Oral Testosterone Supplementation Increases Muscle and Decreases Fat Mass in Healthy Elderly Males With Low–Normal Gonadal Status

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Background. Loss of muscle mass (sarcopenia) leads to frailty in older men. The decline in testosterone over the life span may contribute to this muscle loss. We studied the ability of oral testosterone to prevent muscle loss in older men over a 12-month period.

Methods. A standard dose (80 mg twice daily) of testosterone undecanoate or placebo was administered for 1 year to 76 healthy men aged 60 years or older. All men had a free testosterone index of 0.3–0.5, which represents a value below the normal lower limit for young men (19–30 years), but remains within the overall normal male range. Measurements of body composition, muscle strength, hormones, and safety parameters were obtained at 0, 6, and 12 months.

Results. Lean body mass increased ($p = .0001$) and fat mass decreased ($p = .02$) in the testosterone as compared with the placebo-treated group. There were no significant effects on muscle strength. There was a significant increase in hematocrit (0.02%) in the testosterone-treated group ($p = .03$). Plasma triglycerides, total cholesterol, and low-density lipoprotein cholesterol levels were similar in both groups, but there was a decrease in high-density lipoprotein cholesterol (-0.1 mmol/L) at 12 months in the testosterone group as compared to the placebo group ($p = 0.026$). There were no differences in prostate-specific antigen or systolic or diastolic blood pressure between the groups.

Conclusion. Oral testosterone administration to older relatively hypogonadal men results in an increase in muscle mass and a decrease in body fat.

A decrease in muscle mass (sarcopenia) is a cause of age-related frailty in aging men (1–3). In older men there is a relationship between muscle mass and various measures of androgen status including the free testosterone index (FTI) (testosterone/sex hormone-binding globulin [SHBG]) (4). Moreover, bioavailable testosterone, the fraction of testosterone that is not bound to SHBG, is associated with both muscle strength and functional status in older men (5).

In men, plasma total testosterone (TT) levels decline progressively over the life span (6–10). Because there is a concomitant increase in plasma SHBG concentration with increasing age, plasma-free and bioavailable testosterone decline even more (11,12).

In young eugonadal men, pharmacological testosterone replacement has been demonstrated to increase both muscle mass and strength (13). In elderly men with low bioavailable testosterone levels (14–16) and low–normal TT levels (17), testosterone treatment has been shown to increase muscle mass (14,15), muscle strength (16–18), and a measure of functional independence in those undergoing rehabilitation (19). Other positive effects of testosterone treatment include decreased overall and visceral adipose tissue. Controversy exists, however, concerning the effect of testosterone treatment on body composition and muscle strength in men who

have a decrease in plasma testosterone concentration over the life span but whose serum levels remain within the normal range.

An association between the FTI and muscle strength has been reported (20), but there is no such relationship with TT. In preliminary studies, we have established that, in healthy young men, the FTI is usually above 0.5, but up to 50% of elderly men have an FTI of less than 0.5. In elderly men, when the FTI is above 0.3, the TT is usually greater than 8 nmol/L, which is the conventional cut-off for the diagnosis of hypogonadism.

The aim of this study was to determine the effect of oral testosterone on body composition and muscle strength in healthy men older than age 60, with a TT >8 nmol/L and an FTI above the defined lower limit of normal (0.3), and below 0.5, therefore low–normal gonadal status relative to young men.

METHODS

Subjects

Seventy-six healthy men aged over 60 years (68.5 ± 6 years mean ± *SE*, range 60–86 years) were recruited by community advertisement. Men were included if they had at least 2 symptoms on the Saint Louis University Androgen

Deficiency in the Aging Male (ADAM) questionnaire (21), an FTI of between 0.3 and 0.5 (based on a single value obtained while fasting between 8:00 AM and 10:00 AM) and a TT >8 nmol/L. These cut-offs were established in a series of preliminary studies in which we determined that, in men with unequivocal hypogonadism (TT <8 nmol/L), the FTI was always <0.3, and in young (aged 20–30 years) healthy blood donors, the FTI was >0.5. A second value was obtained at baseline, and we have reported the mean of these two values. Exclusion criteria included a history or presence of prostate cancer or a prostate-specific antigen (PSA) >5 ng/ml (the upper limit of normal for men aged 60 years); a score of >20 on the International Prostate Symptom Score, suggesting significant urinary obstruction (13); or an abnormal prostate on digital rectal examination. In addition, subjects were excluded if they had a history of testicular, liver, or renal disease, diabetes mellitus, cardiac failure, severe dysphoria (score of >15 on the Geriatric Depression Scale), joint pain that limited their ability to perform muscle strength testing, prior use of androgen, bisphosphonate, or glucocorticoid treatment (within the preceding 6 months), or a hematocrit >50%.

