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Testosterone Replacement in Older Hypogonadal Men: A 12-Month Randomized Controlled Trial

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ABSTRACT

A decline in testicular function is recognized as a common occurrence in older men. However data are sparse regarding the effects of hypogonadism on age-associated physical and cognitive declines. This study was undertaken to examine the year-long effects of testosterone administration in this patient population.

Fifteen hypogonadal men (mean age 68 ± 6 yr) were randomly assigned to receive a placebo, and 17 hypogonadal men (mean age 65 ± 7 yr) were randomly assigned to receive testosterone. Hypogonadism was defined as a bioavailable testosterone <60 ng/dL. The men received injections of placebo or 200 mg testosterone cypionate biweekly for 12 months. The main outcomes measured included grip strength, hemoglobin, prostate-specific antigen, leptin, and memory.

Testosterone improved bilateral grip strength ($P < 0.05$ by ANOVA) and increased hemoglobin ($P < 0.001$ by ANOVA). The men assigned to testosterone had greater decreases in leptin than those assigned to the control group (mean ± SEM: −2.0 ± 0.9 ng/dL *vs.* 0.8 ± 0.7 ng/dL; $P < 0.02$). There were no significant changes in prostate-specific antigen or memory. Three subjects receiving placebo and seven subjects receiving testosterone withdrew from the study. Three of those seven withdrew because of an abnormal elevation in hematocrit.

Testosterone supplementation improved strength, increased hemoglobin, and lowered leptin levels in older hypogonadal men. Testosterone may have a role in the treatment of frailty in males with hypogonadism; however, older men receiving testosterone must be carefully monitored because of its potential risks. (*J Clin Endocrinol* **82:** 1661–1667, 1997)

A DECLINE in testicular function with a consequent decline in testosterone and bioavailable testosterone is recognized as a common occurrence in older men (1–5). Although there is great interindividual variability in testosterone and bioavailable testosterone (BT) levels with advancing age, half of healthy men between the ages of 50–70 yr will have a BT level below the lowest level seen in healthy men who are 20–40 yr of age (6).

Studies have suggested that androgens have many important physiological actions including effects on sexual function, muscle, body composition, bone, bone marrow, prostate, and the central nervous system (7–11). However, data are sparse regarding the effects of the age-associated decline in testosterone secretion on these target systems.

Few studies have assessed the role of testosterone replacement in older hypogonadal men and whether putative improvements in strength, body composition, and bone will occur without significant risks in this patient population. In a 6-month cross-over trial of testosterone, Tenover (12) found no change in muscle strength, an increase in hematocrit and prostate-specific antigen (PSA), a decrease in total cholesterol, and an increase in weight and lean body mass without changes in percent body fat. Morley *et al.* (13) found an increase in right-hand grip strength, an increase in hematocrit, and a decrease in total cholesterol after 3 months of testosterone administration.

Given the high prevalence of hypogonadism in the older male population and the association of aging with muscle weakness, alterations in body composition, and the development of frailty syndromes (14–16), this study was undertaken to determine whether testosterone administration could increase upper extremity strength, and whether it could be given for 1 yr without unacceptable side effects.

Materials and Methods

Community-dwelling healthy men ≥50 yr were recruited through advertisements. Inclusion criteria included: no evidence of significant prostate disease, chronic obstructive pulmonary disease, and congestive heart failure or angina; a Folstein Mini-Mental State Examination (a 30-item screening tool for cognitive disorders) of >23 and a Yesavage Geriatric Depression Scale (a 30-question instrument used to assess dysphoria) of <16; normal liver function tests, PSA, and hematocrit; and a BT (non-SHBG bound testosterone) level ≤60 ng/dL. Following initial telephone contact, 59 men aged 51–79 yr (mean 65 ± 1.2 yr) were screened with a physical examination including a digital rectal examination and laboratory testing. Thirty-five men (59%) were eligible for entry into the study, and 32 agreed to participate.

The St. Louis University Institutional Review Board for Human Studies approved the study protocol. Informed written consent was obtained at the time of the screening visit. Subjects were assigned by random number to the treatment or control group. The treatment group received 200 mg (1 ml) testosterone cypionate IM every 14–17 days for 12 months. Those in the control group received 1 ml normal saline IM every 14–17 days for 12 months. Injections were administered by a physician or a nurse in the clinic. Subjects and technicians performing the assays were blind about which treatment was given.

