0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(3):1502–1510

doi: 10.1210/jc.2004-1933

Exogenous Testosterone (T) Alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T

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Testosterone (T) therapy in older men with low serum T levels increases lean body mass and decreases fat mass. These changes might improve physical performance and strength; however, it has not been established whether T therapy improves functional outcome in older men. Moreover, concerns exist about the impact of T therapy on the prostate in older men. The administration of finasteride (F), which partially blocks the conversion of T to the more potent androgen, dihydrotestosterone, attenuates the impact of T replacement on prostate size and prostate-specific antigen. We hypothesized that T replacement in older, hypogonadal men would improve physical function and that the addition of F to this regimen would continue to provide the T-induced improvements in physical performance, strength, and body composition. Seventy men with low serum T (<350 ng/dl), age 65 yr and older, were randomly assigned to receive one of three regimens for 36 months: 1) T enanthate, 200 mg im every 2 wk, with placebo pills daily (T-only); 2) T enanthate, 200 mg every 2 wk, with 5 mg F daily (T + F); or 3) placebo injections and pills (placebo). We obtained serial measurements of timed physical performance, grip strength, lower extremity strength, body composition (by dual-energy x-ray absorptiometry), fasting cholesterol profiles, and hormones. Fifty men completed the 36-month protocol. After 36 months, T therapy significantly improved performance in a timed functional test when compared with baseline and placebo [4.3 ± 1.6% (mean ± SEM, T-only) and 3.8 ± 1.0% (T + F) *vs.* −5.6 ± 1.9% for placebo ($P < 0.002$ for both T and T + F *vs.* placebo)] and increased handgrip strength compared with baseline and placebo ($P < 0.05$). T therapy increased lean body mass [3.77 ± 0.55 kg (T-only) and 3.64 ± 0.56 kg (T + F) *vs.* −0.21 ± 0.55 kg for placebo ($P < 0.0001$)], decreased fat mass, and significantly decreased total cholesterol, low-density lipoprotein, and leptin, without affecting high-density lipoprotein, adiponectin, or fasting insulin levels. These results demonstrate that T therapy in older men with low serum T improves physical performance and strength over 36 months, when administered alone or when combined with F, and suggest that high serum levels of dihydrotestosterone are not essential for these beneficial effects of T in men. (*J Clin Endocrinol Metab* 90: 1502–1510, 2005)

As MEN AGE, they experience a decline in strength and physical function (1–3). Aging is also associated with changes in body composition, lean body mass (LBM) decreases, and fat mass (FM) increases (4–7), and these changes may be associated with increased risk of cardiovascular disease. Twenty percent of men over age 60 have serum testosterone (T) concentrations below the normal range for young eugonadal men (8, 9). Exogenous T replacement in older men increases LBM, decreases FM (10–12), and increases bone mineral density (BMD) (13), yet these changes in body composition have not been shown to impact physical function. Even when given for as long as 3 yr, T replacement has not been shown to improve measures of physical performance in placebo-controlled trials in older men (10). Whereas some studies have shown an increase in strength in older men treated with T when compared with placebo (14, 15), this has not been a uniform finding, even in longer term studies (10). In addition, variable effects on serum lipids have been found with use of T in hypogonadal men (16), although replacement doses in older men are generally associated with decreases in low-density lipoprotein cholesterol (LDL-C) and maintenance of high-density lipoprotein cholesterol (HDL-C) (17). Therefore, questions still exist as to whether androgen supplementation will improve physical function without causing significant morbidity in older men with low serum T.

The relative roles of T and its metabolite, dihydrotestosterone (DHT), in mediating the end-organ effects of T are not clear. Because DHT contributes to the development of benign prostatic hyperplasia and possibly prostate cancer, androgen supplementation that does not increase DHT might be preferable in older men. Finasteride (F) inhibits DHT production by blocking the enzyme type 2, but not type 1, 5α-reductase that converts T to DHT. F has been safely and effectively used to treat benign prostatic hyperplasia in older men (18). We have recently shown that treatment with a combination of T plus F achieved comparable effects in improving BMD while

First Published Online November 30, 2004

Abbreviations: BMD, Bone mineral density; CV, coefficient(s) of variation; DHT, dihydrotestosterone; F, finasteride; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; PO, orally; PPT, physical performance test; PSA, prostate-specific antigen; T, testosterone; TE, T enanthate; WHR, waist-to-hip circumference ratio.

abolishing effects on prostate size when compared with treatment with T alone or placebo (13). These results were found despite having achieved a 50% reduction in serum DHT in the subjects receiving T plus F compared with placebo or T alone (13). Furthermore, treatment with F reduces body mass index in men with baseline T levels in the low or low-normal range who experience an increase in serum T with F treatment (19), suggesting that normal DHT levels are not critical for T to affect body composition.

We hypothesized that long-term im T therapy in older men who had serum T below the range of normal for young adult men would significantly increase physical function and strength, and that these changes would be associated with increased LBM, decreased FM, and decreased serum LDL-C. Furthermore, we hypothesized that the addition of the 5α-reductase inhibitor F would continue to provide these T-mediated changes. We conducted a randomized, double blind, placebo-controlled trial of im T administration, with or without F, to test these hypotheses.

Subjects and Methods

Subjects

Men age 65 and older were recruited and screened as reported previously (13). The principal inclusion criteria were a morning serum total T level less than 12.1 nmol/liter (350 ng/dl) on 2 d and classification as sedentary (no more than 60 min/wk of moderate-intensity recreational physical activity). Exclusion criteria included the following: severe illness; medications including anabolic steroids, antiandrogens, glucocorticoids, bisphosphonates, diuretics, calcitonin, seizure medications, or warfarin; Paget's disease; smoking or heavy alcohol use; sleep apnea; hematocrit more than 48%; total cholesterol more than 300 mg/dl; abnormal kidney, liver, thyroid, adrenal, or pituitary function; prostate cancer; a prostate nodule on exam; prostate-specific antigen (PSA) more than 4.0 ng/ml; International Prostate Symptom Score more than 8; urinary postvoid residual by ultrasound of at least 150 ml; or an abnormal transrectal ultrasound. The Institutional Review Board of Emory University, where all subject interactions occurred, approved the study, and subjects gave written informed consent before screening.

