CLINICAL STUDY

Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men

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Abstract

Objective: One of the factors that may promote deterioration in quality of life and body composition in elderly men is the relative decline in serum testosterone levels with aging. In this study, we assessed the effects of modest doses of testosterone and a home-based strengthening program on quality of life and body composition in elderly men with relative testosterone insufficiency.

Design: Double-blind, placebo-controlled randomized study (testosterone), and additional randomization to a resistance exercise program or no additional exercise for 12 weeks in men between ages of 65 and 85 years with relative testosterone insufficiency.

Methods: Seventy sedentary, community dwelling men were randomized to a 5 mg testoderm transdermal system applied daily vs placebo system, and additionally randomized to a home-based resistance exercise program. Subjects were randomized to Group 1 (testosterone plus exercise), Group 2 (testosterone plus no exercise), Group 3 (placebo plus exercise), and Group 4 (placebo plus no exercise). Endpoints included quality of life (assessed by the short form-36 questionnaire) and body composition (measured by dual x-ray absorptiometry scan).

Results: Serum testosterone increased by a mean of 10.0 ± 1.9, 6.6 ± 1.6, 0.52 ± 0.6, and 0.5 ± 0.6 nmol/l in Groups 1, 2, 3, and 4 respectively. There was a significant interaction of testosterone and exercise on quality of life in the domains of physical functioning ($P = 0.03$), role physical ($P = 0.01$), general health ($P = 0.049$), and social functioning ($P = 0.04$). There were no effects of testosterone or exercise on quality of life alone, nor in body composition parameters.

Conclusions: Modest testosterone supplementation to elderly men with relative testosterone insufficiency improved quality of life when accompanied by an exercise program. The combination of testosterone and exercise may be an important strategy in the elderly, though further studies are necessary to determine the long-term impact on body composition and function and for analysis of risk/benefit ratios as well.

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Introduction

Normal aging is associated with changes in body composition and mood, which may result in age-related functional deterioration. Multiple factors appear to be associated with reduction in function, including decreases in muscle mass and strength (1, 2). Functional deterioration may lead to loss of independence with a significant personal and economic cost (3). Due of the growing size of the elderly population, it is critical to develop interventional strategies that may promote health and limit disability.

One of the factors that may promote deterioration in body composition and mood is the decline in serum testosterone levels with age (4, 5). Male hypogonadism is associated with a reduction in lean body mass and testosterone replacement therapy leads to increases in body mass and strength in men (6–8). However, the relationship between gonadal hormone status and age-related changes in function and body composition is not well elucidated. Clearly, it would be important to establish interventional strategies that may promote health and limit disability in aging men; use of testosterone supplementation is one such potential strategy. Another strategy for reversing or improving age-related decline in function is a strength-training program. High-intensity strength training may improve body composition and strength, but these programs often require a highly supervised training regimen at a health club that may be inconvenient or inaccessible to elders (9).

It is possible that strength training may augment the effects of testosterone supplementation on both quality of life and body composition in older men. In animal studies, exercise increases production of local growth factors including brain-derived neuotropic factor

(BDNF) that may affect brain function (10). Testosterone and BDNF interact to maintain dendritic morphology in the rat spinal nucleus (11). Therefore, it is conceivable that the addition of an exercise program to testosterone administration may have additive effects on mental function and quality of life in elderly men as well. Furthermore, the combination of exercise training and testosterone supplementation has been shown to augment changes in body composition in other populations (12).

In this study, we investigated the use of short-term testosterone administration at modest doses on body composition and quality of life in older men with serum testosterone levels in both the lower range of normal and hypogonadal range. We also assessed the added benefit of a home-based resistance exercise program to determine whether the combination of interventions may have additive effects on such outcomes.

