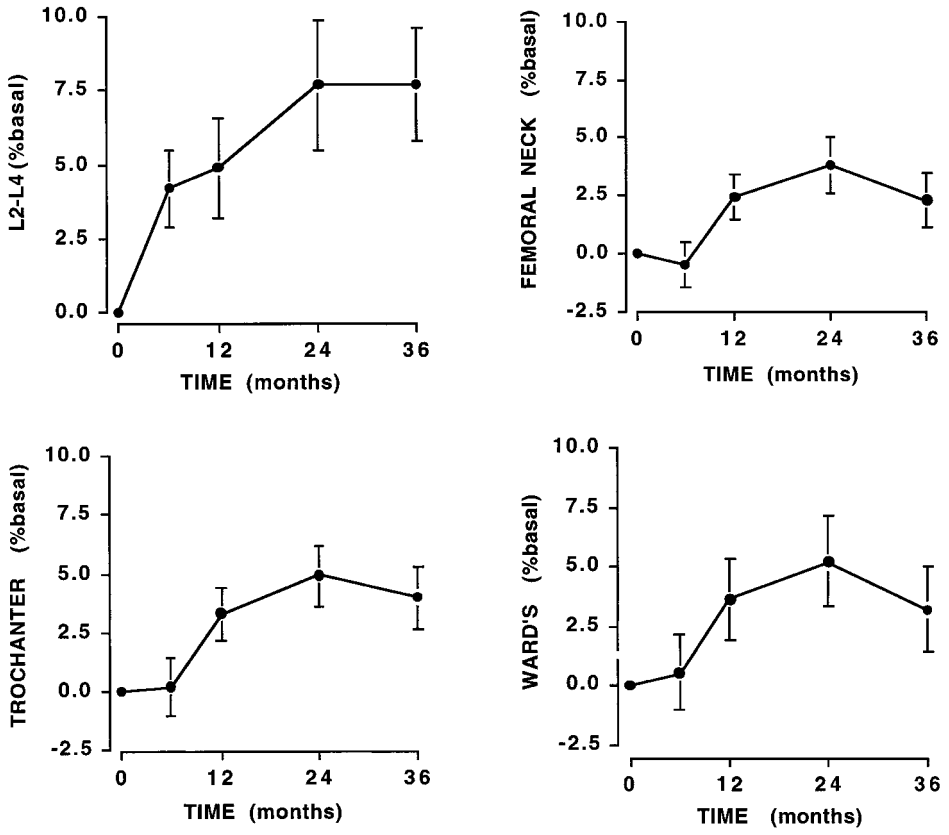

FIG. 2. Mean (±SE) bone mineral density of the lumbar spine (L2–L4), trochanter, femoral neck, and Ward's triangle as a percentage of the basal value in 16 men with previously untreated hypogonadism who were replaced with testosterone for 36 months. The increase from 0 to 36 months by paired t test was statistically significant for L2–L4 ($P < 0.001$) and the trochanter ($P = 0.02$), but not for the femoral neck or Ward's triangle, but by repeated measures ANOVA it was significant for all sites ($P < 0.001$, $P < 0.001$, $P = 0.001$, and $P < 0.02$, respectively).

TABLE 2. Parameters of body mass and composition in previously untreated hypogonadal men before and after 36 months of testosterone replacement