Baseline assessments included memory, depression, strength, body fat, laboratory testing, and a physical exam. Memory testing included the Rey Auditory Verbal Learning Test (RAVLT) and RAVLT recall,

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TABLE 1. Medical diagnoses and medications of control and treatment (testo) groups at entry into study

Diagnosis	Control	Testo	Medication	Control	Testo
Arthritis	5[a]	6	Aspirin	4	7
Hypertension	2	4	Antihypertensives	2	4
Asthma	3	1	Vitamin supplements	6	9
Diabetes mellitus	1	2	Nonsteroidal antiinflammatory agents	4	2
Glaucoma	1	2	Antiglaucoma ophthalmic agents	1	2
Hypercholesterolemia	1	2	Insulin/oral hypoglycemics	1	2
Atrial fibrillation	0	2	Lipid-lowering agents	1	2
Depression/anxiety	2	1	Antidepressants/anxiolytics	2	0
Hypothyroidism	1	1	Calcium carbonate	0	3
Asbestosis	0	1	Levothyroxine	1	1
s/p coronary artery bypass graft no angina	1	0	Allopurinol	0	1
Gastroesophageal reflux	0	1	Carbemazepine	0	1
Gout	0	1	Digoxin	0	1
Irritable bowel syndrome	1	0	H2 blocker	0	1
Peripheral vascular disease	1	0	Prednisone	1	0
Seizure	0	1	Pentoxifyllin	1	0
			Theophylline	1	0
			Warfarin	0	1

[a] Numbers represent number of subjects who had listed diagnosis or were taking listed medication.

TABLE 2. Baseline age, height, weight, BMI, and education for all subjects and for subjects completing 6 and 12 months of study

Variable	All subjects		6 months		12 months	
	Control (n = 15)	Testosterone (n = 17)	Control (n = 14)	Testosterone (n = 14)	Control (n = 12)	Testosterone (n = 10)
Age (yr)	68 ± 6	65 ± 7	69 ± 5	65 ± 7	69 ± 5	66 ± 6
Height (cm)	175 ± 5	178 ± 5	178 ± 5	178 ± 5	178 ± 5	178 ± 5
Weight (kg)	85 ± 11	91 ± 15	85 ± 11	89 ± 13	85 ± 12	86 ± 12
BMI (kg/m^2)	27.3 ± 3.8	29.1 ± 5.2	27.1 ± 3.9	28.2 ± 3.8	27.1 ± 4.1	27.2 ± 3.1
Education (yr)	15 ± 4	16 ± 4	15 ± 4	16 ± 5	16 ± 4	16 ± 5

Values are expressed as the mean ± SD.

which assesses verbal learning and memory; Rey Visual Design Learning Test (RVDLT) and RVDLT recall, which assesses nonverbal (visual) learning and memory (17); and Animal Naming, which tests verbal fluency (18). Depression was tested using the Yesavage Geriatric Depression Scale (19).

Hand grip strength was measured three times in each hand utilizing a Jamar dynamometer (subject seated, upper arm parallel to the body, elbow at 90° and forearm in neutral position). In our hands this has an intercorrelative coefficient of 0.97. Body fat was measured utilizing bioelectrical impedance (20). Weight, height, waist, hip, and midarm circumferences were measured.

Following baseline bloodwork, all blood was sampled 14–17 days after the subjects received their testosterone or placebo injection (just before the next injection). Hormones were batched throughout the study, but measures such as complete blood count (CBC), PSA, and serum chemistries were analyzed as they were obtained, with the exception of leptin, which was measured in a single assay. CBC, PSA, serum chemistries, and lipoproteins were determined by Metro Corning Clinical Laboratories (St. Louis, MO). Testosterone and BT were measured as previously described (20). The inter- and intraassay coefficients of variation for testosterone were 3.7% and 3.6%, respectively, and for BT 4.7% and 5.8%, respectively. The normal young adult male range for testosterone is 300-1000 ng/dL and for BT is 72–250 ng/dL. LH (ICN, Costa Mesa, CA) and estradiol [Pantex RIA (extraction assay), Santa Monica, CA] were determined in our laboratory. The inter- and intraassay coefficients for LH were 5.5% and 4.7%, respectively, and for estradiol 5.8% and 3.8%, respectively. The normal young adult male range for LH is 4–20 IU/L and for estradiol is 10–60 pg/ml. Leptin (Linco Research, St. Charles, MO) was determined in our laboratory. The inter- and intraassay coefficients of variation were 3.8% and 4.9%, respectively. Osteocalcin (Incstar, Stillwater, MN), 25 hydroxyvitamin D (Incstar), 1,25 dihydroxyvitamin D (Incstar), and PTH (C-terminal) (Incstar) were determined. The normal ranges are: osteocalcin, 1.8–6.6 ng/mL; 25 hydroxyvitamin D, 13–54 ng/mL; 1,25 dihydroxyvitamin D, 20–40 pg/mL; and PTH, 29–85 pmol/L. The inter- and intraassay coefficients are: osteocalcin, 9.3% and 4.8%, respectively; 25 hydroxyvitamin D, 16.4% and 8.8%, respectively; 1,25 dihydroxyvitamin D, 11.0% and 7.7%, respectively; and PTH, 9.8% and 5.6%, respectively. Fructosamine was determined as previously described (21).