Methods

Study subjects

Ambulatory, community dwelling, sedentary men between the age of 65 and 85 years were recruited from the metropolitan Boston area between January 1999 and December 2002. Recruitment was performed through advertisements in local newspapers and local general medicine and geriatric clinics. We also sent recruitment letters to men whose age was within the study age range and who lived within a 10-mile radius of Massachusetts General Hospital. Names and addresses were anonymous to the research team and were purchased through a third party. Inclusion criteria included a single fasting serum free-testosterone value < 14.5 pg/ml and body mass index (BMI) between 18 and 32 kg/m^2. This serum free-testosterone concentration was 1 S.D. below the mean for samples measured from young, ambulatory blood donors at Massachusetts General Hospital, Boston (data unpublished). Sedentary status was defined as lack of participation in an exercise program including walking more than 90 min per week, jogging, or exercise in a gymnasium based on the physical activity scale for the elderly (13). Exclusion criteria included clinically unstable coronary artery or cerebrovascular disease, osteoarthritis of the lower extremity that could limit ambulation, clinically significant benign prostatic hypertropy (BPH), prostate cancer, an elevated prostate-specific antigen (PSA) value, hematocrit $> 52\%$, disorders known to affect body composition including hypokalemia, renal insufficiency, liver dysfunction (serum glutamic oxaloacetic transaminase (SGOT) $>$ twice normal, elevated total bilirubin level), diabetes mellitus, hypothyroidism, alcoholism, thromoboembolic disease or coagulopathy, supraphysiologic glucocorticoid medication during the previous 12 months, androgen medications including

supplements during the past 5 years, clinically significant psychiatric disease, or known pituitary disease, or radiation of the hypothalamus or pituitary gland.

There were a total of 196 subjects screened as outpatients, including 184 whites, 6 African American, 5 Asian, no Hispanics and one unknown. Seventy subjects met study criteria (including 62 whites, 3 African Americans, 3 Asians, and 3 unknown) and were enrolled. The study was approved by the Institutional Review Board and all subjects received informed consent.

Eligible patients underwent a baseline, outpatient visit in the General Clinical Research Center at Massachusetts General Hospital. During this visit, baseline, fasting hormone values were drawn and body composition analysis was performed.

Study design

Following the baseline visit, subjects were enrolled in a 12-week randomized, double-blind, placebo-controlled, outpatient protocol of testosterone supplementation, with an additional randomization to an exercise program or no exercise. Randomization was performed in a block design, in groups of ten, to ensure adequate randomization. Subjects were placed on a single daily testosterone transdermal system (Testoderm TTS; Alza Corp., Mountain View, CA, USA) vs placebo patch (supplied by Alza Pharmaceuticals) applied between 0600 and 0800 h. Testoderm TTS is a 60 cm^2 system that contains 328 mg testosterone and is designed to achieve a nominal delivery of 5 mg testosterone over the 24-h application period (14, 15). Additionally, subjects were randomized to a home-based resistance exercise program or were told to continue with their normal daily routine. Subjects were given calendars to fill in daily for assessment of compliance for both the study drug patch and exercise.

The exercise program consisted of 11 resistive strengthening exercises, adapted from the *Strong for Life* video (Health and Disability Research Institute, Boston University) (16). Large color-coded elastic bands of varying thickness (Therabands, The Hygenic Corp., Akron, OH, USA) were used to provide resistance to the targeted muscle group. At 50% elongation, the average force (lbs) was 2 for yellow, 2.5 for red, 3 for green, 4.5 for blue, 6.5 for black, 8.5 for silver, and 14 for gold bands. The exercises included movement patterns in both standing and sitting positions, targeted extremity and trunk muscles, and incorporated motions associated with functional activities, e.g. rising from a chair. Subjects were given verbal and written detailed descriptions of each exercise. Exercise instruction was performed at the baseline visit. Subjects then returned for an out-patient visit every 2 weeks to review the exercises, ensure adherence to the program, and progress to the next level of Theraband resistance as indicated. Perceived exertion was measured with the borg scale of perceived exertion that ranged from very, very light exertion to very, very heavy exertion. (17).