The Research Ethics Committee of the Royal Adelaide Hospital approved the study. Informed consent was obtained from all subjects. The study was performed according to International Conference on Harmonisation/Good Clinical Practice.

Study Design

Subjects were treated for 12 months with either testosterone undecanoate (Andriol; Organon, Oss, The Netherlands) 80 mg orally, twice daily, or identical placebo, in a randomized, double-blind manner. The testosterone or placebo was taken prior to the onset of breakfast and dinner. Assessments were performed at 0 (baseline), 1, 3, 6, and 12 months. The dose of testosterone was halved if the hematocrit increased above 50%.

Randomization was done using a block design of 4, and the randomization was performed in the Almedica Drug Labeling System (ADLS), version 5. No person involved in the execution or monitoring of the study had access to the randomization list, other than through the Emergency Drug Identification Record (EDIR). The EDIR identified the treatment code for each individual subject.

Measurements

Body composition.—Body fat and lean body mass was measured by whole body dual x-ray absorptiometry (DEXA) (Norland Densitometry XR36; Norland Medical Systems, Fort Atkinson, WI). The within-subject coefficients of variation for fat and lean body mass were 1.6% and 1.2%, respectively.

Muscle strength.—Muscle function testing was performed at the School of Physiotherapy, University of South Australia. Quadriceps and calf peak torque were measured during concentric and eccentric maximal voluntary contraction (MVC) using a KinCom isokinetic dynamometer (Chattanooga, TN) at 60°/s and 30°/s, respectively. Subjects were instructed to move only the dominant limb through a comfortable range of motion and complete 15 repetitions. Bilateral grip peak force was measured during maximal isometric contraction using a grip dynamometer. Subjects were instructed to complete 15 repetitions on each hand. Prior to the actual test, subjects completed a minimum of 3 repetitions at 50% of maximum followed by 3 at 75% and 1 at maximum. The subjects were then rested for 2 minutes before starting the test. During the test, subjects were verbally motivated by the tester in order to maintain maximal contraction throughout the 15 repetitions. Complete strength data was not obtained in 9 subjects in the testosterone group and 7 subjects in the placebo group. The interclass correlation coefficient (ICC) for between-day comparisons of force using the KinCom dynamometer is above 0.99 (22). During analysis of the KinCom data, torque data was imported into Microsoft Excel (Redmond, WA) and filtered to remove nonisokinetic data (±2.5%).

Assays.—Blood was drawn from a forearm vein at baseline, 1, 3, 6, and 12 months. At month 1, blood samples for the measurement of plasma testosterone were drawn 4 hours after the morning dose of testosterone undecanoate. At 3, 6, and 12 months, blood samples were obtained during fasting, between 8:00 AM and 9:00 AM, and prior to the morning dose.

Total Testosterone (TT)

Serum TT concentration was determined by chemiluminescent immunoassay using Elecsys (Roche, Indianapolis, IN). The interassay coefficient of variation (CV) for this assay was 9.3% at a concentration of 10.7 nmol/L.

Sex Hormone-Binding Globulin (SHBG)

SHBG was analyzed in subject serum diluted to 1:21 by adding SHBG sample dilutent. DPC Immulite SHBG (Diagnostic Products Corporation, Los Angeles, CA), a solid-phase, 2-site, chemiluminescent, immunometric assay was used (interassay CV 4.0% at 32.3 nmol/L).

Calculated Bioavailable Testosterone (cBT)

Bioavailable testosterone was calculated from TT and SHBG concentrations using an equilibrium dissociation constant (Kd) of 5.88×10^{-9} M as previously described (23). The correlation between cBT values and BT values obtained by the ammonium sulphate precipitation method was 0.96 in 143 healthy male blood donors aged 19–65 years, and 0.79 in 131 clinic patients aged 60–88 years, self-selected for symptoms of androgen deficiency (23).

Prostate-Specific Antigen (PSA)

PSA was measured by monoclonal enzyme immunoassay (MEIA, monoassay) using AxSYM instrumentation (Abbott, Abbott Park, IL). The interassay CV was 5.1% at 2.5 μg/L.