At 3-month intervals, depression, weight, mean hand grip strength, waist, and hip and mid arm circumferences were measured, and physical examinations, CBCs, PSAs, serum chemistries, and tests for lipoproteins, testosterone, BT, LH, and estradiol were repeated. At 6-month intervals, memory and fructosamine tests were repeated. At 12 months, body fat, leptin, 25 hydroxyvitamin D, 1,25 dihydroxyvitamin D, osteocalcin, and PTH were measured.

In the four men receiving testosterone whose hematocrits rose ≥52%, injections were withheld until the hematocrit dropped to <49% (up to 6 weeks). If the rise in hematocrit redeveloped with the reinstitution of testosterone, subjects were given the option of therapeutic phlebotomy with continued testosterone or withdrawal from the study.

Table 1 summarizes the subjects' diagnoses and medications. Except for the subjects who withdrew for known medical reasons, diagnoses and medications for each subject remained stable throughout the study. Seventeen subjects entered the treatment group; one withdrew due to lymphoma prior to the 3 month evaluation; one withdrew because of uncontrolled atrial fibrillation with congestive heart failure, one was lost to follow-up before the 6-month evaluation; one was lost to follow-up, and three withdrew because of increases in hematocrit before the 9-month evaluation. Fifteen men entered the control group: one was lost to follow up before the 3-month evaluation; one withdrew because of a stroke, and one was lost to follow-up before the 9-month evaluation. Hypertension was believed to be the underlying cause of atrial fibrillation in the subject who withdrew with congestive heart failure, however, 3-month blood pressure measurements were similar to baseline.

The mean of three hand grip trials were used to calculate the group mean. Statistical analysis was performed on a personal computer using commercially available statistical software, Statistica (Statsoft, Tulsa, OK). The baseline, 3-, 6-, 9-, and 12-month data, as well as the differences from baseline (Δ) for the 3-, 6-, 9-, and 12-month data, were compared in treatment *vs* control groups utilizing a repeated measures ANOVA. Post hoc testing was done using Tukey's least significant differences.