Study design

Seventy men with a mean age of 71 ± 4 yr (range, 65–83 yr) were enrolled in the study and randomized to one of three treatment groups: 1) 24 subjects received T only [T enanthate (TE); Schein Pharmaceuticals, Florham Park, NJ] 200 mg im every 2 wk, plus a placebo pill orally (PO) daily; 2) 22 subjects received T + F [TE 200 mg im every 2 wk plus F (Merck & Co., Rahway, NJ), 5 mg PO daily]; and 3) 24 subjects received placebo (sesame oil placebo), 1 ml im every 2 wk, plus placebo pill PO daily, as reported previously (13). Participants were treated for 36 months. Only the research pharmacist and safety monitoring board knew the results of the randomization. A nurse administered the injections, and 98% occurred within 2 d of the scheduled time. There was 95% compliance with the daily F or placebo based on pill counts. The study design included the potential for dose reduction of T or placebo injection by decrements of 0.2 ml (40 mg of TE for subjects actually receiving T) for a hematocrit of more than 52% on safety monitoring performed at 2, 4, 8, 12, 18, 24, and 30 months. Participants were seen monthly. In addition to hematocrit, safety monitoring included measurement of transaminases, PSA, and prostate volume by digital rectal exam and transrectal ultrasound, as described previously (13). Participants were asked not to institute a regular exercise program for the duration of the study, and all participants reported compliance with this request.

Fifty men completed the entire 36 months of the study. Of the 20 men who did not complete the study, six were in the placebo group, and seven each were in the T-only and T + F groups (13). Ten subjects dropped out of the study for personal reasons, and, as reported previously (13), three dropped out for prostate-related disease (one in the placebo group and two in the T-only group). The nonprostate intercurrent illnesses, which resulted in premature study cessation, were by treatment group and month of study cessation as follows: gastrointestinal bleeding (placebo, month 2); recurrent hematuria with negative workup (T-only, month 7); new onset atrial fibrillation (T-only, month 10); recurrence of old sciatica (T-only, month 14); adrenal cancer (T + F, month 5); appendicitis with peritonitis (T + F, month 7); and pancreatic cancer (T + F, month 16).

Reduction of T dosage for elevated hematocrit was necessary in 14 men (seven in the T-only group and seven in the T + F group). After the decrease in T dosage, the final mean dose of TE was 158 ± 36 mg for the T-only group and 164 ± 40 mg for the T + F group every 2 wk.

Function and strength measurements

At baseline and at months 12, 24, and 36, aspects of integrated physical function were measured using a timed, modified physical performance test (PPT) (20), consisting of two subtests done in succession. The first subtest required the participant to rise from a chair without using his arms and then walk (but not run) as quickly as possible for 50 ft. The second subtest had the participant stepping over stacked boxes of various heights, walking through an open door, closing and opening the door again, and then walking to a tiered platform to ascend and descend the stairs. The completion times for each subtest were combined for the composite PPT score used in the analysis.

Muscle strength testing was performed at baseline and at months 6, 12, 24, and 36. Handgrip strength was measured using a Harpenden handheld dynamometer. With hands at their sides, the participants were urged to exert maximum effort during three trials for each hand, and testing was initiated using the dominant hand. The maximum result was used for analysis. Knee and ankle strength was assessed using a Cybex II isokinetic dynamometer, with torque calibration before each session using known loads. Peak torques for extension and flexion at 30°/sec and 120°/sec of the knee and ankle of the dominant leg were measured; joints and speeds were tested in random order. After familiarization with the procedures, participants were warmed up by three trials using submaximal effort and two to three trials using maximal effort. After a 1-min rest, testing proceeded with five consecutive pairs of reciprocal repetitions, first using maximal extension and passive flexion. After 10–20 sec of rest, the procedures were repeated using passive extension and maximum flexion. Five minutes of rest was provided between test runs at each speed and joint. The maximum value for extension and flexion at 30° and 120° was used in the analysis.

Body composition measurements

At baseline and after 6, 12, and 36 months of treatment, body composition was measured by dual x-ray absorptiometry using a Hologic QDR-2000 densitometer (Hologic, Waltham, MA) and standard QDR body composition software. Standardization of the densitometer was performed daily using a body composition calibration phantom, and the same technician and densitometer were used throughout the study to minimize errors due to technique. The intraperson coefficient of variation (CV) was 0.40% for LM and 0.96% for total body fat. Standing height and body weight were measured using a beam scale monthly for the first 6 months; at months 8, 10, and 12; and then every 6 months thereafter through month 36. Circumferences over the waist and hip regions were measured at months 8, 12, 24, and 36, as recommended by the World Health Organization report (21), and waist-to-hip circumference ratio (WHR) was calculated. Measurements were performed by the same person throughout the study.

Hormone measurements

Blood was drawn for hormone measurements in the morning at baseline and immediately before injections after 2, 4, 6, 8, 12, 18, 24, 30, and 36 months of treatment. Blood was drawn for serum lipids after a 12-h fast at baseline and after 6, 12, 18, 24, and 36 months of treatment. All samples, except those used in lipid measurements, were stored frozen at −70 C until the end of the study, when serum samples from each participant were assayed concurrently. For each hormone, all samples from each individual were measured in duplicate in one assay. T, DHT, bioavailable T, and estradiol assays have been reported previously (13). Leptin and adiponectin were measured by RIA (both from Linco

Research Inc., St. Charles, MO). The assay sensitivity for leptin was 0.5 ng/ml, and intraassay and interassay CV were 5 and 7.1%, respectively. The assay sensitivity for adiponectin was 1.0 ng/ml. Intraassay and interassay CV for adiponectin were 6.21% and 9.25%, respectively. Total insulin was measured by double-antibody RIA (Diabetes Endocrinology Research Center Immunoassay Core Laboratory, Seattle, WA). Intraassay and interassay CV for insulin were 6.9and 8.5%, respectively.

Statistical analysis

The primary analysis was performed according to patients' original treatment assignment (*i.e.* an intention-to-treat analysis), and all men were included in the analyses for as long as they contributed data. Baseline differences between treatment groups were assessed using nonparametric Kruskal-Wallis tests. We applied linear statistical models to analyze the longitudinal physical performance and body mass response variables. The response variables were modeled as change from baseline using cell means for each treatment group and measurement occasion. The linear models included correlated random errors to account for correlation between serial measurements from a given individual. First-order autoregressive structures were employed to model the variance-covariance matrices for the error terms. Autoregressive covariance models assume that repeated measurements from an individual that are closer in time are more highly correlated than more distant measurements.