Subjects were instructed to increase resistance when they could perform ten repetitions of the exercise with a perceived exertion of less than moderate, as well as proper execution of the exercise. Subjects were instructed to perform the exercise program at home 3–4 times a week. Weekly phone calls were also made to motivate subjects to continue exercising, to ensure compliance, and answer exercise related questions. Subjects documented exercise sessions at home in a log book both to encourage patient compliance and allow for determination of exercise adherence. Exercise adherence was defined as the number of days that the subject exercised over the total number of potential exercise times (defined as three per week). Based on the log books, patients maintained 90.4% compliance overall with exercises, including 87% in the testosterone plus exercise group and 94% in the placebo plus exercise group (not significantly different).

Subjects returned at 4-week intervals for collection of old drug patches, administration of new patches, and an interval medical history and physical examination. At the 8-week visit, subjects underwent a fasting serum testosterone level drawn 3–5 h (between 1000 and 1200 h, prior to exercise) after study drug patch placement for assessment of peak serum testosterone level. Given scheduling conflicts on the final, week 12 visit, it was preferable to measure peak hormone levels at the 8-week visit, prior to the final visit. At the 12-week visit, fasting venous samples were drawn for hormone testing complete blood count, chemistry, and PSA levels. Full physical examination, body composition assessments, and quality of life testing were also performed at this visit.

The following endpoints were performed at baseline and 12 weeks.

Hormone measurements

Following an overnight fast and prior to exercise, an i.v. catheter was placed and serum was drawn at 20 min intervals for 1 h starting at 0800 h. The sera was combined, and frozen at −80 °C for hormone assays to be performed at study completion. At baseline and 12 weeks, the following laboratory tests were performed: cbc, liver function, total cholesterol, low-density and high-density lipoprotein cholesterol, triglycerides, glucose, PSA, serum insulin-like growth factor (IGF-I), estradiol, and sex hormone binding globulin (SHBG).

Quality of life

The short form (SF)-36 questionnaire (18, 19) recorded general well being during the previous 36 days. The items are formulated as statements or questions to assess eight health concepts; (i) limitations in physical activities because of health problems (physical functioning), (ii) limitations in social activities because of physical or emotional problems (role limitations due to emotional problems), (iii) limitations in usual role activities because of physical health problems (role limitations due to physical health), (iv) bodily pain, (v) general mental health, (vi) social functioning, (vii) vitality, and (viii) general health perceptions and changes in health. Higher scores are associated with a better quality of life. Antidepressant use was recorded for each patient and was categorized as current use or nonuse. Prior use of antidepressants was not recorded. The SF-36 was administered over the course of the study by two technicians who were blinded to randomization assignments.

Body composition

Weight and height were measured on all subjects and expressed as BMI. Fat and lean body mass were determined by dual energy x-ray absorptiometry (DEXA) using a Hologic-2000 densitometer (Hologic, Waltham, MA, USA). The DEXA technique has a precision error of 3% for fat and 1.5% for lean body mass (20).

Assays

Serum total and free testosterone were measured by a RIA kit (Diagnostics Products Corporation, Los Angeles, CA, USA) with intra-assay coefficients of variation (CVs) of 5–12% for total testosterone and 3.2–4.3% for free testosterone. The normal range of free testosterone at the Massachusetts General Hospital (12.0–35.0 pg/ml) was established with the diagnostic products corporation assay based on a sample population of 101 healthy male volunteers. Estradiol was measured by a RIA kit (Diagnostics Systems Laboratories, Inc., Webster, TX, USA; sensitivity 5.0 pg/ml, intra-assay CVs 6.5–8.9%). Baseline and 12 week IGF-I samples were also batched for subsequent analysis by RIA, in which paired samples from baseline and 12 week were run in the same RIA following acid ethanol extraction to remove IGF binding proteins (IGFBPs) with an intra-assay coefficient of variation of 2.4–3.0% (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). SHBG was measured in batch by an in-house IRMA (Esoterix Endocrinology), with a lower limit of detection of 10 nM, intra-assay CV of 2.4–3.9% and a normal female range of 40–120 nM. Estradiol was determined in batch using a RIA kit (Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 2.2 pg/ml (to convert estradiol to picomoles per liter, multiply picograms per milliliter by 3.671), an intraassay CV of 6.5–8.9%. Lipid panels, cbc, liver panel, and PSA were measured by standard techniques.