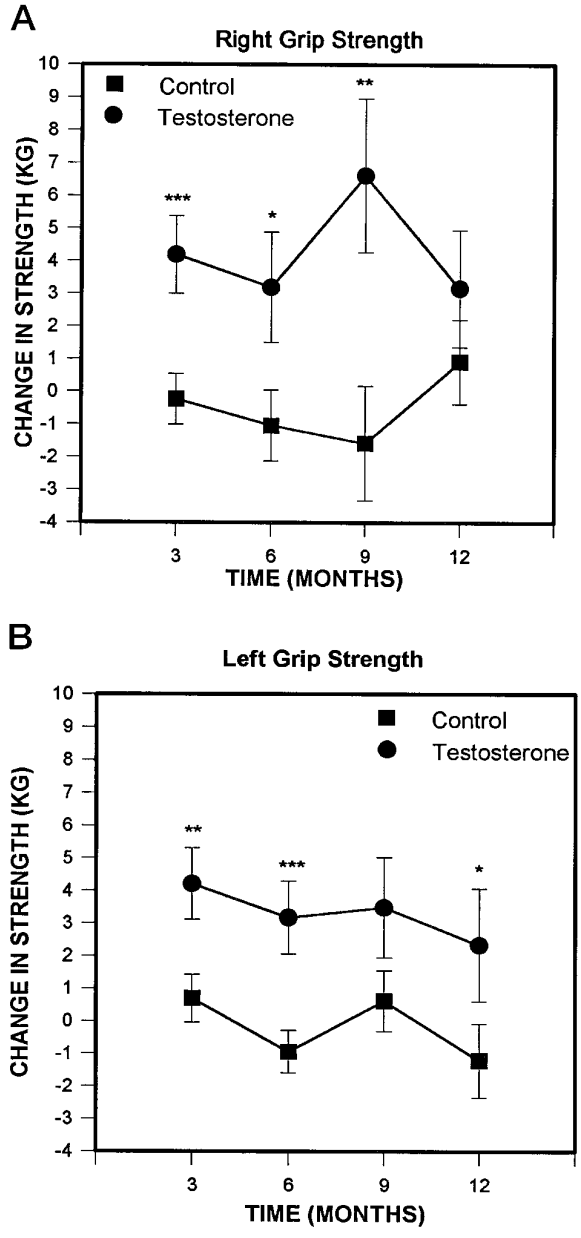

FIG. 1. Effects of testosterone administration on right and left grip strength in those subjects completing study. Mean change from baseline ± SEM in right and left grip strength at 3, 6, 9, and 12 months in control and testosterone-treated groups. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$ from appropriate controls as determined by Tukey's least significant differences in pairwise comparisons. $P < 0.05$ by ANOVA for both right and left grip strength.

Student's t tests were performed on the Δ for single comparisons between groups. Baseline demographic data are presented at the mean ± SD. Results are presented as the mean ± SEM.

Results

Baseline demographics

Fifteen men were randomly assigned to the control group and 17 men were randomly assigned to treatment. Twelve men in the control group and 10 men in the testosterone group completed the study. Age, height, weight, and education were similar between groups (Table 2).

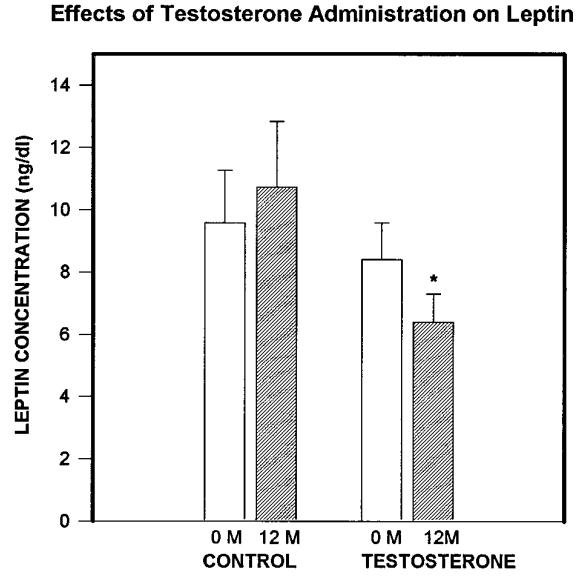

FIG. 2. Effects of testosterone administration on leptin concentrations at baseline (0 M) and 12 months (12 M) in control and testosterone-treated groups. *, $P < 0.02$ for difference from baseline (Δ) as determined by Student's t test.

Major outcomes

Strength. Testosterone significantly increased upper body strength as measured by grip strength ($P < 0.05$). Figure 1 summarizes the mean change from baseline strength at 3, 6, 9, and 12 months. The Δ mean right and left grip strength at 3, 6, and 9 months and Δ mean left grip strength at 12 months were all significant ($P \leq 0.05$). Changes in the maximum grip strength in both hands were similar to the means (data not shown). Δ BT correlated strongly with Δ right grip strength (r = 0.279; $P = 0.005$); Δ BT and Δ left grip strength neared significance (r = 0.193; $P < 0.06$).

Hemoglobin and PSA. Hemoglobin increased significantly with testosterone by 3 months and was sustained throughout the study (Table 3). Four men (24%) in the testosterone group developed elevations in hematocrit >52%. Changes in hematocrit directly reflected changes in hemoglobin.

PSA did not change significantly with testosterone compared with controls throughout the study (Table 3). In no case was PSA ≥ 4.0 ng/dL. Prostate nodules were not detected on digital rectal examination.