Serum Lipids

Determination of serum lipids was done enzymatically using a Hitachi 911 (Boehringer, Germany). The interassay

Table 1. Characteristics, at Baseline, of All Subjects Randomized
to the Testosterone and Placebo Treatment Groups

	Testosterone ($n = 39$)	Placebo ($n = 37$)	p
Age (years)	69 ± 6 (60–86)	68 ± 5 (60–77)	NS
BMI (kg/m²)	27 ± 4	29 ± 5	NS
Systolic BP (mmHg)	131 ± 19	134 ± 21	NS
Diastolic BP (mmHg)	79 ± 8	78 ± 8	NS
Smokers (number)	2	1	NS
Mini Nutritional Assessment score	27.9 ± 1.2 (24.5–30)	27.3 ± 1.5 (24–30)	NS
Currently exercise (% who responded yes)	78.9	84.2	NS
Relevant Concomitant Meds (number of cases)	7	8	NS
Total testosterone (nmol/L)	17.0 ± 4.4	15.6 ± 4.5	NS
SHBG (nmol/L)	42.5 ± 13	38.9 ± 12	NS
FTI (T/SHBG)	0.41 ± 0.07	0.41 ± 0.07	NS
cBT (nmol/L)	3.17 ± 0.87	2.82 ± 0.66	NS
LH (IU/L)	5 ± 3	5 ± 3	NS
FSH (IU/L)	7 ± 4	8 ± 5	NS
IGF-1 (nmol/L)	20 ± 8	22 ± 9	NS
Total body mass (kg)	81.0 ± 14.2	84.7 ± 14.1	NS
Lean body mass (kg)	54.8 ± 7.2	56.9 ± 7.9	NS
Fat mass (kg)	23.5 ± 7.9	24.8 ± 8.6	NS
ADAM score (0–10)	5.6 ± 2	5.7 ± 2.1	NS
GDS (0–30)	6.4 ± 3.8	5.6 ± 4.4	NS

Notes: Data for age, BMI, blood pressure, and nutritional score are expressed as mean ± SD and the ranges (where appropriate are included in brackets). Exercise is expressed as the percent of subjects who say they currently undertake some form of exercise. All other data are presented as mean ± SEM. Age, BMI, nutritional score (Mini Mutritional Assessment), smoking status, and exercise habit at baseline were analyzed as potential confopunders in an intent-to-treat analysis. Relevant concomitant medications include St. John's Wort, Viagra, Xenical, Caverject, and dose change in lipid-lowering medications.

BMI = body mass index; BP = blood pressure; SHBG = sex hormone-binding globulin; FTI = free testosterone index; cBT = calculated bioavailable testosterone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor-1; ADAM = androgen deficiency in the aging male; GDS = geriatric depression scale.

CVs for the measurement of serum lipids are as follows: triglyceride 3%, total cholesterol 2.3%, high-density lipoprotein (HDL) 6.7%, and low-density lipoprotein (LDL) 3.7%.

Insulin-Like Growth Factor (IGF-1)

Serum IGF-1 concentration was measured using an enzyme-linked immunosorbent assay (ELISA) with an interassay CV of 9.2% at 18.4 nmol/L.

Hematocrit (Hct) and Hemoglobin (Hb)

Hematocrit and hemoglobin were measured using a Technicon H2 autoanalyzer (Bayer, Tarrytown, NY). The coefficients of variation for Hb are as follows: 0.67% at 15 g/dL (interassay) and 0.5% at 12.9 g/dL (intra-assay). Hematocrit is determined from red blood cell (RBC) and mean cell volume (MCV) measurements. The coefficients of variation for these measurements are as follows: RBC, 0.8% at 5.0×10^6 μL (interassay) and 0.7% at 4.39×10^9 μL (intra-assay); MCV, 0.78% at 90 fL (interassay) and 0.3% at 89.4 fL (intra-assay).

Table 2. The Timing and Nature of Early Withdrawal of Treated
Subjects and an Overview of Adverse Events

	Testosterone ($n = 39$)	Placebo ($n = 37$)	p
Number of withdrawals			
1 month	1	1	NA
3 months	1	4	NA
6 months	0	2	NA
12 months	4	5	NA
Reason for early withdrawal			
Adverse event	2	4	NA
Intercurrent illness	0	1	NA
Protocol violations	1	1	NA
Unwilling to continue	3	6	NA
Adverse events			
At least 1 AE	34	31	NA
At least 1 SAE	7	4	NA
Discontinued for an AE	2	4	NA
Drug-related AEs	11	8	NA

Notes: NA = comparative statistics not performed; NS = different not statistically significant; AE = adverse event; SAE = serious adverse event.

