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Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men: A Randomized, Double-Blind, Placebo-Controlled Study

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Context: Physical frailty is associated with reduced muscle strength, impaired physical function, and quality of life. Testosterone (T) increases muscle mass and strength in hypogonadal patients. It is unclear whether T has similar effects in intermediate-frail and frail elderly men with low to borderline-low T.

Objective: Our objective was to determine the effects of 6 months T treatment in intermediate-frail and frail elderly men, on muscle mass and strength, physical function, and quality of life.

Design and Setting: We conducted a randomized, double-blind, placebo-controlled, parallel-group, single-center study.

Participants: Participants were community-dwelling intermediate-frail and frail elderly men at least 65 yr of age with a total T at or below 12 nmol/liter or free T at or below 250 pmol/liter.

Methods: Two hundred seventy-four participants were randomized to transdermal T (50 mg/d) or placebo gel for 6 months. Outcome measures included muscle strength, lean and fat mass, physical function, and self-reported quality of life.

Results: Isometric knee extension peak torque improved in the T group (*vs.* placebo at 6 months), adjusted difference was 8.6 (95% confidence interval, 1.3–16.0; $P = 0.02$) Newton-meters. Lean body mass increased and fat mass decreased significantly in the T group by 1.08 ± 1.8 and 0.9 ± 1.6 kg, respectively. Physical function improved among older and frailer men. Somatic and sexual symptom scores decreased with T treatment; adjusted difference was -1.2 (-2.4 to -0.04) and -1.3 (-2.5 to -0.2), respectively.

Conclusions: T treatment in intermediate-frail and frail elderly men with low to borderline-low T for 6 months may prevent age-associated loss of lower limb muscle strength and improve body composition, quality of life, and physical function. Further investigations are warranted to extend these results. **(*J Clin Endocrinol Metab* 95: 0000–0000, 2010)**

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Abbreviations: ALF, Aggregate locomotor function test; AMS, Aging Males' Symptom scale; ANCOVA, analysis of covariance; CI, confidence interval; CV, coefficient of variation; FM, fat mass; IKE, isokinetic knee extension; IKF, isokinetic knee flexion; IME, isometric knee extension; IMF, isometric knee flexion; IPSS, International Prostate Symptom Score; LBM, lean body mass; MMSE, Mini Mental State Examination; 6MWT, 6-min walk test; PASE, Physical Activity Scale of the Elderly; PPT, physical performance test; PSA, prostate-specific antigen; PT, peak torque; QoL, quality of life; 1-RM, one-repetition maximum; T, testosterone.

Physical frailty is a clinical state characterized by reduced physiological reserve affecting multiple organ systems and presages adverse outcomes, including falls, disability, hospitalization, and death (1). Testosterone (T) levels decline with aging, and this is associated with decreased muscle mass and strength. Low T is an important cause of sarcopenia (2) and may therefore contribute to the development of frailty in elderly men. In cross-sectional and longitudinal studies, lower sex hormone levels are associated with greater dependency, impaired balance, and falls, whereas higher levels are associated with better performance of activities of daily living (3, 4). Although gains in muscle strength with T treatment are not age dependent (5), the effects of T on muscle strength in older men are inconsistent. Some studies in healthy older men have reported improvements in grip strength (6, 7), whereas others have not (8–11). There are limited data on the beneficial effects of T on lower limb muscle strength in elderly men (12, 13). Men with chronic obstructive pulmonary disease (14), those receiving glucocorticoids (15), and elderly men in rehabilitation (16) treated with T showed improvements in muscle strength or physical function. These small studies suggest that T treatment may yield clinically significant improvements in muscle strength and physical function in frail elderly men. The aim of this study was to determine the effects of T treatment on muscle mass and strength, physical function, and quality of life (QoL) in intermediate-frail and frail elderly men with low to borderline-low T.

Participants and Methods

Study design

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group study.