Statistical analysis

Baseline characteristics of the study subjects were compared among the four study groups by means of one-way ANOVA. The analysis was conducted based on intention to treat analysis. The effects of testosterone

supplementation and exercise on the longitudinal change in all endpoint variables were examined by longitudinal mixed models ANOVA approach. The factor variables in the model were study group (4 levels by design), time (baseline, 4, 8, and 12 weeks), study group×time interaction, where the subject level intercept was the random effect and the assumed longitudinal correlation structure was exchangeable. All comparisons were performed by two-sided tests and resulting P values <0.05 were considered statistically significant. All analyses were performed using Statistical Analysis System (SAS) V8.2. All data are expressed as mean±s.e.m. or otherwise noted. Efficacy of testosterone supplementation with regard to achieved serum testosterone values was determined by comparison of the mid-day (peak) serum level at week 8 with the baseline measurement.

Sample size was determined largely for analysis of body composition. For body composition, we calculated that 16 subjects per group would reach a power of 80% to detect a decrease in fat mass with testosterone using DEXA scan by 2.5 ± 1.6 kg (s.d.), based on a study with testosterone supplementation in elderly men (21). Given the factorial nature of the present analysis, it was felt that the present sample size would be sufficient.

Results

Seventy subjects were enrolled in the study. At baseline, there were no significant differences in serum testosterone values across randomization groups (Table 1). The median (range) of baseline serum testosterone was 14.9 nmol/l (5.7–24.4) for Group 1, 13.6 nmol/l (0.9–17.8) for Group 2, 13.9 nmol/l (0.7–23.8) for Group 3, and 14.6 nmol/l (6.9–22.2) for Group 4. Eight subjects withdrew from the study (two in Group 1, one in Group 2, three in Group 3, one in Group 4, $P=$ NS between groups), 5 were due to events unrelated to study drug, including bruised ribs, need for knee replacement, angina prior to the baseline visit, nausea during the first week of the study, and excessive time commitments. Another subject in the placebo arm withdrew because of depression. One subject on the testosterone patch discontinued due to increased bladder outlet obstruction symptoms at 10 weeks (the PSA level was normal). Another subject on the testosterone patch discontinued

because of rash. Therefore, 15 subjects completed the study in Group 1, 16 in Group 2, 15 in Group 3, and 16 in Group 4. Table 2 outlines the progression of resistance used in the two exercise groups. All subjects increased the level of resistance during the course of the exercise intervention ($P=0.003$).

Serum testosterone increased significantly in Groups 1 and 2 compared with the placebo Groups 3 and 4 ($P=0.0008$, Fig. 1). There was no significant interaction of exercise on serum testosterone. As shown in Fig. 1, serum testosterone increased by a mean of 10.0 ± 1.9, 6.6 ± 1.6, 0.52 ± 0.6, and 0.5 ± 0.6 nmol/l in Groups 1, 2, 3, and 4 respectively. Interestingly, the increase in serum testosterone was higher in Group 1 vs Group 2 ($P=0.04$). There was no significant change in serum estradiol, SHBG, or IGF-I (Table 3).

Quality of life

Data are shown in Table 4. SF-36 scores were similar between groups at baseline. The interaction of testosterone and exercise was significant for physical functioning ($P=0.03$), role physical ($P=0.01$), general health ($P=0.049$), and social functioning ($P=0.04$). There were no effects of testosterone or exercise alone.

Body composition

At baseline, body composition assessments were similar between Groups. (Tables 1 and 5) Following the 12-week study, there were no significant changes in fat or lean measurements, measured by DEXA, due to drug, exercise, or the interaction. Results of DEXA scans are shown in Table 5.

Safety

There were no significant changes in lipid profiles (Table 3). No patient had a serum hematocrit $>52\%$. At week 12, an elevated PSA was noted in four subjects in the testosterone groups, including two in the exercise group and two in the no exercise group; in three of these, the PSA returned to normal at follow up. The other patient was lost to follow-up. In all four subjects with an elevated PSA value, the PSA value also increased by ≥1.5 ng/ml. There were no instances of PSA >4 ng/ml in the subjects who received the placebo

Table 1 Baseline characteristics. Data are expressed as mean±s.d.