Statistical Analyses

Data are reported as mean ± *SE* except where otherwise specified. Analyses for the primary outcome measures (body composition and muscle strength) were performed using an intent-to-treat approach. Data on all patients randomized were analyzed. Where patients had discontinued, their last observations were carried forward in analyses of subsequent time-points to prevent bias due to differential drop-out (last-observation-carried-forward approach). All other analyses were performed for all subjects treated. The mean change over time between the treatment and placebo groups for continuous variables was compared using a two-tailed independent sample t test. Categorical data were analyzed by Fisher's exact test. $p < .05$ was considered significant.

RESULTS

Of the 76 men enrolled in the study, 39 were treated with testosterone and 37 with placebo. The characteristics of the 2 groups at baseline are shown in Table 1. There were no significant differences between the groups. There were 18 early withdrawals: 12 in the placebo group and 6 in the testosterone group ($p = .11$). The reasons for withdrawal are shown in Table 2.

Of the patients completing the study, 69.7% in the testosterone group and 80% in the placebo group took 90% or more of their tablets, and 27.3% took between 51% and 89% of the dose in the testosterone group and 20% did the same in the placebo group.

Plasma Androgen Levels

To evaluate efficacy of drug absorption, at 1 month, serum samples were obtained 4 hours after the ingestion of the morning dose taken together with food. Data were analyzed for all subjects treated. The FTI was 0.67 ± 0.05 in the testosterone group compared with 0.38 ± 0.02 in the placebo group. This represented an increase of 26.9% from
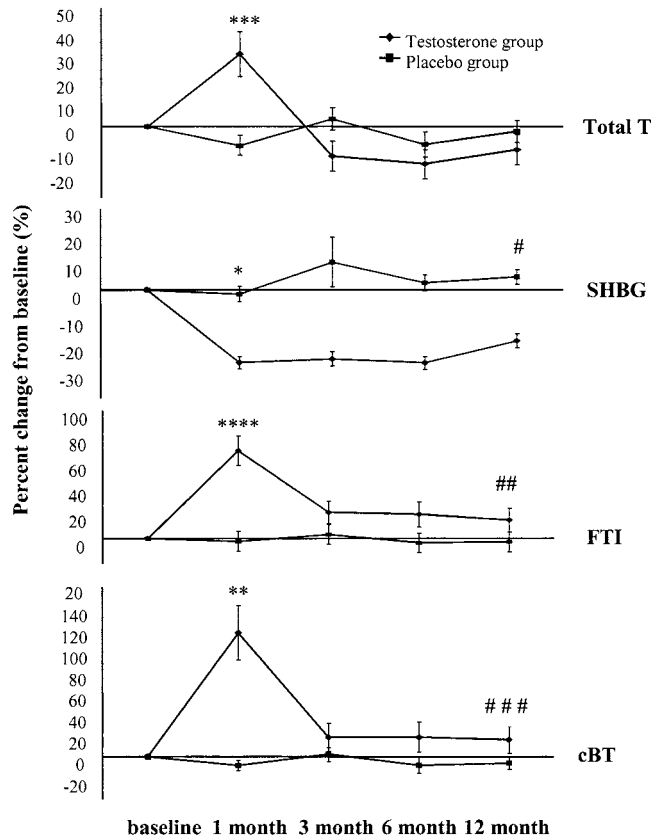
Figure 1. Plasma concentrations of total testosterone (TT), sex hormone-binding globulin (SHBG), free testosterone index (FTI), and calculated bioavailable testosterone (cBT) at baseline, 1 month, 3 months, 6 months, and 12 months in testosterone and placebo groups. Month 1 data is from plasma samples obtained 4 hours post-treatment dose; month 3, 6, and 12 data is from fasting morning blood samples prior to the morning treatment dose. $*p = .032$; $**p = .016$; $***p = .0005$; $****p < .0001$; $^{\#}p = .057$ (NS); $^{\#\#}p = .025$; $^{\#\#\#}p = .021$.
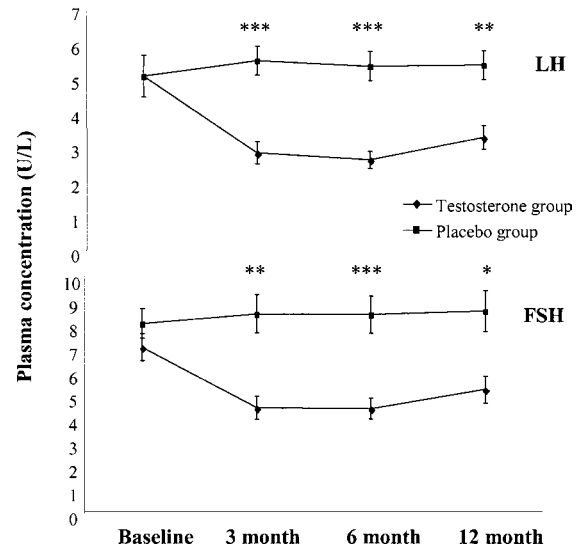