To address the study objectives, we applied F tests with multiple degrees of freedom to evaluate the null hypothesis of no change from baseline throughout the study for a designated treatment group. Furthermore, we tested whether the change-from-baseline profiles for each of the T-only and T + F groups were significantly different from the change-from-baseline profile in the placebo group. We also conducted serial hypothesis tests, evaluating differences between the treatment groups and testing treatment-specific changes from baseline at each measurement time. For serial hypothesis tests, a Bonferroni-adjusted significance level of 0.0167 was required to preserve a familywise type-I error rate of 0.05, and an adjusted significance level of 0.033 achieved a familywise error rate of 0.10. We implemented our statistical analyses of the longitudinal physical performance and body mass measures using SAS PROC MIXED (SAAS OnlineDoc, version 8, SAS Institute Inc., Cary, NC).

Results

At baseline, the three treatment groups did not differ significantly from each other in age, body mass index, serum lipids, prostate volume, PSA, or strength (Table 1 and Ref. 13). At baseline, the placebo group had a mean PPT time that was slightly shorter than the two T treatment groups ($P = 0.04$; Table 1) and a slightly lower level of adiponectin ($P = 0.04$; Table 1).

Detailed analyses of serum sex steroid levels in this study have been reported previously (13). In brief, mean nadir serum total T levels in the T-only and T + F groups were significantly increased throughout the treatment period [T-only baseline, 10.0 ± 1.1 to 16.6 ± 1.1 nmol/liter (mean ± SEM); and T + F baseline, 9.9 ± 1.1 to 18.6 ± 1.1 nmol/liter] but stayed within the normal range, whereas these hormone levels did not change in the placebo group (baseline, 9.8 ± 1.1 to 11.3 ± 1.2 nmol/liter). Mean nadir serum DHT levels did not change throughout the study in the placebo group, increased significantly in the T-only group (baseline, 0.74 ± 1.1 to 1.32 ± 1.1 nmol/liter), and decreased significantly in the T + F group (baseline, 0.82 ± 1.1 to 0.44 ± 1.1 nmol/liter) ($P < 0.001$ for T and T + F groups compared with baseline and placebo). Estradiol and bioavailable T levels in the T and T + F groups were significantly elevated above baseline, whereas they were unchanged in the placebo group (13).

Physical function

In a timed function PPT involving rising from a chair, walking, stair climbing, and opening/closing a door, subjects in both groups receiving T had improvements in physical performance testing, noted by month 12 ($P < 0.05$ *vs.* baseline for both T and T + F; Fig. 1A), that continued through the completion of the study, with the exception of the T + F group where improvement at 36 months did not quite reach significance ($P = 0.07$ *vs.* baseline). After 36 months, subjects receiving T and T + F had a mean decrease in time to complete the PPT of −1.3 ± 0.6 sec (−4.3 ± 1.6%) and −1.1 ± 0.6 sec (−3.8 ± 1.0%), respectively ($P < 0.002$ *vs.* placebo at 36 months for both groups). In contrast, by 24 months, the placebo group became significantly slower to complete the tasks of the PPT, an effect that persisted through month 35 ($P < 0.05$ *vs.* baseline; Fig. 1A). At the end of the study, subjects in the placebo group had a mean increase in time to complete the PPT of 1.3 ± 0.6 sec (+5.61 ± 1.92%) over baseline. Overall, the groups receiving T or T + F had improvement in the timed, combined PPT over the duration of the study compared with placebo ($P < 0.001$ for T and $P < 0.01$ for T + F; Fig. 1A). There were no significant differences between subjects receiving T and T + F ($P = 0.51$). For the two T treatment groups, changes in PPT over time correlated significantly with both change from baseline in total T level ($P = 0.014$) and change from baseline in bioavailable T level ($P = 0.003$), but not with baseline total T level.

TABLE 1. Baseline characteristics (mean ± SD) of older men administered im T (T-only), T + F, or placebo for 36 months

Characteristic	Placebo (n = 24)	T-only (n = 24)	T + F (n = 22)
Age (yr)	71 ± 5	71 ± 4	71 ± 4
Weight (kg)	84.9 ± 14.4	88.2 ± 11.5	83.0 ± 10.0
Body mass index (kg/m^2)	27.8 ± 3.6	28.7 ± 3.6	27.0 ± 2.7
Hormones			
Total T (nmol/liter)	10.5 ± 1.7	9.9 ± 1.6	10.1 ± 2.1
DHT (nmol/liter)	1.0 ± 0.5	0.8 ± 0.3	0.9 ± 0.2
Leptin (ng/ml)	3.9 ± 1.9	4.8 ± 2.4	4.3 ± 2.1
Adiponectin (μg/ml)	7.4 ± 4.1[a]	9.8 ± 4.3	11.3 ± 5.5
Fasting insulin (μU/ml)	27.2 ± 19.6	36.0 ± 27.9	24.1 ± 11.3
Serum lipids			
Total cholesterol (mg/dl)	213 ± 6	197 ± 6	214 ± 7
LDL-C (mg/dl)	135 ± 6	122 ± 6	137 ± 6
HDL-C (mg/dl)	48 ± 2.4	43 ± 2	46 ± 2
Triglycerides (mg/dl)	135 ± 1	143 ± 1	137 ± 1
Body composition			
Total LBM (kg)	54.6 ± 7.4	55.5 ± 5.1	52.9 ± 5.8
Total FM (kg)	26.0 ± 9.9	28.0 ± 8.7	25.8 ± 6.4
Total % body fat	30.5 ± 8.1	31.8 ± 6.5	31.4 ± 5.3
Right leg fat (kg)	3.6 ± 1.6	4.2 ± 1.5	3.7 ± 1.3
Right leg % fat	27.5 ± 9.0	30.7 ± 7.3	30.4 ± 6.4
Trunk fat (kg)	14.8 ± 6.4	15.0 ± 5.3	13.5 ± 4.2
Trunk % fat	33.5 ± 9.8	34.3 ± 8.1	31.9 ± 9.5
WHR	0.99 ± 0.04	0.99 ± 0.04	0.99 ± 0.02
Strength and function			
Right handgrip (kg)	41.0 ± 9.6	37.7 ± 7.4	37.8 ± 6.2
Left handgrip (kg)	36.3 ± 8.7	34.6 ± 6.2	34.4 ± 6.5
Timed PPT (sec)	26.0 ± 4.0[a]	29.4 ± 4.9	28.2 ± 4.3

[a] $P < 0.05$ compared to other groups.