Parameter	Measurement		Change	P
	Pretreatment	36 months of treatment		
Wt (kg)	88.9 ± 10.5	91.1 ± 13.9	3.3 ± 6.6	0.1
Tissue mass (kg)	83.6 ± 8.3	83.6 ± 9.9	1.0 ± 6.2	0.6
Fat mass (kg)	31.7 ± 7.4	29.6 ± 9.0	−1.5 ± 4.9	0.2
Fat-free mass (kg)	53.3 ± 5.8	56.3 ± 5.7	3.1 ± 3.3	0.004
Arm tissue (kg)	11.2 ± 1.9	11.9 ± 1.0	0.9 ± 3.5	0.4
Arm fat mass (kg)	4.8 ± 1.6	4.3 ± 2.0	−0.3 ± 2.2	0.6
Arm fat-free mass (kg)	6.4 ± 1.0	7.7 ± 1.3	1.2 ± 1.5	0.01
Leg tissue (kg)	26.2 ± 1.6	26.6 ± 7.7	0.8 ± 3.2	0.4
Leg fat mass (kg)	8.7 ± 2.5	7.9 ± 3.0	−0.4 ± 1.7	0.4
Leg fat-free mass (kg)	17.5 ± 2.4	18.7 ± 2.6	1.2 ± 1.6	0.02
Trunk tissue (kg)	42.4 ± 5.9	42.2 ± 6.3	−0.2 ± 3.5	0.8
Trunk fat mass (kg)	17.0 ± 4.1	15.1 ± 4.9	−1.1 ± 3.0	0.2
Trunk fat-free mass (kg)	25.4 ± 1.1	26.3 ± 2.7	0.9 ± 2.3	0.2

Values are the mean ± SD. The number of subjects is 16 for pretreatment and 14 for 36 months and for the change from 0 to 36 months. The P values are based on the paired t test for the change from 0 to 36 months.

3 months. One subject experienced an increase above the upper limit of normal (52%) at one time point.

Prostate parameters

Prostate volume, as determined by ultrasound, increased significantly during treatment (Table 4); most of the increase occurred during the first 6 months (Fig. 5). Prostate-specific antigen did not increase significantly. No man was diagnosed with prostate cancer during the study.

Prostate symptom score, urine flow rate, and postvoiding residual urine in the bladder after voiding did not change significantly during the course of the study.

Energy and sexual function

The subjects' self-evaluation of their sense of energy ($P = 0.01$) and sexual function ($P < 0.001$) both increased dramatically during the course of treatment; most of the change in each occurred during the first 3 months of treatment (Fig. 6).

Lipids

Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides did not change during the course of treatment (Table 5).

Discussion

Administration of testosterone transdermally to hypogonadal men for 3 yr increased their mean serum testosterone concentrations to within the normal range and demonstrated the magnitude and time course of the effects of this treatment on bone, body composition, erythrocytosis, the prostate, energy, and sexual function.

Testosterone replacement for 36 months increased bone mineral density of the lumbar spine by 7.5%, confirming the observation that treatment of 29 hypogonadal men with 100 mg testosterone enanthate once a week for 18 months increased bone mineral density of the lumbar spine by 5% (1). Continuing the determination of bone mineral density for 36 months allowed the observation that the peak effect occurred by 24 months of treatment. Testosterone replacement was also associated with a 4% increase in the bone mineral density of the trochanter, also by 24 months. An effect of testosterone on bone mineral density of the hip has not been previously reported. Part of the increase in bone mineral density of the spine and hip could have been the result of the calcium and vitamin D supplementation 12 of the 16 subjects received, because in previous studies in elderly men, such supplementation for 3 yr resulted in an approximately 2% increase in spine bone mineral density (18, 19).

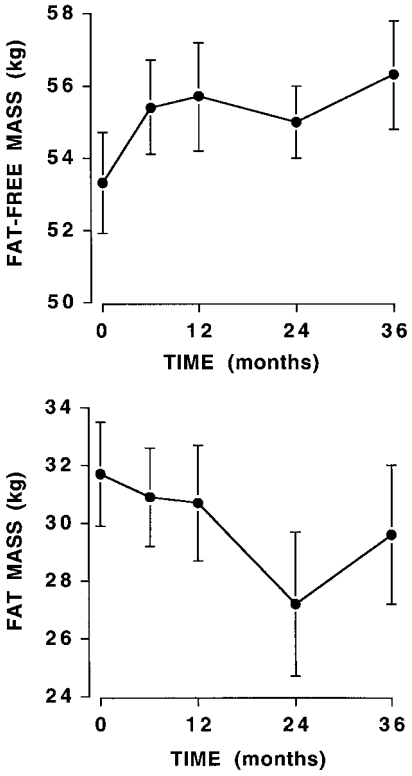

FIG. 3. Mean (±SE) fat-free mass and fat mass in 16 men with previously untreated hypogonadism who were replaced with testosterone for 36 months. The change from 0 to 36 months was statistically significant for fat-free mass ($P = 0.004$), but not for fat mass.