Leptin. Testosterone significantly decreased leptin levels (control, Δ 0.8 ± 0.7 ng/dL; testosterone, Δ −2.0 ± 0.9 ng/dL; $P < 0.02$) (Fig. 2). Leptin levels correlated strongly with body mass index (BMI) (r = 0.850; $P = 0.000$), body fat (r = 0.690; $P < 0.01$), and triglycerides (r = 0.529; $P < 0.02$) (Table 4). There was no relation to age, testosterone, BT, or estradiol.

Cognition. Testosterone had no effect on memory, recall, or verbal fluency tests. By chance, the testosterone group had higher baseline scores on the RAVLT, RAVLT recall, and RVDLT than the controls. These differences were maintained throughout the study, however changes from baseline scores were not significant. There were no effects on the Yesavage Geriatric Depression Scale (data not shown).

TABLE 3A. Effects of testosterone on PSA and other variables

Variable	Baseline		3 months		6 months	
	Control (n = 15)	Testo (n = 17)	Control (n = 14)	Testo (n = 16)	Control (n = 14)	Testo (n = 14)
PSA (ng/dL)	1.5 ± 0.3	1.0 ± 0.2	1.8 ± 0.4 (0.2 ± 0.2)	1.3 ± 0.2 (0.3 ± 0.1)	1.7 ± 0.4 (0.2 ± 0.1)	1.6 ± 0.2 (0.5 ± 0.1)
AST (U/L)	21 ± 1	23 ± 3	24 ± 1 (3 ± 1)	22 ± 1 (−2 ± 3)	27 ± 3 (5 ± 3)	23 ± 2 (−2 ± 4)
TC (mg/dL)	212 ± 8	187 ± 6[a]	211 ± 7 (−1 ± 6)	175 ± 6[c] (−12 ± 4)	214 ± 8 (2 ± 9)	187 ± 7[a] (−2 ± 4)
BMI (kg/m^2)	27.3 ± 1.0	29.1 ± 1.3	26.8 ± 1.2 (0.3 ± 0.5)	28.6 ± 1.0 (0.3 ± 0.2)	27.6 ± 1.0 (0.5 ± 0.2)	28.8 ± 1.1 (0.4 ± 0.2)
MAC (cm)	32.4 ± 1.2	34.7 ± 0.8[a]	32.5 ± 0.9 (0.9 ± 0.2)	35.4 ± 0.8[a] (0.9 ± 0.5)	32.4 ± 0.9 (0.9 ± 0.4)	34.6 ± 0.9 (0.0 ± 1.0)
HGB (mg/dL)	15.1 ± 0.3	15.0 ± 0.3	14.8 ± 0.4 (−0.2 ± 0.2)	16.2 ± 0.4 (0.9 ± 0.4)[b]	14.6 ± 0.4 (−0.4 ± 0.3)	16.1 ± 0.4 (1.0 ± 0.3)[b]
SBP (mm Hg)	142 ± 5	143 ± 5			138 ± 5 (−4 ± 4)	144 ± 4 (1 ± 3)
FRA (μM/L)	251 ± 8	265 ± 8			251 ± 6 (5 ± 10)	260 ± 13 (4 ± 12)
Body fat (%)	20.2 ± 2.3	20.3 ± 1.4				

TABLE 3B.

Variable	9 months		12 months	
	Control (n = 12)	Testo (n = 10)	Control (n = 12)	Testo (n = 10)
PSA (ng/dL)	1.9 ± 0.4 (0.1 ± 0.2)	1.7 ± 0.4 (0.6 ± 0.2)	2.0 ± 0.4 (0.4 ± 0.2)	1.9 ± 0.3 (0.7 ± 0.2)
AST (U/L)	23 ± 1 (1 ± 1)	25 ± 2 (−2 ± 5)	23 ± 2 (1 ± 1)	22 ± 2 (−4 ± 5)
TC (mg/dL)	216 ± 8 (4 ± 7)	184 ± 12[a] (−6 ± 12)	238 ± 10 (25 ± 9)	200 ± 8[a] (9 ± 8)
BMI (kg/m^2)	27.8 ± 1.2 (0.7 ± 0.4)	26.5 ± 1.0 (−0.1 ± 0.4)	27.7 ± 1.2 (0.5 ± 0.3)	27.3 ± 1.2 (0.2 ± 0.4)
MAC (cm)	32.6 ± 1.1 (1.0 ± 0.7)	33.6 ± 0.6 (0.4 ± 0.5)	32.7 ± 1.2 (1.1 ± 0.5)	33.9 ± 0.9 (0.2 ± 0.4)
HGB (mg/dL)	14.9 ± 0.4 (−0.2 ± 0.2)	15.5 ± 0.4 (0.9 ± 0.2)[a]	15.0 ± 0.5 (−0.1 ± 0.2)	16.0 ± 0.3 (1.4 ± 0.3)[c]
SBP (mm Hg)			144 ± 7 (−2 ± 3)	151 ± 7 (5 ± 4)
FRA (μM/L)			242 ± 5 (−5 ± 12)	286 ± 21 (26 ± 18)
Body fat (%)			24.1 ± 2.4 (4.4 ± 2.3)	19.9 ± 1.4 (1.6 ± 2.6)