Strength

Right handgrip strength increased significantly from baseline in both groups receiving T ($P < 0.0001$ for T-only and $P = 0.008$ for T + F compared with baseline; Fig. 1B), and these

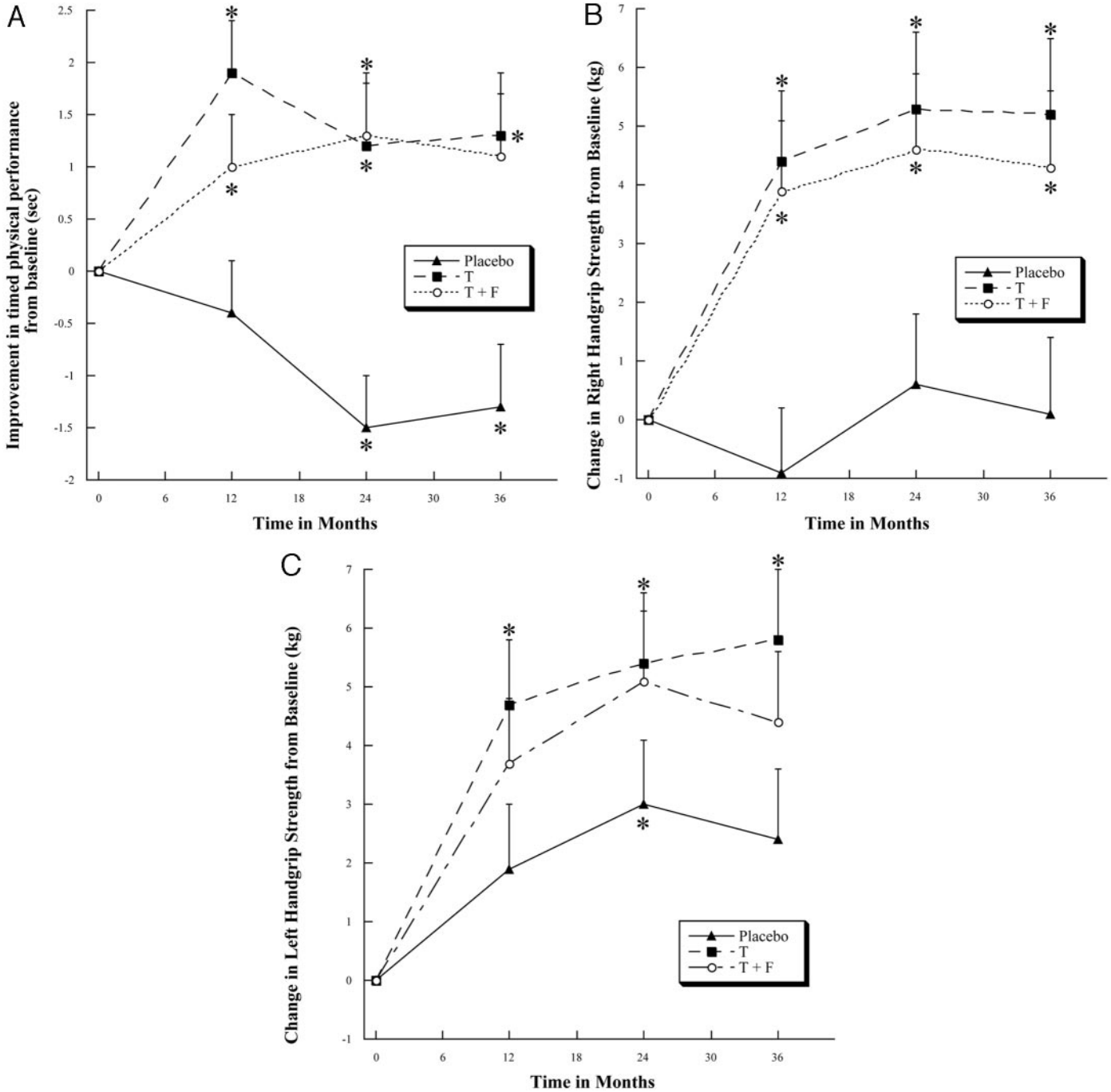

FIG. 1. Change in physical function and strength in older men with low T treated with T, T + F, or placebo for 36 months. Change (mean ± SEM) in timed PPT (A), right handgrip strength (B), and left handgrip strength (C). *, $P < 0.05$ *vs.* baseline. Overall, the T groups were significantly different from the placebo group for the timed performance test and right handgrip strength ($P < 0.002$ for both T and T + F *vs.* placebo for both measures).

changes were significantly different from the placebo group ($P = 0.01$ for T-only and $P = 0.047$ for T + F compared with placebo), which showed no significant change over time. Similarly, left handgrip strength improved significantly compared with baseline in both groups receiving T and at 24 months in the placebo group (Fig. 1C). Although there was a trend toward a greater improvement in left handgrip strength in the two T-treated groups compared with placebo, there was not a significant difference in left handgrip strength between the T and placebo groups because of the increase in strength in the placebo group. The change in right handgrip strength with time in the T-treatment groups did not correlate significantly with either baseline or change in total or bioavailable T levels. Overall, isokinetic lower extremity strength measured at both the ankle and the knee was not significantly different in the groups receiving T compared with the placebo group, and there were no

differences between subjects receiving T and those receiving T + F (data not shown).

Body composition

There were no significant changes in weight in any of the groups over the entire 36-month period (Table 2), although both groups receiving T had a transient increase between months 2 and 4 (maximum increase at month 3 of 1.6 ± 0.8 kg for T-only, and 2.3 ± 0.8 for T + F; $P < 0.05$ *vs.* baseline), which resolved by month 5. LBM increased significantly in both the T-only and the T + F groups during the study period ($P < 0.001$ in both groups *vs.* baseline), whereas it remained unchanged in the placebo group ($P = 0.45$; Fig. 2A). The mean total increase in LBM over the 36-month period for both groups receiving T was 3.7 ± 0.6 kg. These changes in LBM in the two T-treatment groups correlated significantly with changes from baseline in total T levels ($P = 0.017$), were less well-correlated with changes from baseline in bioavailable T ($P = 0.05$), and did not correlate with baseline total T levels ($P = 0.11$). Both total FM and percent body fat decreased significantly in the two groups receiving T ($P < 0.0001$ for all changes from baseline and for treatment *vs.* placebo comparisons) and were unchanged in the placebo group (Fig. 2B and Table 2). The total body fat changes in the two T groups correlated with changes from baseline in total T levels ($P = 0.047$), but not with baseline total T levels ($P = 0.70$) or changes from baseline of bioavailable T ($P = 0.06$).