Participants

Community-dwelling men aged at least 65 yr were recruited by advertisements or mailed invitations from family practice registers and screened for the presence of frailty, according to the criteria of Fried *et al.* (1). These comprised 1) unintentional weight loss of more than 10 pounds in the preceding year, 2) self-reported exhaustion (CES-D Depression scale), 3) low physical activity ($<$270 kcal/wk, based on the Minnesota Leisure Time Physical Activity Questionnaire), 4) slow walk time (for a 15-ft. walk, cutoff times for height $\leq$173 and $>$173 cm were $\geq$7 and $\geq$6 sec, respectively), and 5) low handgrip strength (threshold for body mass index $\leq$24 was 24.1–28 and $>$28, $\leq$29, $\leq$30, and $\leq$32 kg, respectively). Those with one or more of these frailty criteria and a morning (before 1100 h) total T of 12 nmol/liter (345 ng/dl) or less or calculated free T of 250 pmol/liter (7.2 ng/dl) or less were recruited. Those with one to two criteria were categorized as intermediate-frail, and those with three or more criteria as frail (1).

Exclusion criteria were prostate cancer, benign prostatic hyperplasia [International Prostate Symptom Score (IPSS) $>$21], prostate-specific antigen (PSA) higher than 4ng/ml, chronic renal impairment (serum creatinine $>$180 mmol/liter), active liver disease, moderate to severe peripheral vascular disease, severe chronic obstructive pulmonary disease, congestive heart failure (New York Heart Association $\geq$2), angina requiring nitrates more than once weekly, untreated sleep apnea, major psychiatric illness, medications interfering with sex steroid metabolism, stroke causing persistent motor weakness, active disease of muscle and joint, and cognitive impairment [Mini Mental State Examination (MMSE) score $<$18]. The study was approved by Central Manchester Research Ethics Committee and written, informed consent obtained from each participant.

Interventions

Men in the active group applied transdermal hydro-alcoholic T gel (Testogel 1%; Bayer Schering Pharma, Berlin, Germany) at a dose of 50 mg/d for 6 months, and those in the control group received matched placebo gel. The dose of gel was adjusted to 75 or 25 mg/d according to serum T at d 10 and 3 months. Dose adjustment was undertaken if T levels remained outside the target range (18–30 nmol/liter); the placebo group therefore received the maximum dose.

Outcomes

Primary outcomes were isometric knee extension peak torque (IME-PT) and isokinetic knee extension peak torque (IKE-PT). Secondary outcomes included isometric knee flexion peak torque (IMF-PT), isokinetic knee flexion peak torque (IKF-PT), physical function tests, body composition, and QoL. All outcome assessments were carried out by a single assessor at baseline and at 6 months (end of treatment).

Sample size

Preliminary data (10) indicated interpatient SD of 27% in lower limb muscle strength assessments. We took a conservative estimate that this represented the coefficient of variation (CV) of the change (*i.e.* a low intra-individual correlation) giving 115 participants per arm to provide 80% power to detect a 10% improvement in the primary endpoint (IME-PT) at 5% significance level. This number was increased to 130 to allow for an estimated 13% dropout rate.

Randomization and blinding

The study physician, research participants, outcome assessor, and other research staff remained blinded to group assignment throughout the study. Participants were randomized into active and placebo groups in blocks of 10 by computer-generated sequence produced by the trial pharmacist, who had no contact with research participants. The dose of the T gel was adjusted by a clinician not involved in participant monitoring or outcome assessment. Precautions were taken to ensure that the outcome assessor, monitoring clinician, and the nurses remained unaware of trial medication type/dose for individual participants. For any given participant, the presence or absence of a dose adjustment did not provide sufficient information to determine which treatment had been allocated, except possibly in 27 participants who required dose reduction.

Muscle strength

IME- and IKE-PT were used as primary outcome measures (17, 18). Assessment was performed on the dominant lower limb