Figure 2. Plasma concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) at baseline, 3 months, 6 months, and 12 months in testosterone and placebo groups. Data presented are mean $\pm$ *SEM*. LH (top) and FSH (bottom) both decreased by month 3 in the testosterone group and remained significantly lower than the placebo group at month 12. $*p < .01$; $**p < .001$; $***p < .0001$.

pretreatment in the testosterone group and a decline of 2.3% in the placebo group ($p < .0001$). Calculated BT increased from 3.17 ± 0.15 nmol/L at baseline to 6.52 ± 0.82 nmol/L at 1 month in the testosterone group, and decreased from 2.82 ± 0.1 nmol/L at baseline to 2.57 ± 0.15 nmol/L at 1 month in the placebo group ($p = .016$).

At 12 months, TT, as measured fasting prior to the morning dose of testosterone undecanoate, had declined by 1.7 ± 1.2 nmol/L and 0.7 ± 0.11 nmol/L in the testosterone and placebo groups, respectively ($p = .56$). In the testosterone group, SHBG levels declined by $18.6 \pm 2.6\%$ and increased by $4.76 \pm 2.7\%$ in the placebo group ($p < .0001$). Accordingly, the FTI ($p = .021$) and cBT ($p = .025$) were higher in the testosterone group as compared with the placebo group (Figure 1).

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) decreased in the testosterone group. At 3, 6, and 12 months, LH ($p = .0000$, $p = .0000$, and $p = .0002$) and FSH ($p = .0001$, $p = .0000$, $p = .0015$) were lower in the testosterone group, as compared with the placebo group (Figure 2).

Body Composition

There was no change in body weight during the course of the study. After 6 months, lean body mass decreased by $1.47 \pm 0.52\%$ (0.91 ± 0.03 kg) and increased by $2.16 \pm 0.51\%$ (1.04 ± 0.07 kg) in the placebo and testosterone groups, respectively ($p < .00001$). At month 12, lean body mass had decreased by $1.65 \pm 0.49\%$ (0.98 ± 0.08 kg) in the placebo group and increased by $1.54 \pm 0.58\%$ (0.67 ± 0.05 kg) in the testosterone group ($p < .0001$, Figure 3). There was no significant change in lean body mass between 6 and 12 months in either the placebo or testosterone groups. At 6 months, fat mass decreased by $4.31 \pm 1.63\%$ (0.2 ± 0.1 kg) and increased by $4.21 \pm 1.13\%$ (0.85 ± 0.19 kg) in the testosterone and placebo groups, respectively ($p < .0001$). Over the 12 months, fat mass declined by $1.07 \pm 1.33\%$ in the testosterone group. In the placebo group, fat mass increased by $4.61 \pm 1.96\%$ (0.7 ± 0) ($p < .01$: Figure 3). These changes were significant and independent of age, body mass index, nutritional status, smoking, physical activity, and concomitant medications.

Muscle Strength

There were no significant differences in grip, quadriceps, or calf strength between the treatment and placebo groups at either 6 or 12 months (Table 3). In the treatment group, but not in the placebo group, there was a significant positive correlation between increase in lean body mass and increase in quadriceps strength (treatment group $r = .46$, $p = .02$; placebo group $r = .336$, $p = .16$, data not shown).