	T+**E** (17)	**T**+**NE** (17)	**P**+**E** (19)	**P**+**NE** (17)	*P*-value
Age (year)	73±5.1	72±5.0	72±5.4	72±5.2	NS
Weight (kg)	79.6±13.0	85.7±12.3	81.0±14.26	81.4±13.9	NS
BMI (kg/m²)	27±3.4	28.2±2.5	27.7±3.8	27±4.0	NS
%Body fat (BIA)	25.3±6.3	23.7±4.9	22.2±7.4	25.5±6.0	NS
W/H ratio	0.97±0.06	0.98±0.05	0.97±0.05	0.96±0.04	NS

T, testosterone; P, placebo; E, exercise; NE, no exercise. BMI, body mass index; W/H ratio, waist-to-hip ratio; NS, not significant. BIA, bioelectrical impedance analysis.

Table 2 Progression of resistance with Therabands based on number of subjects per biweekly visit.

	Time (week)						
Theraband	0	2	4	6	8	10	12
Group 1 (T plus exercise)							
Yellow	0	0	0	0	0	0	0
Red	9	1	0	0	0	0	0
Green	3	7	2	0	1	1	1
Blue	3	4	7	2	2	1	1
Black	0	3	5	8	2	1	1
Silver	0	0	1	3	7	2	2
Gold	0	0	0	1	3	10	10
Group 3 (Placebo plus exercise)							
Yellow	2	0	0	0	0	0	0
Red	6	4	2	0	0	0	0
Green	7	4	3	0	0	0	0
Blue	1	8	4	6	1	1	0
Black	0	0	6	4	6	0	0
Silver	0	0	1	5	3	5	5
Gold	0	0	0	1	6	8	8

The descending colors reflect increasing resistance. In both groups, there was a progressive increase in number of subjects using greater resistance exercise during the 12-week study period.

drug. As described above, one subject discontinued because of fatigue, another because of bladder outlet symptoms (in the testosterone group), and another because of rash.

Discussion

The topic of the decline in serum testosterone with age, and whether testosterone supplementation should be administered in elderly men, has generated enormous interest. A decline in serum testosterone levels with age has been reported in multiple studies, raising the hypothesis that testosterone supplementation may improve function and quality of life (22–24). As the population continues to age and life expectancy increases, the issues of androgen insufficiency in senescence, including use of testosterone preparations to minimize the effects of aging, become increasingly important.

Though studies have suggested a relationship between aging, reduction in serum testosterone, and quality of life, the association has not clearly been established (25). In a study by Finas *et al.* (26) of 65 older men hospitalized for prostate disease, hypogonadal men had the impression of a reduced physical ability compared with eugonadal men, using the SF-12 questionnaire. Other quality of life domains were similar between the groups. Other studies have shown variable associations between androgen levels and quality of life and depression in older men (27, 28).

In our study, we demonstrated a beneficial effect of the combination of modest doses of testosterone via a transdermal preparation and a home-based exercise program on quality of life. The improvements in quality of life were particularly noted in the domains of physical functioning, role physical, general health, and social functioning subscales of the SF-36. Our data show that

the addition of an exercise program may augment the effects of testosterone on quality of life, as there was no effect of either the testosterone administration or resistance exercise alone on quality of life. This lack of benefit of either testosterone or exercise alone was not due to lack of compliance with either the study medication or the graded exercise program, but possibly due to the relatively short time period or limited number of subjects (resulting in a type B statistical error). In a prior study, administration of testosterone for 12 months improved quality of life in elderly subjects with low normal serum testosterone (29). However,
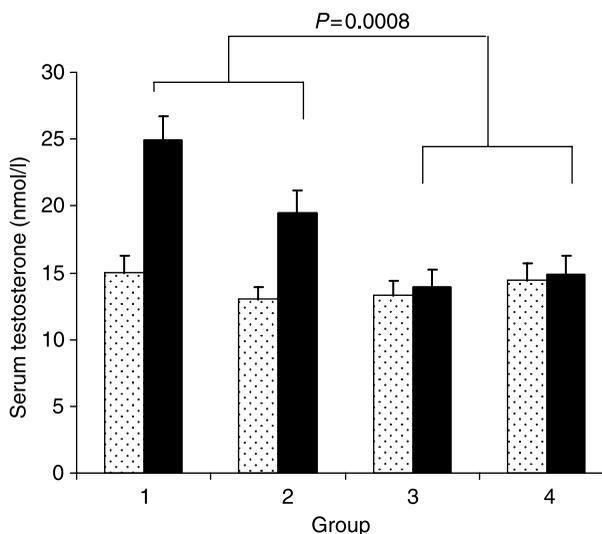