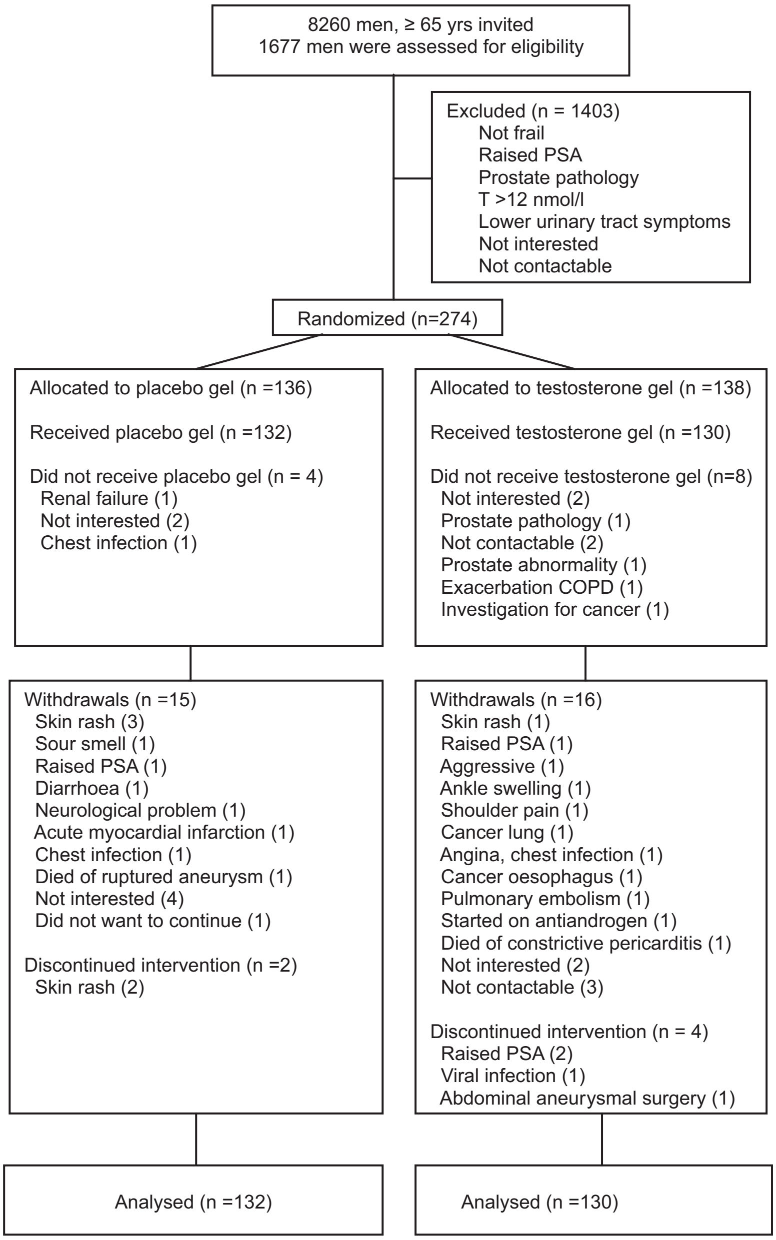

FIG. 1. Schematic diagram shows the participants invited for screening and assessed for eligibility, common reasons for exclusion, numbers of eligible participants randomized to placebo and T groups, reasons for withdrawal from the study, and final numbers of participants in the placebo and T groups.

by measuring PT (Newton-meters) in IKE, IKF, IME, and IMF contractions using an Isokom dynamometer (Biodex Medical, Shirley, NY). PT of three maximal IME and IMF contractions was measured with twitch interpolation (19) to ensure maximal muscle contraction. Twitch interpolation gives an indication of the voluntary activation of the muscle. Percutaneous stimulating electrodes were placed on the muscle being tested. Contractions were evoked using square wave pulses of 1 msec duration. The maximal twitch response was determined using stepwise voltage increases every 30 sec until voltage increment produced no further increase in torque (20). A supramaximal twitch (110%) was applied during contraction, when the force trace output reached a plateau, and participants were asked to abolish any twitch force increments observed visually. IME and IMF contractions were maintained for 5 sec and performed from a 90° knee flexion and full extension, respectively. The PT of five maximal IKE and IKF contractions was measured at an angular velocity of 90°/sec with a pause of 15 sec. One practice session for all muscle performance measures was performed a week earlier. The CV of repeatability were between 10.5 and 12.4% for IME-PT and IKE-PT, respectively. Handgrip (Jaymar's dynamometer; Asimow Engineering Co., Los Angeles, CA) was assessed by calculating average PT of three maximal isometric contractions (kilograms) in the dominant hand, after a practice session, using the methodology of the Cardiovascular Health Study (1).