Insulin Growth Factor-1

At baseline, plasma IGF-1 levels were 20.4 ± 7.7 nmol/L and 21.7 ± 8.8 nmol/L in the testosterone- and placebo-

treated groups, respectively. At months 3, 6, and 12, IGF-1 levels were 22.3 ± 7.1 nmol/L, 22.0 ± 6.7 nmol/L, and 21.7 ± 7.5 nmol/L in the testosterone group, and 22.6 ± 4.8 nmol/L, 22.4 ± 7.7 nmol/L, and 21.7 ± 8.1 nmol/L in the placebo group. There were no significant differences either between or within these groups at any time.

Other Measurements

The results of safety parameter monitoring are given in Table 4. There was a small but not statistically significant improvement in the International Prostate Symptom Score, from baseline to 12 months, in the testosterone-treated group as compared with the placebo-treated group (-0.3 ± 4.0 vs 0.9 ± 5.1 [mean ± SD], $p = .25$). In absolute terms, at 3 months, 2 (6.3%) patients, and at 12 months, 1 (4.0%) patient in the placebo group had abnormal urine flow, whereas no patient had abnormal urine flow in the testosterone group at any time.

In the testosterone-treated group, there was a small but nonsignificant increase in PSA of 0.34 ± 0.89 ng/L, 0.42 ± 1.02 ng/L, and 0.38 ± 0.76 ng/L at months 1, 3, and 6, respectively. The change in the plasma PSA levels from baseline to 12 months was similar (0.1 ± 0.8 vs 0.4 ± 1.2 ng/L [mean ± SD]), in the testosterone and placebo groups, respectively ($p = .47$). A similar number of subjects in each group (6 in the testosterone-treated group and 5 in the placebo group) developed an elevated PSA (>5 ng/L) at some time during the study.

There were no differences in either LDL cholesterol ($p = .21$) or triglyceride ($p = .26$) levels between the groups. At 12 months, plasma HDL levels decreased by 0.128 ± 0.03 (mean ± SD) mmol/L and increased by 0.148 ± 0.0 (mean ± SD) mmol/L in the testosterone and placebo groups, respectively ($p = .03$).

Hematocrit increased by 2% over 12 months in the testosterone group and did not change in the placebo group ($p = .026$). After 6 and 12 months, 5 (14.7%) and 2 (6.3%) subjects, respectively, in the testosterone-treated group had a hematocrit greater than 50%, whereas none of the subjects in the placebo group did ($p = .012$).

There were no changes in either systolic or diastolic blood pressure at any time during the course of the study.

DISCUSSION

This study has demonstrated that a standard dose of oral testosterone undecanoate administered for 12 months to older men without overt hypogonadism increases muscle
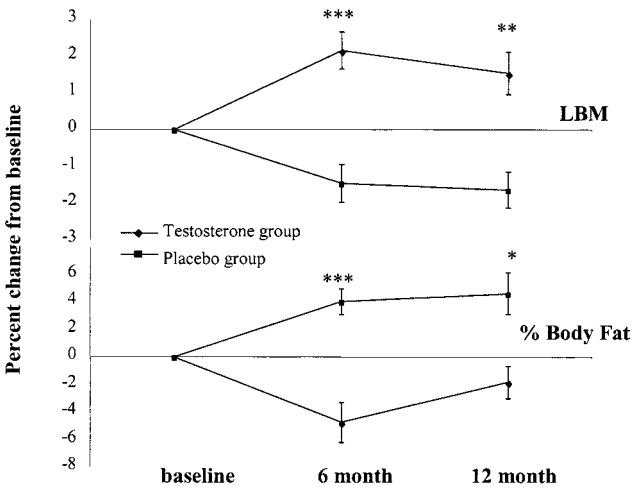

Figure 3. Percent change from baseline in lean body mass (LBM) and body fat after 6 months and 12 months of treatment with testosterone or placebo. LBM (top) increased in the testosterone group and decreased in the placebo group by month 6 and remained significantly different at month 12. Percent body fat (bottom) decreased in the testosterone group and increased in the placebo group by month 6 and remained significantly different at month 12. *$p < .01$; **$p < .001$; ***$p < .0001$.

mass and decreases fat mass. The decrease in body fat may be of significance, as it has been shown that the combination of adipose excess and muscle loss in older persons (the "fat frail") results in markedly increased morbidity (13).