Abbreviations: AST, aspartate aminotransferase; TC, total cholesterol; MAC, midarm circumference; HGB, hemoglobin; SBP, systolic blood pressure; FRA, fructosamine. PSA, AST, TC, BMI, MAC, and HGB were measured at baseline and 3, 6, 9, and 12 months. SBP and FRA were measured at baseline and 6 and 12 months. Body fat was measured at baseline and 12 months. Values are expressed as the mean ± SEM. Numbers in parentheses represent differences from baseline (Δ) and SE of Δ. [a] $P < 0.05$; [b] $P < 0.005$; [c] $P < 0.0005$ from appropriate controls as determined by Tukey's least significant differences in pairwise comparisons.

TABLE 4. Correlations and their significance of leptin with baseline age, testosterone, BT, estradiol, BMI, body fat, and triglycerides

	Correlation coefficient (r)	*P* value
Age (yr)	0.219	NS
Testosterone (ng/dL)	−0.292	NS
BT (ng/dL)	−0.067	NS
Estradiol (ng/dL)	−0.320	NS
BMI (kg/m^2)	0.850	0.000
Body fat (%)	0.690	0.001
Triglycerides (mg/dL)	0.529	0.011

Other measures

The mean baseline BT level was greater in the treatment group than controls by chance ($P < 0.05$) (Table 5). Overall, testosterone and BT levels increased from baseline in the treatment group, however, only ΔBT at 6 months was statistically significant ($P < 0.05$). The rise in estradiol tended to be greater with testosterone, but the differences were not significant. Testosterone resulted in a significant decline in LH at 3, 6, 9, and 12 months.

Serum hepatic tests [aspartate aminotransferase, ALT (alanine aminotransferase), GGT (gamma glutamyl-transferase), LDH (lactate dehydrogenase)], fructosamine, and blood pressure measurements did not change throughout the study (Table 3). By chance, baseline serum cholesterol was higher in the testosterone group. This difference was evident throughout the study, however Δ cholesterol was not different between the groups. Changes in high density lipoproteins, low density lipoproteins, and triglycerides were not different.

1,25 dihydroxyvitamin D was higher in the control group than the testosterone group after 12 months (Δ 6.8 ± 3.3 pg/mL *vs.* Δ −1.7 ± 1.5 pg/mL; $P < 0.05$). There were no changes in osteocalcin, calcium, phosphate, alkaline phosphatase, 25 hydroxyvitamin D, and PTH levels.

BMI and body fat were not different between groups (Table 3). No differences were noted in waist-to-hip ratio or midarm circumference.

Subjects who withdrew vs subjects who completed study

Four subjects receiving testosterone developed a persistently abnormal increase in hematocrit of ≥52%. Three opted to withdraw from the study after 6 months rather than undergo therapeutic phlebotomy. At 6 months those who withdrew were younger (56 ± 2 yr *vs.* 66 ± 2 yr; $P < 0.05$) and had higher serum testosterone (835 ± 218 ng/dL *vs.* 312 ± 66 ng/dL; $P < 0.00005$) and BT (310 ± 102 ng/dL *vs.* 62 ± 19 ng/dL; $P < 0.0005$) than those who completed the study. Baseline hemoglobin was higher in those who withdrew (15.5 ± 0.8 g/dL *vs* .14.8 ± 0.2 g/dL; P = NS). Six-month Δ hemoglobin was not different. Baseline grip strength was higher in those who withdrew and increased more at 6 months than in those who completed the study, but the differences were not statistically significant (right grip base-