Physical function tests

These included the aggregate locomotor function test (ALF) (21), physical performance test (PPT) (22), 6-min walk test (6MWT) (23), and Tinetti gait and balance test (24). Self-reported physical activity was assessed using the Physical Activity Scale of the Elderly (PASE) questionnaire (25). Walk time for the PPT was obtained from the ALF. We used the seven-item PPT that did not include the stair climb. Tests were done in a prespecified sequence in one clinic visit with rest periods in between.

Body composition

Lean body mass (LBM) and fat mass (FM) were measured by whole-body dual-energy x-ray absorptiometry using a Hologic QDR-4500, Discovery densitometer (Hologic, Bedford, MA). Departmental precision (CV percent) for whole-body DXA is 0.56% for LBM and 1.75% for FM.

QoL

QoL was assessed with the Aging Males' Symptom scale (AMS) (26), a self-administered questionnaire.

Monitoring

Levels of T, LH, FSH, and SHBG were measured by chemiluminescent immunoassay with a Roche Elecys E170 platform at baseline, 10 d, and 3 and 6 months. Inter- and intr-assay CV for T was 1.1 and 3.7%, FSH 2.6 and 3.9%, LH 1.9 and 3.0%, and SHBG 1.7 and 3.2%, respectively. Free T was calculated using the Vermeulen equation (27). Reference ranges in our laboratory for total T and free T were 10.5–35.0 nmo/liter and 250–700 pmol/liter, respectively. Digital rectal examination of the prostate and measurements of PSA, lipids, and full blood count were performed at baseline and 3 and 6 months. Treatment was withdrawn and participants referred to a urologist if PSA increased above the age-adjusted criteria (PSA ≥4.5 ng/ml if ≤70 yr and ≥6.5 ng/ml if >70 yr), in accordance with local urological practice.

Statistical analysis

The primary analysis included all randomized participants completing baseline assessment on an intention-to-treat basis.

Data were log transformed if the distribution was not normal (6MWT, Tinetti gait and balance, and ALF scores). The primary results were based on an analysis of covariance (ANCOVA) with adjustments for baseline value of the covariates as appropriate. In a blinded preanalysis, the probability of a participant withdrawing from the study or missing a particular outcome assessment appeared to reduce as the study progressed and to depend on baseline level of physical function. Hence the randomization number, 6MWT, and baseline frailty status were included among the covariates. For the joint primary endpoints, adjustment was made for multiple testing using the Holm-Sidak method. The prespecified analyses included a formal interaction test for heterogeneity of response for participants with different numbers of frailty criteria. Because this showed potential heterogeneity in some of the physical function tests, subgroup analyses (*post hoc*) were conducted for differential treatment effects with respect to age and frailty criteria, with formal tests of significance based on addition of the appropriate interaction terms in the model. Level of significance was set at $P < 0.05$.

Results

From a total 1677 men screened, 274 met the recruitment criteria and were randomized into T (138) and placebo groups (136) (Fig. 1). Twelve men withdrew before baseline assessment and 31 men after commencing treatment. Baseline characteristics of the groups were well matched (Table 1).

Hormone levels

Mean total and free T increased to the target range in the treatment group after 10 d and was maintained throughout the 6-month treatment period (Fig. 2, A and B).

Muscle strength

IKE-PT increased by 4.7 ± 31.0 Nm (mean ± SD) in the T group and decreased by 4.7 ± 27.5 Nm in the placebo group at 6 months compared with baseline (Table 2 and Fig. 3A). The mean treatment effect was 8.6 [95% confidence interval (CI) = 1.3–16.0; $P = 0.02$] Nm in the T group (*vs.* placebo). IKE-PT increased by 5.5 ± 20.7 and 1.9 ± 19.8 Nm in the T and placebo groups, respectively. The treatment effect was 3.6 (−1.6–8.7; $P = 0.17$) Nm. IMF-PT increased by 8.8 (21.9) and 3.0 (24) Nm in the T and placebo groups, respectively, at 6 months compared with baseline. Adjusted difference between the two groups was 4.8 (−0.8–10.4; $P = 0.09$) Nm (Table 2 and Fig. 3A). IKF-PT increased by 7.4 ± 13.4 and by 3.6 ± 14.2 Nm in the T and placebo groups, respectively, at 6 months compared with baseline. Adjusted difference between the two groups was 3.6 (−0.3–7.4; $P = 0.07$) Nm. Grip strength improved more in the T group than the placebo. However, adjusted difference between groups was not significant. *Post hoc* analysis revealed a positive correlation ($r = 0.17$; $P = 0.012$) between change in the IME-PT and the number of frailty criteria.