Regarding fat distribution, both right leg fat and trunk fat decreased significantly in the groups receiving T (Table 2) and were unchanged in the placebo group. For subjects in the T and T + F groups, the decrease in percentage fat in the leg and trunk were similar by month 36 (right leg, −5.7 ± 0.7% fat; trunk, −6.0 ± 0.9% fat) and significantly different from the placebo group, where they remained unchanged ($P < 0.0001$). Over the 36 months, subjects in both groups receiving T had a small but significant increase in WHR when compared with placebo ($P = 0.04$ for both T and T + F *vs.* placebo). In all cases, the majority of the changes in body composition occurred within the first 6 months of treatment and were maintained through the remainder of the study (Fig. 2). There were no significant differences in any measures of body composition between the group of subjects receiving T and those receiving T + F.

Serum lipids, leptin, adiponectin, and insulin

Fasting total serum cholesterol and triglycerides significantly decreased in subjects receiving T or T + F by the 12th month of treatment, and LDL-C was decreased in these groups by month 36 (Table 3) when compared with baseline ($P < 0.05$; Table 3). Serum lipids were unchanged in the placebo group at all time points examined. HDL-C remained stable in all three groups throughout the study. Similar to changes in FM, leptin decreased in subjects in both groups receiving T but was unchanged in the placebo group ($P < 0.02$ for differences between groups over time) (Table 3 and Fig. 2C). In contrast, serum adiponectin and fasting insulin levels were unchanged when compared with baseline in any of the groups (Table 3).

Discussion

This study demonstrates that T therapy, alone or in combination with F, when compared with placebo can increase physical function in generally healthy older men with low serum T. T therapy has been shown to alter body composition and increase LBM in other studies in men who were

TABLE 2. Body composition (95% CI) measured by DXA in older men administered im T alone, T + F, or placebo

	Baseline	6 months	12 months	36 months	Difference in trend over time (*vs.* placebo)
Weight (kg)					
T-only	88.2 (83.7–92.7)	89.9 (85.2–94.5)	88.2 (82.5–94.0)	87.5 (81.1–93.9)	0.42
T + F	83.0 (78.9–87.1)	82.9 (78.2–87.6)	83.7 (78.4–88.9)	80.9 (74.9–86.9)	0.66
Placebo	84.9 (79.1–90.7)	85.2 (78.8–91.7)	84.4 (77.9–90.8)	82.2 (75.0–89.5)	
Percentage total body fat (%)					
T-only	31.8 (29.2–34.4)	28.3 (25.5–31.1)[a]	26.7 (23.5–29.8)[a]	26.3 (23.0–29.8)[a]	<0.0001
T + F	31.4 (29.2–33.6)	31.3 (29.0–33.7)[a]	26.9 (24.3–29.5)[a]	25.1 (22.4–27.7)[a]	<0.0001
Placebo	30.5 (27.3–33.7)	30.8 (27.3–34.3)	30.4 (27.0–33.8)	30.8 (26.6–35.0)	
Right leg fat (kg)					
T-only	4.2 (3.6–4.8)	3.7 (3.1–4.3)[a]	3.5 (2.8–4.2)[a]	3.3 (2.6–4.0)[a]	<0.0001
T + F	3.7 (3.2–4.2)	3.3 (2.8–3.7)[b]	3.2 (2.8–3.6)[a]	2.9 (2.2–3.5)[a]	<0.0001
Placebo	3.6 (3.0–4.2)	3.6 (2.9–4.3)	3.5 (2.8–4.2)	3.7 (2.7–4.5)	
Trunk fat (kg)					
T-only	15.0 (12.8–17.2)	13.8 (11.5–16.2)	ND	13.1 (10.1–16.2)	0.04
T + F	13.5 (11.7–15.3)	12.0 (10.1–13.9)	ND	10.3 (8.6–12.0)	0.05
Placebo	14.8 (12.2–17.4)	15.8 (12.6–19.0)	ND	14.4 (11.4–17.5)	
WHR[c]					
T-only	0.993 (0.979–1.007)	1.000 (0.988–1.012)	1.008 (0.993–1.023)	1.002 (0.984–1.021)	0.04
T + F	0.990 (0.989–1.00)	0.996 (0.977–1.016)	0.997 (0.981–1.013)	1.004 (0.987–1.002)	0.04
Placebo	0.990 (0.989–1.00)	0.985 (0.967–1.003)	0.989 (0.970–1.008)	0.983 (0.960–1.006)	

There were no significant differences in T *vs.* T + F for any measures shown. CI, Confidence interval; DXA, dual-energy x-ray absorptiometry; ND, not determined.

[a] $P < 0.0001$ compared with baseline.

[b] $P < 0.001$ compared with baseline.

[c] WHR was measured at 8, 12, and 36 months.