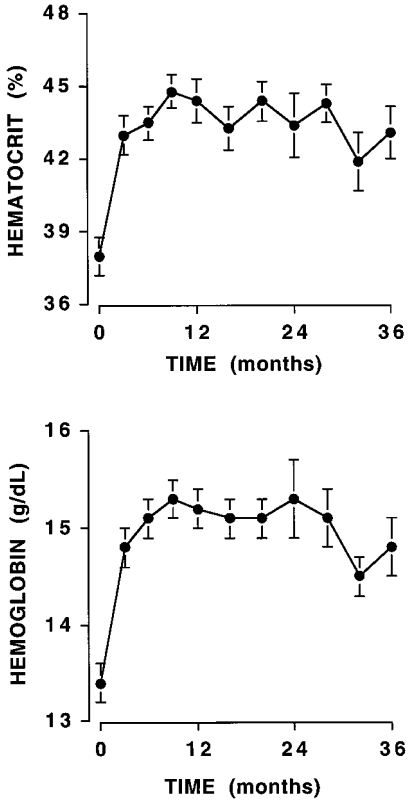

FIG. 4. Mean (±SE) hematocrit and hemoglobin values in 16 men with previously untreated hypogonadism who were replaced with testosterone for 36 months. The increase in both parameters from 0 to 36 months was statistically significant ($P = 0.002$).

TABLE 3. Parameters of muscle strength in previously untreated hypogonadal men before and after 12 months of testosterone replacement

Parameter	Measurement		Change	*P*
	Pretreatment	12 months of treatment		
Knee extension, 60°/s (ft lb)	115 ± 41	111 ± 51	0 ± 21	0.9
Knee extension, 180°/s (ft lb)	76 ± 28	78 ± 39	7 ± 22	0.3
Knee flexion, 60°/s (ft lb)	63 ± 25	67 ± 24	6 ± 17	0.3
Knee flexion, 180°/s (ft lb)	51 ± 19	54 ± 17	3 ± 13	0.5
Hand grip (ft lb)	40 ± 14	40 ± 13	2 ± 5	0.2

Values are the mean ± SD for the 13 subjects whose muscle strength was tested before and after 12 months of testosterone treatment. *P* values are paired *t* tests results for the change from 0 to 12 months.

TABLE 4. Parameters related to the prostate in previously untreated hypogonadal men before and after 36 months of testosterone replacement

Parameter	Measurement		Change	*P*
	Pretreatment	36 months of treatment		
Prostate vol (mL)	12.0 ± 6.4	22.4 ± 8.4	10.2 ± 10.2	0.004
PSA (ng/mL)	2.0 ± 0.6	2.0 ± 0.2	−0.1 ± 0.5	0.6
Symptom score	3.8 ± 2.2	4.5 ± 3.3	1.4 ± 2.7	0.1
Urine flow rate (mL/min)	23.7 ± 7.7	26.5 ± 8.7	3.5 ± 6.9	0.1
Postvoiding residual urine vol	22.6 ± 27.2	30.7 ± 42.9	2.6 ± 44.8	0.8

Values are the mean ± SD. The number of subjects is 16 for pretreatment and 13 for 36 months and for the change from pretreatment to 36 months. *P* values are paired *t* test results for the change from 0 to 36 months.