TABLE 1. Baseline characteristics in the placebo and T groups

Variable	Placebo group (n = 132)	T group (n = 130)
Age (yr)	73.9 ± 6.4	73.7 ± 5.7
Weight (kg)	80.7 ± 13.4	81.0 ± 14.0
BMI (kg/m^2)	27.7 ± 4.0	27.9 ± 4.1
Frail (3–5 criteria)	20 (15%)	18 (14%)
Intermediate frail (1–2 criteria)	112 (85%)	112 (86%)
Frailty criteria present, n (%)		
Exhaustion	65 (49)	68 (52)
Weight loss	32 (24)	26 (20)
Physical activity	21 (16)	13 (10)
Walk time	11 (8)	9 (7)
Grip strength	81 (62)	81 (62)
No. of frailty criteria present, n (%)[a]		
1 criterion	79 (59.8)	83 (63.8)
2 criteria	33 (25)	29 (22.3)
3 criteria	15 (11.4)	16 (12.3)
4 criteria	5 (3.8)	2 (1.5)
No. of prescription medications used, n (%)		
0	13 (9.8)	9 (6.9)
1–2	28 (21.2)	26 (20.0)
3–11	91 (68.9)	95 (73.1)
Number of comorbidities	2.6 ± 1.5	2.5 ± 1.4
MMSE score	28.2 (1.7)	28.1 (1.9)
MMSE score, 18–24	4 (3%)	6 (4.6%)
Total T (nmol/liter)	10.9 ± 3.1	11.0 ± 3.2
Free T (pmol/liter)	180 ± 50	180 ± 50
SHBG (nmol/liter)	47.3 ± 18.3	47.6 ± 18.2
FSH (IU/liter)	6.5 (5.6–15.3)	8.3 (5.8–14.1)
LH (IU/liter)	6.3 (4.4–9.7)	6.1 (4.5–9.3)
PSA (ng/ml)	1.5 ± 0.9	1.5 ± 0.9
IPSS[b]	5.9 ± 4.3	7.0 ± 5.0
Total cholesterol (mmol/liter)	4.6 (3.9–5.3)	4.6 (3.9–5.3)
LDL cholesterol (mmol/liter)	2.3 (1.7–2.9)	2.5 (1.7–3.0)
HDL cholesterol (mmol/liter)	1.5 (1.1–1.8)	1.4 (1.2–1.6)
Triglycerides (mmol/liter)	1.4 (1.0–2.0)	1.5 (1.0–2.1)
Hemoglobin (g/dl)	14.2 ± 1.3	14.6 ± 1.2
Hematocrit (%)	42 ± 4.0	44 ± 3.0

Data are presented as mean ± SD or median (25–75, interquartile range). The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. To convert values for total T to ng/dl, multiply by 28.8; to convert values for free T to ng/dl, divide by 34.7; to convert values for low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol to mg/dl, multiply by 38.7; to convert values for triglycerides to mg/dl, multiply by 88.57.

[a] No participant in both the groups fulfilled all the five Fried's criteria.

[b] IPSS range, 0–35.