Our intention in this study was to investigate men with borderline low plasma testosterone concentrations resulting from normal aging, and to exclude those who were frankly hypogonadal. Because SHBG increases with age, we utilized the FTI to define our population group. Although the FTI has limitations and its use is controversial (24,25), it does correlate significantly with a marker of testosterone action, namely muscle mass (4). We chose the range of 0.3–0.5 based on a study of 214 healthy men aged 19–83 years. When the FTI was above 0.3, the TT was always above 8 nmol/L, the cut-off used to diagnose hypogonadism in Australia. Of those aged 19–30 years ($n = 56$), all had an FTI above 0.5 and a cBT above 3.09 nmol/L [the lower reference value for cBT, calculated as 2 SD below the mean for male blood donors aged 19–29 years (23)]. Their mean cBT was 6.92 nmol/L (range: 3.26 nmol/L to 13.46 nmol/L). The cBT values of the aging men included in our study were low, relative to healthy young males, and also correlated well with the calculated FTI.

Table 3. Maximum Isometric Right and Left Grip Strength and Maximal Concentric, Isokinetic Quadriceps, and Calf Strength (Dominant Limb Only) at Baseline, Month 6, and Month 12 in Testosterone (T) and Placebo-Treated Subjects

	Right grip (Kg)		Left grip (Kg)		Quadriceps (Nm)		Calf (Nm)	
	T	Placebo	T	Placebo	T	Placebo	T	Placebo
Baseline	37.5 (1.3)	38.4 (1.6)	36.1 (1.3)	36.1 (1.4)	124.7 (9.78)	125.9 (10.24)	217.1 (12.88)	248.1 (12.93)
Month 6	39.9 (1.5)	38.6 (2.1)	37.9 (1.5)	38.9 (1.7)	168.1 (11.35)	159.8 (9.6)	224.1 (11.84)	251.6 (12.61)
Month 12	40.9 (1.4)	40.7 (2.0)	38.0 (1.3)	39.6 (1.7)	184.4 (10.52)	181.8 (9.36)	212.36 (12.60)	223.7 (10.63)

Notes: Data shown are mean (±SE). The mean differences between baseline–month 6, month 6–month 12, and baseline–month 12 were compared between the Testosterone and Placebo groups using a two-tailed independent samples *t* test. There were no significant differences between the Testosterone and Placebo groups at any time point.

T = testosterone.

Table 4. Change From Baseline to Month 12 for Safety Measures in the Testosterone and Placebo-Treated Groups

	Testosterone		Placebo		
	Mean	SD	Mean	SD	p
Hematocrit (%)	0.02	0.03	0.00	0.02	.026
PSA (ng/L)	0.09	0.83	0.36	1.19	.47
Urine flow (IPSS, 0–30)	−0.30	4.00	0.90	5.10	.25
Systolic BP (mmHg)	8.00	23.00	3.00	16.00	.40
Diastolic BP (mmHg)	2.00	10.00	1.00	11.00	.65
HDL (nmol/L)	−0.10	0.20	0.00	0.10	.03
LDL (nmol/L)	−0.10	0.60	−0.30	0.50	.21
Cholesterol total (mmol/L)	−0.20	0.60	−0.20	0.60	.81
Triglycerides (mmol/L)	0.00	0.50	−0.10	0.70	.26

Notes: The change from baseline to month 12 in hematocrit and HDL cholesterol was significantly greater in the Testosterone compared to the Placebo-treated group ($p = .026$ and .03, respectively).

PSA = prostate-specific antigen; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; IPSS = International Prostate Symptom Score.

The dose of oral testosterone (Andriol) chosen has been widely used throughout the world to treat hypogonadal men (26). In accordance with known pharmacokinetics, plasma TT, FTI, and cBT increased 4 hours after the morning dose. Trough levels of TT were decreased due to a significant and sustained reduction in SHBG. The suppression of LH and FSH reflected the efficacy of the dose used.

The effect of oral testosterone treatment to decrease body fat is consistent with observations on the effects of supplemental testosterone in either hypogonadal or a mixed population of eugonadal and hypogonadal men (14–16,32).