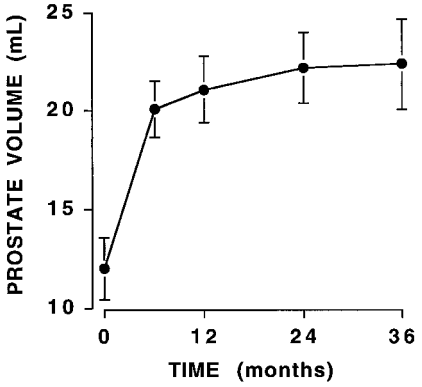

FIG. 5. Mean (±SE) prostate volume in 16 men with previously untreated hypogonadism who were replaced with testosterone for 36 months. The change from 0 to 36 months was statistically significant ($P = 0.004$).

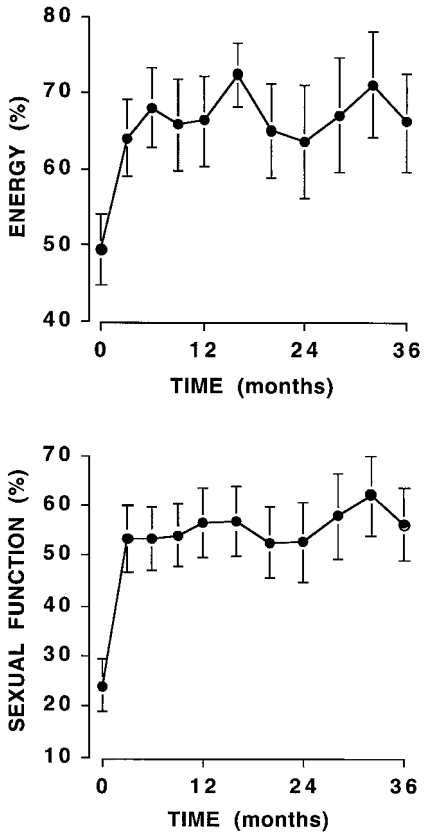

FIG. 6. Mean (±SE) self-reported scores from 0–100% for energy and sexual function in 16 men with previously untreated hypogonadism replaced with testosterone for 36 months. The changes from 0 to 36 months were statistically significant for both energy ($P = 0.01$) and sexual function ($P < 0.001$).

Testosterone replacement increased fat-free body mass by approximately 3 kg, or 5.8%, mostly within the first 6 months. This increase is within the range reported in other studies in which testosterone was administered to hypogonadal men. When 5 previously untreated hypogonadal men were treated with testosterone cypionate (3 mg/kg BW; ~250–300 mg) every 2 weeks for 6 months, fat-free mass increased by 15% (8). When 13 hypogonadal men were treated with 100 mg testosterone enanthate once a week for 18 months, lean muscle mass increased by 6.8%, as determined by computed tomographic scanning (1). When 7 hypogonadal men were treated with 100 mg testosterone enanthate once a week for 10 weeks, their fat-free mass, as determined by underwater weighing, increased by 5 kg (9). When 51 men who had hypogonadism associated with acquired immunodeficiency syndrome wasting were randomized to receive either 300 mg testosterone enanthate every 3 weeks or a placebo injection for 6 months, the testosterone-treated men experienced an increase in fat-free mass (as well as lean mass and muscle mass) of approximately 2 kg, whereas the placebo-treated men experienced a loss of approximately 0.5 kg (10). When 41 men who had hypogonadism associated with acquired immunodeficiency syndrome wasting were randomized to receive either 5 mg testosterone/day transdermally or placebo for 12 weeks, the testosterone-treated men experienced an increase in fat-free mass of approximately 1.4 kg and the placebo-treated men experienced no increase, but the change was not significantly different between the 2 groups (11).

Fat mass tended to decrease during testosterone treatment, but the change from 0 to 36 months was not of statistical significance. Other studies of the effect of testosterone replacement in hypogonadal men found variable results. In three of the studies described above, fat mass decreased significantly (1, 8, 11), and in the other two, fat mass did not change significantly (9, 10).