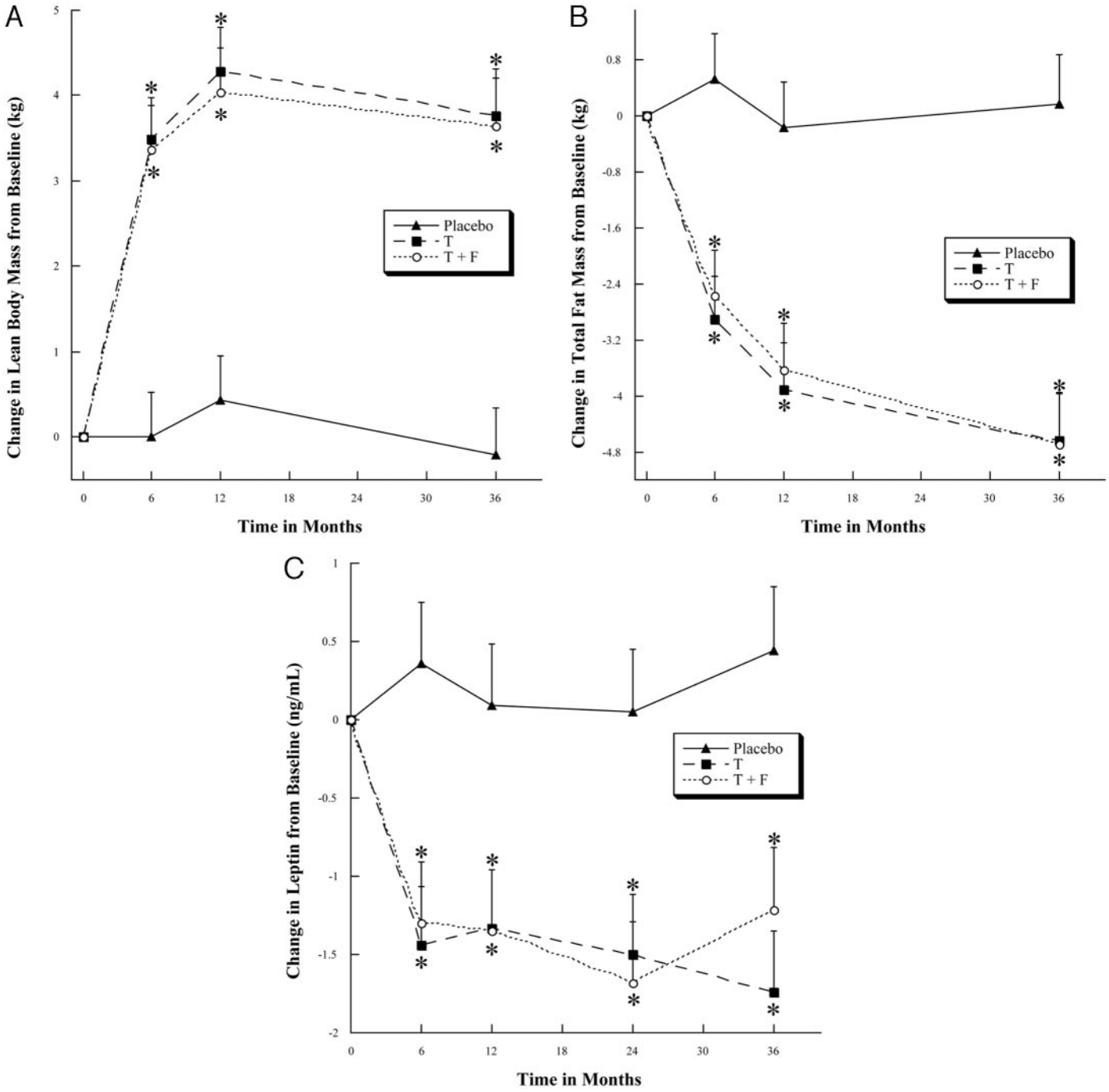

FIG. 2. Change in body composition and leptin in older men with low T treated with T, T + F, or placebo for 36 months. Change (mean ± SEM) in LBM (A), FM (B), and leptin (C). *, $P < 0.005$ compared with baseline. Overall, both groups receiving T were significantly different from placebo for all three measures ($P < 0.0001$ for total LBM and FM; $P < 0.02$ for leptin for T and T + F *vs.* placebo).

similar in age and general health to our study participants, but these changes have not translated into improved physical performance. For example, in a study of elderly, hypogonadal men, Snyder *et al.* (10) found no difference in timed walking or stair climbing, and Kenny *et al.* (22) found no change in self-reported physical activity with transdermal T administration. One group reported improvements in timed walking and stair climbing with T administration to elderly, eugonadal men of similar magnitude to those reported here (23); however, this was not in a placebo-controlled trial, and their improved performance compared with baseline might be explained by a "learned effect." Improvement with T therapy has not been a consistent finding with other measures of physical function such as maximum rate of O_2 consumption (24). Our ability to demonstrate a positive effect on physical function may reflect differences in T delivery and T levels. In particular, injectable TE, used in this study, achieves higher average and peak T levels than those

TABLE 3. Mean (±SEM), serum total, HDL-C, and LDL-C, triglycerides, leptin, adiponectin, and fasting insulin at baseline and after 12 and 36 months of treatment with im T (T-only), T + F, or placebo in older men with low serum T

	Placebo			T-only			T + F		
	Baseline	Month 12	Month 36	Baseline	Month 12	Month 36	Baseline	Month 12	Month 36
Serum lipids									
Cholesterol (mg/dl)	213 (200–226)	206 (192–220)	206 (193–220)	197 (185–210)	181 (168–195)[a]	172 (159–185)[b]	214 (201–228)	203 (190–217)[b]	196 (182–210)[b]
LDL-C (mg/dl)	135 (124–147)	126 (114–138)	131 (117–144)	122 (111–134)	115 (103–127)	105 (92–119)[a]	137 (125–148)	132 (120–144)	121 (108–135)[b]
HDL-C (mg/dl)	48 (43–53)	47 (44–51)	47 (42–53)	43 (38–48)	43 (39–47)	41 (36–47)	46 (41–51)	45 (41–49)	47 (42–53)
Triglycerides (mg/dl)	135 (109–166)	135 (109–167)	135 (106–171)	143 (116–177)	108 (87–134)[a]	111 (87–141)[a]	137 (110–171)	108 (87–134)[a]	107 (83–138)[a]
Hormones									
Leptin (ng/ml)	3.9 (3.0–4.8)	4.1 (2.9–5.3)	3.9 (2.5–5.4)	4.8 (3.6–6.0)	3.5 (2.5–4.4)[a]	3.4 (2.4–4.4)[a]	4.3 (3.3–5.4)	3.0 (2.2–3.9)[a]	3.1 (2.1–4.1)[a]
Adiponectin (μg/ml)	7.4 (5.6–9.3)	8.7 (6.6–10.9)	9.6 (7.5–11.8)	9.8 (7.8–11.8)	12.3 (9.5–15.1)[b]	10.9 (8.6–13.2)	11.3 (8.7–13.9)	11.7 (8.9–14.4)	12.7 (9.9–15.5)
Fasting insulin (μU/ml)	27 (18–36)	26 (19–34)	21 (13–28)	35 (23–48)	25 (18–32)	23 (14–31)	24 (18–29)	26 (19–34)	23 (16–30)

Bonferroni-adjusted thresholds are 0.025 (for familywise error of 0.05) and 0.05 (for familywise error rate of 0.10).
[a] $P < 0.01$ compared with baseline.
[b] $P < 0.05$ compared with baseline.

achieved with the T patch used by Snyder *et al*. (10) or Kenny *et al*. (22). It may be that there is a threshold in T level, or a certain fractional change from baseline, required before significant improvements in physical performance are achieved, because we observed the greatest improvement in physical performance in those with the greatest incremental increase in their T level from baseline.