Testosterone replacement in young hypogonadal men (27,28) and supraphysiological treatment in eugonadal young men have been shown to increase muscle mass and strength (20). In older men with low bioavailable testosterone (16) or low–normal TT (17,18), replacement therapy increases muscle mass and strength. In longitudinal studies, men have been shown to have a decline in testosterone with increasing age at the rate of approximately 0.3 nM/year (9); these men are therefore relatively hypogonadal compared to when they were young. The finding of an increase in muscle mass in this study in response to supplemental testosterone is therefore not surprising. Moreover, it is in keeping with epidemiological studies suggesting that the FTI is a predictor of both muscle mass and strength (4). We did not, however, observe any increase in muscle strength, a finding that is in accordance with other studies where a large proportion of men with normal TT levels were included (14,15). A subjective improvement in physical functioning in response to testosterone as compared with the placebo has been reported (15). Bhasin and colleagues (29) have recently shown in young men that the muscle response to testosterone is related to dose. Therefore, if we had used a higher dose of oral testosterone, it is possible that we would have seen an effect on muscle strength as well as muscle mass. However, comparison of muscle strength between the 2 groups may not be clear because there was an apparent increase in muscle strength in both the placebo and treatment groups, raising the possibility that a neural learning effect may confound the data. There was, in fact, a significant correlation between the increase in lean body mass and increase in quadriceps muscle strength in the testosterone-treated but not the placebo-treated subjects. This suggests that the increase in muscle mass in the testosterone group may have resulted in an increase in quadriceps strength over and above a possible neural learning effect.

In addition, the relevance of muscle function testing in the elderly is confounded by wide variability in most measures. Motivation, tolerance to pain, and potential learning effects may be some of the major factors limiting the ability of these tests to identify differences between the treatment groups in this study. Accordingly, large study groups may be required to determine small treatment benefits (30). Furthermore, it should be noted that isokinetic movement rarely occurs in actual everyday tasks, limiting the interpretation of the testing used in this study. Nevertheless, quadriceps strength measured on the KinCom isokinetic dynamometer has been show to relate to gait time on a standardized walk-turn-walk test at maximal gait speed (31).

Testosterone therapy in this study was associated with half the number of dropouts compared with placebo, suggesting that patients had some perceived benefit from the therapy. Furthermore, because there were significantly more dropouts in the placebo group than in the testosterone-treated group, and because an intent-to-treat analysis was used, it is possible that significant changes may have either been overestimated or obscured.

Urban and colleagues (17) have reported previously that testosterone increased muscle IGF-1 mRNA, and Snyder and colleagues (15) reported an increase in serum IGF-1 in men receiving testosterone. There was no effect of testosterone therapy on IGF-1 levels in this study, possibly due to the dose of testosterone used. This would suggest that the increase in muscle mass is independent of any change in circulating IGF-1 levels.

There were minimal adverse effects of the testosterone therapy. Testosterone increased hematocrit, as has been demonstrated in previous studies (see Ref. 13 for a review). Levels of PSA increased transiently but not significantly, and, if anything, there was a reduction in symptom scores on the International Prostate Symptoms Score. Previously, testosterone replacement has been shown to have either no effect, or to decrease the occurrence of benign prostatic hyperplasia (33,34).

There were no significant changes in plasma total, LDL cholesterol, or triglyceride levels in this study. However, a small but significant decrease in HDL cholesterol occurred. Small decreases in plasma total and LDL cholesterol have been found in some (32,35,36) but not all (16,31,37) studies of testosterone treatment in older men, and the majority have not found a significant decrease in HDL cholesterol (16,32,35–37). There is very little other published data on the effect of oral testosterone undecanoate on plasma lipids. Uyanik and colleagues (36) reported that oral testosterone undecanoate decreased plasma LDL cholesterol, but had no effect on HDL cholesterol in healthy older men, but the dose used (120 mg/day) was lower than in our study and the duration (90 days) was shorter. The most important factor in determining the effect on plasma lipids appears to be mode of delivery, although the dose may also be a significant

factor. Intramuscular testosterone administration has consistently been reported to decrease total, LDL, and HDL cholesterol in both eugonadal and hypogonadal men (38). In contrast, transdermal testosterone has been found not to effect plasma HDL cholesterol either in eugonadal, mildly hypogonadal, or profoundly hypogonadal men irrespective of age (28,32,37,39). However, a recently reported randomized controlled trial did show a decrease in HDL cholesterol after 12 months of transdermal testosterone treatment (40). There are no long-term studies on the cardiovascular risk of testosterone replacement in older men. However, Andriol has been shown to decrease the symptoms of angina in elderly men, and a transdermal delivery system of testosterone decreases ST segment during stress testing (41).

Conclusion

This study has demonstrated that oral testosterone therapy increased muscle mass and decreased fat mass in older persons with minimal side effects. If this benefit is sustained, the development of age-related sarcopenia and frailty may be delayed or prevented.

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