Strength of knee extension and flexion, as determined by Biodex dynamometer, did not change significantly during 36 months of testosterone treatment in the present study. Some studies have shown an effect of testosterone on muscle strength in hypogonadal men. In a study of seven hypogonadal men who were treated with 100 mg testosterone en-

TABLE 5. Lipid parameters in previously untreated hypogonadal men before and after 36 months of testosterone replacement

Parameter	Measurement		Change	*P*
	Pretreatment	36 months of treatment		
Cholesterol (mg/dL)	216 ± 33	223 ± 31	1 ± 33	0.9
LDL cholesterol (mg/dL)	148 ± 34	151 ± 31	−5 ± 24	0.5
HDL cholesterol (mg/dL)	38 ± 9	39 ± 7	1 ± 10	0.8
Triglycerides	201 ± 94	237 ± 202	32 ± 145	0.4

Values are the mean ± SD. The number of subjects is 16 for pretreatment and 14 for 36 months and for the change from pretreatment to 36 months. *p* values are paired *t* test results for the change from 0 to 36 months.

anthate for 10 weeks, bench press strength and squat strength both increased significantly (9). In a study of six normal young men, muscle strength decreased 10 weeks after they were made hypogonadal by administration of a GnRH analog (20).

One of the most striking changes in response to testosterone treatment was the increase in hematocrit and hemoglobin from minimally subnormal to midnormal, mostly within the first 3 months, and maintenance of the increase for the remainder of the 36 months. It has been known for decades that men have higher hematocrit and hemoglobin concentrations than women (21). It has also been demonstrated previously that men who are hypogonadal have lower than normal hematocrit and hemoglobin concentrations and that testosterone treatment increases those parameters to normal (5). The present study, however, is first to demonstrate the magnitude and time course of the effect of a physiological replacement dose of testosterone on erythropoiesis.

Prostate volume also increased dramatically during testosterone treatment, mostly during the first 6 months, from subnormal to normal. The mean values before treatment and after 3 yr of testosterone treatment were quite similar to those observed in a cross-sectional study of untreated and treated hypogonadal men (6).

The subject's self-reported general energy and sexual function both increased dramatically, mostly during the first 3 months and then remained stable for the remainder of the treatment period. Testosterone treatment has been shown to increase sexual function previously (7, 12, 13), mostly during treatment for 1–2 months. One study, however, observed the effects of testosterone treatment for 1 yr and found a progressive increase in nocturnal erections from pretreatment to 3–6 months, but no further increase at 12 months (22).

Serum concentrations of lipids did not change during the course of testosterone treatment. These results are within the range of what has been observed in six other studies of the effect of testosterone. For serum total cholesterol, three observed a decrease (23–25), two no change (26, 27), and one an increase (28). For serum LDL cholesterol, two observed a decrease (23, 24), three no change (23, 26, 28), and one an increase (28). For serum HDL cholesterol, three observed a decrease (23, 26, 27), and three no change (24, 27, 28). None observed a change in triglycerides. Testosterone treatment does not appear to exert an effect on the serum concentrations of these lipids.

The results presented here, both positive and negative, need to be interpreted cautiously. The positive results, such as bone mineral density, energy, and sexual function, need to be interpreted cautiously because of the lack of a placebo-treated group. The negative results, such as muscle strength and lipids, need to be interpreted cautiously because the relatively small number of subjects did not give the study sufficient statistical power to detect small changes.

We conclude that replacing testosterone in these hypogonadal men increased their bone mineral density of both the spine and hip, fat-free mass, erythropoiesis, prostate volume, energy, and sexual function. The full effect of testosterone on bone took 2 yr, but the other effects took only 3–6 months. These results provide the basis for monitoring the magnitude and the time course of the effects of testosterone replacement in hypogonadal men for both investigation and patient care.

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