TABLE 5A. Testosterone, BT, LH, and estradiol at baseline, 3, 6, 9, and 12 months in control and treatment (testo) groups

Variable	Baseline		3 months		6 months	
	Control (n = 15)	Testo (n = 17)	Control (n = 14)	Testo (n = 16)	Control (n = 14)	Testo (n = 14)
Testosterone (ng/dL)	233 ± 20	294 ± 26	285 ± 29 (53 ± 25)	280 ± 53 (−15 ± 66)	269 ± 20 (29 ± 21)	461 ± 98 (173 ± 95)
BT (ng/dL)	32 ± 4	42 ± 5[a]	44 ± 8 (13 ± 6)	53 ± 19 (12 ± 18)	38 ± 5 (6 ± 4)	133 ± 43 (90 ± 42)[a]
LH (IU/L)	9.1 ± 1.2	9.7 ± 0.9	10.2 ± 1.1 (1.1 ± 0.8)	6.0 ± 1.2[a] (−4.0 ± 1.1)[b]	7.9 ± 0.9 (−1.1 ± 0.7)	4.9 ± 0.7 (−4.9 ± 1.1)[a]
Estradiol (pg/mL)	22.5 ± 1.8	24.0 ± 3.0	23.5 ± 2.3 (1.0 ± 1.5)	28.9 ± 4.7 (4.9 ± 5.8)	27.5 ± 2.1 (5.6 ± 1.8)	34.6 ± 6.6 (11.3 ± 6.5)

TABLE 5B.

Variable	9 months		12 months	
	Control (n = 12)	Testo (n = 10)	Control (n = 12)	Testo (n = 10)
Testosterone (ng/dL)	251 ± 32 (19 ± 26)	472 ± 88 (165 ± 79)	277 ± 24 (44 ± 22)	370 ± 93 (76 ± 86)
BT (ng/dL)	39 ± 6 (8 ± 6)	120 ± 35 (76 ± 32)[a]	40 ± 6 (8 ± 5)	73 ± 28 (32 ± 28)
LH (IU/L)	11.7 ± 1.5 (2.6 ± 0.8)	5.1 ± 0.6 (−5.0 ± 0.9)[b]	8.3 ± 1.2 (−0.8 ± 0.9)	4.36 ± 0.6 (−5.4 ±1.0)[b]
Estradiol (pg/mL)	26 ± 2 (3.2 ± 1.8)	43 ± 7 (14 ± 6)	29.0 ± 2.3 (6.5 ± 1.7)	32.9 ± 5.5 (8.9 ± 5.2)

Values are expressed as mean ± SEM. Numbers in parentheses represent differences from baseline (Δ) and SE of Δ. [a], $P < 0.05$; [b], $P < 0.01$ from appropriate controls as determined by Tukey's least significant differences in pairwise comparisons.

line, 52 ± 13 kg *vs.* 45 ± 2 kg; right grip 6 months, 57 ± 8 kg *vs.* 47 ± 4 kg).

Discussion

This study showed that grip strength and hemoglobin increase with testosterone replacement, and that leptin concentration is altered by testosterone. One focus of this study was to examine the effects of testosterone on muscle. Aging has been associated with a decline in the size and number of muscle fibers (22), and testosterone has been shown to increase muscle mass (10). Grip strength was measured because animal studies have demonstrated that the primary muscle effects of androgens occur in the upper body (23, 24). Consistent with previous work (11, 13), the major finding in this study was an increase in strength as measured by grip strength. Testosterone did not affect midarm circumference. Numerous studies have correlated grip strength with functional ability (25, 26) as measured by manual dexterity (27, 28), activities of daily living (29, 30), and work capacity (31). The implications of increased grip strength may be an improvement in function and a reduction in frailty.

It is well recognized that androgens stimulate erythropoiesis, although the mechanism is not clear (32). Four subjects in this study developed a rise in hematocrit. Three subjects withdrew from the study, and the fourth underwent therapeutic phlebotomy. None developed symptoms or long-term sequelae associated with the hematocrit increase. Although older men do tend to have lower hemoglobin concentrations than younger men, polycythemia should still be considered an undesirable and not uncommon effect of testosterone (33).