Figure 1 Serum testosterone levels at baseline (hatched) and 8 weeks (solid black) in Groups 1 (testosterone plus exercise), 2 (testosterone plus no exercise), 3 (placebo plus exercise), and 4 (placebo and no exercise). Serum levels at week 8 were drawn 3–5 h following morning placement of testosterone patch. Serum testosterone levels at 8 weeks were higher in Groups 1 and 2 vs 3 and 4, as shown, $P=0.0008$.

Table 3 Effect of testosterone supplementation and exercise on hormone and biochemical parameters.

	Time (week)	T+E	T+NE	P+E	P+NE	*P*-value[a]
IGF-I (ng/ml)	0	167.5±19.7	158.6±16.8	136.2±7.6	132.5±8.6	NS
	12	133.0±12.5	166.0±38.2	142.7±16.0	168.3±21.9	
Estradiol (pg/ml)	0	26.9±3.0	26.6±3.4	29.7±3.4	36.9±5.4	NS
	12	30.1±4.9	43.1±6.9	28.8±3.6	36.5±4.0	
SHBG (nmol/l)	0	86.4±8.7	64.9±6.8	75.6±7.9	89.0±10.4	NS
	12	59.9±23.9	60.3±5.0	66.1±11.0	78.6±28.7	
PSA (ng/ml)	0	1.9±0.3	1.6±0.2	1.5±0.2	1.7±0.3	NS
	12	2.2±0.3	2.0±0.3	1.3±0.2	1.8±0.3	
Total cholesterol (mg/dl)	0	179.2±10.8	177.1±7.0	181.0±7.9	182.2±10.9	NS
	12	176.4±6.0	172.8±6.2	174.9±6.8	183.1±13.4	
LDL-cholesterol (mg/dl)	0	110.7±10.5	103.9±6.2	111.8±6.6	106.1±7.3	NS
	12	109.4±6.2	99.6±6.2	103.4±6.1	108.5±12.5	
HDL-cholesterol (mg/dl)	0	46.5±2.5	44.4±2.0	44.4±2.0	46.8±3.4	NS
	12	45.3±2.7	41.2±1.9	45.0±2.6	47.1±3.8	
Total triglycerides (mg/dl)	0	110.5±10.4	152.9±22.4	123.7±12	154.1±44	NS
	12	108.2±12.3	173.4±33.8	131.9±16.6	157.7±40.6	

IGF-I, insulin-like growth factor-I; SHBG, sex hormone binding globulin. T, testosterone; P, placebo; E, exercise; NE, no exercise; LDL, low density lipoprotein; HDL, high density lipoprotein; PSA, prostate-specific antigen.
[a]For comparison of interaction of testosterone treatment and exercise by ANOVA. NS, not significant.

testosterone supplementation to elderly men with normal serum testosterone levels may not improve quality of life. For example, administration of i.m. testosterone to 22 elderly men with normal serum testosterone levels in a randomized, double-blind placebo controlled study for 8 weeks did not affect SF-36 scores (30). However, supraphysiologic testosterone levels were attained in this study, so it is unclear how these data may be applicable to more physiologic dosing. It is possible that, in a population of men without frank hypogonadism, modest increases in serum testosterone levels alone may not have significant quality of life effects, or may take a longer period of time for effect. It is also possible that greater quality of life effects may be achieved in a population receiving substitution therapy only, though the present study did not address that question. We noted that 12% of subjects who received testosterone therapy had an

elevated PSA value. Further studies regarding long-term administration of testosterone need to determine the benefit/risk ratio, particularly with respect to risks involving the prostate gland.