The clinical significance of the magnitude of improvement in physical performance seen in this study is not known. However, cross-sectional analyses suggest that hypogonadism may contribute to fall risk in elderly men (25, 26). The absolute improvement in the PPT for the subjects receiving T was small (1–2 sec), but represents a percentage improvement of approximately 4%. In fact, the degree of change in physical performance we observed is comparable to the percentage change in BMD (3–10%) and LBM (6–7%) seen in this (13) and other studies (10, 27, 28). Furthermore, men in the placebo group had significant deterioration in physical performance by 24 months when compared with baseline, supporting the notion that without intervention, there is a decline in physical function over time. It is possible that the shortened form of the PPT we used in this study had a "ceiling effect" wherein improved physiology was not reflected in improved test times, which were already near maximally shortened. Such a confounder may have been exacerbated by the fact that we studied community-dwelling elderly men, and greater improvements in performance might have been observed in a more frail population. In addition, we cannot exclude the possibility that the PPT was not sensitive enough to detect all clinically important differences between the T and T + F groups. The full PPT has been demonstrated to be an independent predictor of institutionalization and mortality in the elderly (29). We modified the PPT to include those items related to ambulation, balance, and strength. Because we used a modified test, which has not been externally validated, we cannot rule out the possibility that our modified test is less accurate than the full PPT. Nevertheless, our observation that T therapy improves physical performance supports the hypothesis that T therapy in elderly men with low serum T might improve morbidity and mortality. Determination of the effects of T replacement on mortality will require a large-scale, long-term, placebo-controlled intervention study.

The mechanisms through which T replacement improves physical performance are likely multifactorial. Improvements in strength likely contribute to improvements in physical function, because we observed a significant increase in right hand-grip strength in subjects receiving T therapy compared with the placebo group. Despite this improvement in grip strength, we did not consistently detect a difference in lower extremity strength in subjects receiving T compared with the placebo group. Such a discrepancy between improvements in grip strength and lower extremity strength have been observed in other studies (30). Indeed, in one study, T therapy improved muscle strength and power without altering muscle fatigability (31, 32), suggesting that selective components of muscle performance are regulated by T. Overall, our results suggest that changes in muscle mass and strength may not fully account for improved physical performance with T therapy.

Considering other possible mechanisms for improved physical function, we observed marked increases in LBM and decreases in FM over the 36-month treatment period in sub-

jects receiving T therapy, changes that were seen in other studies of T administration to hypogonadal men (10, 15, 22). Such changes in body composition are likely due to increases in muscle mass, as has been reported in younger men receiving T (33). In addition, subjects receiving T therapy had a significant increase in serum hemoglobin compared with baseline and placebo (13). It is possible that the resultant increased oxygen-carrying capacity in the T-treated groups contributed to improved physical performance. Additionally, although we did not include analyses of subjective measures of mood and energy level in this study, other studies have suggested that T replacement results in improvements in these parameters (12, 34), and it is possible that improvements in these factors contributed to improved physical performance in the T-treated subjects.

With the exception of one small study administering somewhat higher doses of TE for 6 months (15), the changes in body composition we report in this study are significantly greater in magnitude than those observed in other long-term studies of T therapy in older men (10, 22, 24). In particular, we observed greater increases in LBM and decreases in FM than observed by others, perhaps due to higher average serum T levels (24) or to higher peak levels with injection compared with transdermal delivery (10, 22). Indeed, we found a positive correlation between changes in LBM and FM and changes in T, supporting the notion that these effects are mediated by increases in T. Temporally, changes in body composition were dramatic over the first 6 months of therapy (Fig. 2) and tended to level off over subsequent months. Similarly, we saw a dramatic decrease in leptin levels over the first 12 months of therapy, likely reflecting decreases in overall FM. Regarding fat distribution, some studies in eugonadal men have suggested that T may preferentially decrease abdominal (35, 36) or visceral fat (37). Although we did not directly examine visceral *vs.* sc fat in this study, we did not observe a greater decrease in trunk compared with limb fat with T administration (Table 2), similar to Snyder *et al.* (10). In fact, we saw a slight increase in WHR in subjects receiving T (Table 2), results that were consistent with those recently described by Woodhouse *et al.* (38).

There has been some concern that T replacement may negatively impact cardiovascular risk in elderly men. In contrast, despite substantial increases in serum T levels, we saw a lowering of total cholesterol and LDL-C in the T treatment groups without changes in HDL-C (Table 3). Similar improvements in lipid profiles have been seen in some other studies of androgen replacement in hypogonadal men (12, 39). Interestingly, despite a significant lowering of FM (Fig. 2B), we did not observe an increase in serum adiponectin or a change in fasting insulin levels in subjects receiving T. In cross-sectional analyses, adiponectin seems to be inversely correlated with FM (40, 41), and levels have been shown to increase with weight loss in normal subjects (42, 43). High levels of adiponectin have been suggested to be cardioprotective (44) and are associated with increased insulin sensitivity (45). However, we (46) and others (41, 47) have demonstrated that adiponectin levels are decreased by T, because acute T deprivation causes a rise in serum adiponectin in mice and men (41, 46). Our data support a model wherein T replacement results in body composition changes, which might increase adiponectin levels, but such an increase is likely mitigated by the negative effects of T on adiponectin at the level of gene or protein expression. With the exception of a small increase in WHR, T replacement was not associated with any increase in markers of cardiovascular risk in this study. Long-term, prospective studies will be required to determine the impact of T therapy on cardiovascular health, but our results suggest that T replacement might reduce the risk of cardiovascular disease in men with low serum T.

The addition of F to T, which decreased serum DHT levels by approximately 50% (13), did not affect gains in physical performance, alterations in body composition, cholesterol, or metabolic markers when compared with T alone in our study. As reported previously (13), the addition of F to T attenuated the age-associated increase in prostate size seen in the placebo and T groups and prevented the increase in PSA seen with T alone. In addition, there was no significant difference in the incidence of prostate cancer in any of the groups (13). Conversely, T and T + F resulted in similar increases in hematocrit and incidence of polycythemia (13), suggesting that F is only effective in reducing the prostatic side effects of T replacement. Similar to the effects of T + F on increases in BMD, these data suggest that normal physiological levels of serum DHT are not required to mediate the beneficial effects of T therapy on performance and body composition in older, hypogonadal men. However, F inhibits only one of two isoenzymes of 5α-reductase (type 2); therefore, we cannot rule out the possibility that limited DHT production via the activity of the type 1 isoenzyme is sufficient to support these effects. Additional studies using a dual-isoenzyme inhibitor are needed to clarify the role of DHT in mediating the end-organ effects of T.

In conclusion, long-term treatment of elderly, hypogonadal men with T or T + F improved physical performance, body composition, and fasting lipid profiles. We have previously found that the addition of F minimized increases in prostate size associated with age and T therapy alone (13). Given the beneficial effects of T on these parameters, larger, long-term, randomized placebo-controlled trials designed to address the specific benefits and risks of T replacement, with and without a 5α-reductase inhibitor, on physical performance, falls, and cardiovascular and prostatic diseases are clearly warranted.