Androgens regulate the function and growth of the prostate (34) and may contribute to the development of prostate cancer and benign prostatic hypertrophy. In these men without significant prostate disease, 12 months of testosterone supplementation did not affect digital rectal examinations and did not cause significant symptoms of prostatism. Although Δ PSA did not differ between groups, the mean PSA values rose with testosterone over the study period. This finding warrants a longer study to measure the effects of testosterone on the prostate.

With advancing age there is a decline in muscle mass and an increase and redistribution of body fat (8). Some of these changes may be attributed to a decline in testosterone. We hypothesized that, similar to animal studies and a recent human study (35–40), testosterone may decrease fat and/or weight in hypogonadal men by modulating leptin. Leptin is the product of the recently discovered obese (*ob*) gene (41) and is postulated to regulate weight and adipose tissue mass (42) by signaling satiety or hunger and energy expenditure or conservation. The present study demonstrated that testosterone replacement significantly decreased serum leptin. This suggests a mechanism for steroid hormone effects on body fat.

Testosterone may suppress *ob* gene expression. Alternatively, testosterone may decrease body fat. The *ob* gene is exclusively expressed in adipose tissue, and levels of expression appear to reflect the size of the body's adipose depot (42). Testosterone did not alter body habitus, body fat, or BMI in this study, suggesting that small differences were not detected and that leptin may be a more sensitive measure of adiposity.

Testosterone levels have been positively correlated with spatial ability (43), and testosterone administration has been shown to improve visuospatial memory in mice (44, 45) and spatial ability in older men (46). We were unable to demonstrate any difference in verbal or nonverbal memory with testosterone administration, however, visuospatial ability was not specifically examined. Previous work suggests testosterone's effect on visuospatial realms was caused by a decline in estradiol levels (46). If testosterone has more gen-

eralized effects on cognition, our inability to demonstrate this may be because of the rise in estradiol levels seen in the treatment group.

Hormonal differences between the sexes may account for the differences in lipoprotein profiles and heart disease prevalence. Unlike shorter studies of testosterone administration showing a decrease in low density lipoprotein (12) and total cholesterol (12, 13), this study found no effect of testosterone on lipoproteins. It may be that these changes in lipoproteins do not persist over the long term. In animals, androgens induce hyperinsulinemia. To address the effect of androgen supplementation, glucose metabolism was measured by fructosamine. Glucose metabolism was unaffected by testosterone administration in our study.

Osteoporosis develops in men with hypogonadism. In young hypogonadal men, testosterone replacement has been shown to increase bone density (47). Although the mechanism is unclear, there is the suggestion that vitamin D metabolites may enhance the ability of skeletal tissue to respond to gonadal steroids (48). In this study 1,25 dihydroxyvitamin D levels did not exhibit the rise with testosterone that was seen in controls. These results differ from previous work that demonstrated an increase in 1,25 dihydroxyvitamin D (49). Given the small numbers of subjects and the absence of changes in other parameters of bone metabolism, this may represent a chance occurrence.

There are several limitations of this study. First, the study population was small and the drop-out rate among the subjects was significant. Second, we were unable to demonstrate an increase in BT at all time points. This is probably because of blood sampling times that occurred when BT was expected to be at a nadir. LH production was significantly suppressed with testosterone administration, suggesting an increase in testosterone and BT levels. We also noted large variations in testosterone metabolism. Younger subjects, in particular, had higher circulating levels of testosterone for a longer time than older subjects. These younger subjects were more likely to develop polycythemia and showed more improvements in strength. These changes may be caused by an age-associated sensitivity on hematopoiesis and muscles to testosterone and/or the higher testosterone levels in these subjects. Third, although grip strength is a correlate of function, we did not specifically examine function. The subjects in this study were healthy and able to perform all basic and instrumental activities of daily living. Given our population, significant improvements in classical methods used to measure function would not have been expected.

Conclusions

This study demonstrated that testosterone supplementation improved grip strength and increased hemoglobin in older hypogonadal men. This is also the first study to describe the hormonal modulation of leptin levels in humans. Alterations in the regulation of leptin may be a suggested mechanism for changes in body composition, size and adipose distribution seen with steroid hormones and with aging. Testosterone may have a role in the treatment and/or reversal of frailty in this patient population; however, testosterone was associated with a significant drop-out rate and cannot be considered harmless therapy. Large studies of testosterone administration that include the frail are necessary to further define which men may best benefit from hormonal replacement and whether improvements in strength translate to an improvement in functional ability and reduction in morbidity.

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