Aging is associated with a reduction in lean body mass and an increase in fat mass (31–33). As hypogonadism is associated with similar changes in body composition, it has been hypothesized that the testosterone decline with aging may have a role in these changes in body mass. Administration of testosterone for relatively short periods may affect body composition. Urban *et al.* (34) administered testosterone for 6 weeks as parenteral, i.m. injections to six elderly men with basal serum testosterone < 15.6 nmol/l, and noted an increase in skeletal muscle protein synthesis and strength, though body composition was not assessed. In this study, peak serum testosterone levels increased by approximately 20.8 nmol/l in several subjects,

Table 4 Effect of testosterone supplementation and exercise on sense of well being using the short form-36 survey.

	Time (week)	T+E	T+NE	P+E	P+NE	*P*-value[a]
Physical functioning	0	65±22	79±15	83±17	70±22	0.03
	12	74±26	73±20	85±12	75±21	
Role physical	0	54±41	83±31	86±24	78±31	0.01
	12	77±29	93±21	81±32	66±42	
Bodily pain	0	76±22	77±22	86±11	80±23	NS
	12	77±18	81±14	81±20	75±24	
General health	0	67±20	79±13	77±21	71±17	0.049
	12	74±15	77±18	83±18	67±21	
Vitality	0	57±19	69±15	70±22	62±18	NS
	12	61±19	69±17	71±17	63±18	
Social functioning	0	86±16	92±12	94±9	79±22	0.04
	12	90±12	94±15	92±12	89±21	
Role emotional	0	75±28	83±31	93±18	76±37	NS
	12	96±12	79±34	94±19	83±25	
Mental health	0	83±12	81±10	85±12	78±19	NS
	12	86±12	83±11	84±12	76±15	

T, testosterone; P, placebo; E, exercise; NE, no exercise.
[a]For comparison of interaction of testosterone treatment and exercise by ANOVA. NS, not significant.

Table 5 Effect of testosterone supplementation and exercise on body composition by dual-energy absorptiometry.

	Time (week)	**T+E**	**T+NE**	**P+E**	**P+NE**	***P*-value**[a]
Total body fat (kg)	0	23.9±6.8	26.3±4.5	23.3±10.7	24.5±9.6	NS
	12	23.6±7.2	26.4±5.1	22.8±10.6	25.2±9.6	
Total lean (kg)	0	52.9±8.1	56.3±8.8	50.3±15	54.2±5.8	NS
	12	53.7±7.4	56.1±7.7	50.8±15	54.9±6.1	
Trunk fat (kg)	0	15.1±4.7	16.5±2.9	14.4±6.7	14.8±6.0	NS
	12	14.8±5.0	16.6±3.2	14.2±6.2	15.1±6.1	
Trunk lean (kg)	0	26.1±4.4	27.8±4.7	25.1±6.9	26.6±3.1	NS
	12	26.5±3.7	27.7±4.1	28.3±13	26.9±3.2	
Extremity/trunk fat ratio	0	0.77±0.1	0.77±0.1	0.78±0.1	0.8±0.1	NS
	12	0.77±0.1	0.76±0.1	0.8±0.1	0.8±0.1	
Extremity/trunk lean ratio	0	0.89±0.1	0.89±0.1	0.9±0.1	0.9±0.1	NS
	12	0.89±0.04	0.89±0.1	0.85±0.2	0.9±0.1	

T, testosterone; P, placebo; E, exercise; NE, no exercise.
[a]For comparison of interaction of testosterone treatment and exercise by ANOVA. NS, not significant.

indicating that the clinical effects were achieved in the setting of relatively large increases in serum levels in at least some of the subjects. Studies of short-term administration of modest doses of testosterone in elderly men with low normal to overt testosterone deficiency have shown variable effects on body composition. Tenover (35) administered testosterone injections for 12 weeks to 13 elderly men with testosterone insufficiency and showed and increase in lean mass, without changes in fat mass as assessed by hydrodensitometry. Brill *et al.* (36) administered Androderm transdermal testosterone 5.0 mg/d for 4 weeks to ten men with basal serum testosterone <15.6 nmol/l and showed no effects on lean mass as assessed by hydrostatic weighing or air displacement plethesmography. These studies suggest that androgen formulation and treatment regimen may have an important impact on body composition effects. The effects of testosterone in young men on body composition are dose dependent and modest increases in serum testosterone may have minimal to moderate effects on fat and lean mass in both young and elderly men (37).