Acknowledgments

We thank Arlen Sarkissian and Dorothy McGuinness for performing hormone assays and Robin Allen for her assistance with the clinical aspects of the study.

Received September 29, 2004. Accepted November 22, 2004.

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This work was supported by National Institutes of Health (NIH) Grant AG10975 and NIH Grant HL007028 (to S.T.P.).

References

1. **Larsson L, Grimby G, Karlsson J** 1979 Muscle strength and speed of movement in relation to age and muscle morphology. J Appl Physiol 46:451–456
2. **Danneskiold-Samsoe B, Kofod V, Munter J, Grimby G, Schnohr P, Jensen G** 1984 Muscle strength and functional capacity in 78–81-year-old men and women. Eur J Appl Physiol Occup Physiol 52:310–314
3. **Frontera WR, Hughes VA, Lutz KJ, Evans WJ** 1991 A cross-sectional study of

muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol 71:644–650
4. **Forbes GB, Reina JC** 1970 Adult lean body mass declines with age: some longitudinal observations. Metabolism 19:653–663
5. **Baumgartner RN, Stauber PM, McHugh D, Koehler KM, Garry PJ** 1995 Cross-sectional age differences in body composition in persons 60+ years of age. J Gerontol A Biol Sci Med Sci 50:M307–M316
6. **Steen B** 1988 Body composition and aging. Nutr Rev 46:45–51
7. **Tenover JS** 1998 Androgen replacement therapy to reverse and/or prevent age-associated sarcopenia in men. Baillieres Clin Endocrinol Metab 12:419–425
8. **Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR** 2001 Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 86:724–731
9. **Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB** 2002 Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87:589–598
10. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL** 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 84:2647–2653
11. **Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A** 1996 Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 81:4358–4365
12. **Tenover JS** 1992 Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 75:1092–1098
13. **Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL** 2004 Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 89:503–510
14. **Sih R, Morley JE, Kaiser FE, Perry 3rd HM, Patrick P, Ross C** 1997 Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 82:1661–1667
15. **Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, Lieberman SA, Tipton K, Wolfe RR, Urban RJ** 2002 Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 282:E601–E607
16. **Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS** 2001 Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 111:261–269
17. **Gruenewald DA, Matsumoto AM** 2003 Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc 51:101–115; discussion 115
18. **Steers WD** 2001 5α-Reductase activity in the prostate. Urology 58:17–24; discussion 24
19. **Roehrborn CG, Lee M, Meehan A, Waldstreicher J** 2003 Effects of finasteride on serum testosterone and body mass index in men with benign prostatic hyperplasia. Urology 62:894–899
20. **Reuben DB, Siu AL** 1990 An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc 38:1105–1112
21. **WHO** 1989 Measuring obesity. Classification and description of anthropometric data. EUR/HFA 15. Copenhagen: World Health Organization
22. **Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG** 2001 Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 56:M266–M272
23. **Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, Urban RJ, Veldhuis JD** 2002 Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab 87:5649–5657
24. **Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St Clair C, Pabst KM, Harman SM** 2002 Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 288:2282–2292
25. **Szulc P, Claustrat B, Marchand F, Delmas PD** 2003 Increased risk of falls and increased bone resorption in elderly men with partial androgen deficiency: the MINOS study. J Clin Endocrinol Metab 88:5240–5247
26. **Jackson JA, Riggs MW, Spiekerman AM** 1992 Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. Am J Med Sci 304:4–8
27. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad Jr JG, Strom BL** 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84:1966–1972
28. **Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N** 2001 Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 54:739–750
29. **Reuben DB, Siu AL, Kimpau S** 1992 The predictive validity of self-report and performance-based measures of function and health. J Gerontol 47:M106–M110
30. **Bhasin S** 2003 Testosterone supplementation for aging-associated sarcopenia. J Gerontol A Biol Sci Med Sci 58:1002–1008
31. **Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, Casaburi R, Bhasin S** 2003 Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. J Clin Endocrinol Metab 88:1478–1485
32. **Sinha-Hikim I, Artaza J, Woodhouse L, Gonzalez-Cadavid N, Singh AB, Lee MI, Storer TW, Casaburi R, Shen R, Bhasin S** 2002 Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. Am J Physiol Endocrinol Metab 283:E154–E164
33. **Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW** 2001 Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 281:E1172–E1181
34. **Holmang S, Marin P, Lindstedt G, Hedelin H** 1993 Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. Prostate 23:99–106
35. **Herbst KL, Anawalt BD, Amory JK, Matsumoto AM, Bremner WJ** 2003 The male contraceptive regimen of testosterone and levonorgestrel significantly increases lean mass in healthy young men in 4 weeks, but attenuates a decrease in fat mass induced by testosterone alone. J Clin Endocrinol Metab 88:1167–1173
36. **Marin P, Krotkiewski M, Bjorntorp P** 1992 Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. Eur J Med 1:329–336
37. **Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P** 1992 The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord 16:991–997
38. **Woodhouse LJ, Gupta N, Bhasin M, Singh AB, Ross R, Phillips J, Bhasin S** 2004 Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. J Clin Endocrinol Metab 89:718–726
39. **Liu PY, Wishart SM, Celermajer DS, Jimenez M, Pierro ID, Conway AJ, Handelsman DJ** 2003 Do reproductive hormones modify insulin sensitivity and metabolism in older men? A randomized, placebo-controlled clinical trial of recombinant human chorionic gonadotropin. Eur J Endocrinol 148:55–66
40. **Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE** 2003 Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 46:459–469
41. **Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda M, Kondo H, Furuyama N, Kihara S, Nakamura T, Tochino Y, Funahashi T, Matsuzawa Y** 2002 Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 51:2734–2741
42. **Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D** 2003 Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 289:1799–1804
43. **Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM** 2001 Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 86:3815–3819
44. **Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB** 2004 Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 291:1730–1737
45. **Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y** 2000 Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20:1595–1599
46. **Page ST, Herbst KL, Amory JK, Coviello AD, Anawalt BD, Matsumoto AM, Bremner WJ** 2005 Testosterone suppresses adiponectin levels in men. J Androl 26: 85–92
47. **Lanfranco F, Zitzmann M, Simoni M, Nieschlag E** 2004 Serum adiponectin levels in hypogonadal males: influence of testosterone replacement therapy. Clin Endocrinol (Oxf) 60:500–507

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