In our study, modest increases in serum testosterone over 12 weeks in sedentary, elderly men did not alter body composition. Exercise alone or in addition to testosterone administration did not affect these findings. In a recent 12 week randomized, blinded, placebo controlled study of testosterone administration and exercise in 71 elderly men with similar serum testosterone cutoffs as in our study, Sullivan *et al.* (38) noted that testosterone supplementation increased midthigh cross sectional muscle area, though lean and fat body mass data were not presented. Of note, testosterone supplementation increased serum testosterone levels in this study by approximately 8.7 nmol/l higher than that was attained in our study, suggesting that a higher testosterone dose may have greater effects on body composition. Also, this study failed to demonstrate an interaction between testosterone supplementation and exercise on body composition. These data support the concept that higher doses, along with a prolonged

treatment regimen, of testosterone are necessary in order to achieve body composition effects. However, in a previous study in HIV-infected eugonadal men, testosterone supplementation resulted in change in body composition within 12 weeks, suggesting that 12 weeks may be sufficient in a study involving testosterone administration (12). Also, more rigorous training regimen may be necessary to promote changes in body composition in a 12 week period.

The goal of the study was to target older men with both low normal testosterone levels and overt hypogonadism. In our study, there are insufficient numbers of subjects to determine whether there are different outcomes between testosterone supplementation in men with low normal serum testosterone values vs replacement therapy in men with overt hypogonadism. A potential limitation of this study is the inclusion criterion for testosterone insufficiency. We used a serum free-testosterone cutoff of 1.0 s.D. below the mean for young men using data generated from blood donors at the research institution. This cutoff was utilized in order to investigate the hypothesis that testosterone administration to men with serum values lower than the mean for young men may have beneficial effects. We used the analog assay for free-testosterone measurement for screening purposes, which may underestimate the true serum free-testosterone value compared with the dialysis method and is presently considered relatively inaccurate in assessing free-testosterone status (39). It would be preferable for future studies to use either the dialysis method or calculated free-testosterone index (40). Though our goal was to recruit subjects who were not strictly hypogonadal, inclusion of men with normal serum testosterone values may, in part, explain the meager effects seen on body composition and quality of life. Another potential limitation is the inclusion of ambulatory, community dwelling men. It seems possible that inclusion of a more frail population would lead to greater responses to the interventions. However, our goal was to investigate the effects of testosterone supplementation and low-impact resistance exercise in

a more general elderly male population. Therefore, we limited recruitment to involve more sedentary subjects to attempt to maximize exercise and testosterone benefits on body composition. Further studies are necessary, with more specific patient sub-populations, to determine those who may have maximal benefit from such interventions.

We noted that, in the groups that received the testosterone patch, those co-randomized to exercise achieved serum testosterone levels higher than those randomized to no exercise. The reasons for this finding are unclear. Though exercise may lead to transient increases in serum testosterone (41), it is unlikely that there were acute effects of exercise on testosterone production or metabolism, as subjects did not perform exercise for 24 h prior to serum sampling. Also, serum testosterone levels following i.m. administration are not affected by exercise, suggesting that exercise does not affect testosterone metabolism following parenteral administration (42). Another possible explanation is that exercise enhanced transdermal testosterone absorption, although we are not familiar with data in this regard.

In summary, our study shows that modest testosterone supplementation in combination with a home based strengthening program improves quality of life. Further studies are needed to determine the long-term benefit of these interventions on quality of life and body composition in elderly men, and assess the risks on prostate health.

Acknowledgements

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