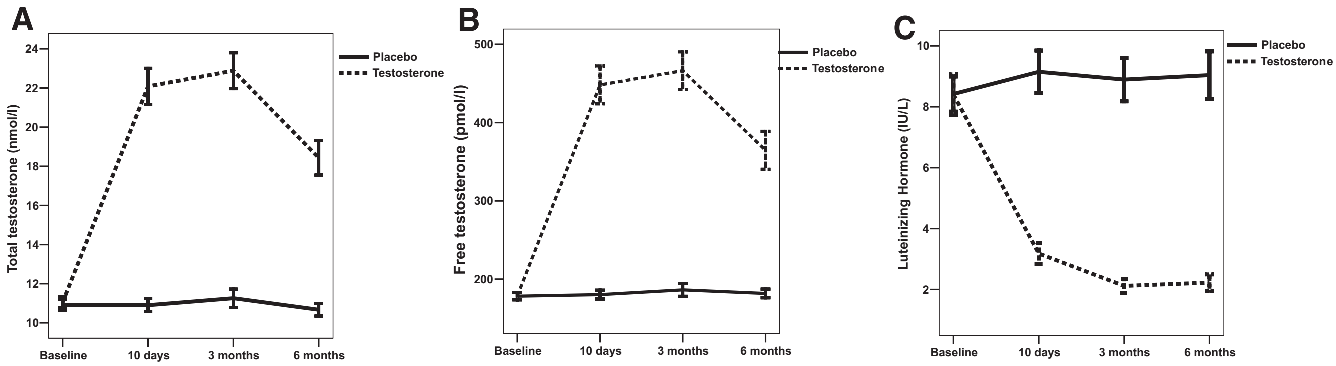

FIG. 2. Total T (A), free T (B), and LH (C) levels (mean ± SEM) in the placebo and T groups at various time points.

Physical function tests

Tinetti gait and balance, ALF, 6MWT, and PPT improved at 6-month assessment (*vs.* baseline) in the T group. However, adjusted differences between treatment groups did not reach statistical significance (Table 2). The PASE score showed no difference between groups, improving slightly in both (Table 2). PPT and ALF showed greater improvements (interaction $P = 0.011$ and 0.004) with the effect size of 1.65 (0.11–3.20) and −3.66 (−8.52–1.20) respectively, in those with at least two frailty criteria. PPT score also showed greater improvement (interaction $P = 0.005$) with the effect size of 1.9 (0.6–3.2) in older men (≥75 yr) (Table 3). There was a positive correlation between change in muscle strength and change in physical function (PPT: $r = 0.25$; $P = 0.003$; 6MWT: $r = 0.239$; $P = 0.001$).

Body composition

LBM increased in the T group (*vs.* placebo) with a mean difference between groups of 1.1 (95% CI = 0.6–1.5; $P < 0.001$) kg (Table 2 and Fig. 3B). FM decreased significantly in the T group (*vs.* placebo) with an adjusted difference of 0.6 (−1.1 to −0.1; $P = 0.01$) kg (Table 2 and Fig. 3B).

QoL

Somatic, psychological, and sexual domain symptom scores of the AMS decreased to a greater extent in the T group compared with placebo. Adjusted differences between groups were significant for somatic and sexual domains but not the psychological domain (Table 2 and Fig. 3C). Among the individual subgroups, the AMS somatic subscale score showed greater improvement in older men and men with at least two frailty criteria subgroups, and the sexual subscale score improved in men with at least two frailty criteria subgroup (Table 3).

Compliance

Treatment compliance was assessed by self-report. Over 85% of participants used more than 95% of study medication, with no significant differences between groups. There was no difference in compliance between those with an MMSE score of 18–24 *vs.* men with MMSE score higher than 24.

Adverse events

PSA levels increased from 1.5 ± 0.9 at baseline to 2.0 ± 1.4 ng/ml at 6 months in the T group with no change in the placebo group (Tables 1 and 4). Four men (three T and one placebo group) had elevated age-adjusted PSA during the treatment phase and were referred for urological assessment. Their PSA levels decreased after stopping treatment. Only one of the men (T group) with raised PSA had prostate biopsy, which revealed benign histology. One man (placebo group) with normal PSA had a palpable prostate nodule on rectal examination, and biopsy revealed adenocarcinoma. Hematocrit increased in the T group compared with baseline and the placebo group; however, no participant developed polycythemia (hematocrit >53%). Triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol levels remained unchanged at 6 months in both groups. Table 4 lists the various adverse events. There were three serious adverse events in the placebo (prostate cancer, acute myocardial infarction, and death from ruptured abdominal aortic aneurysm) and six serious adverse events in the T group (lung cancer, esophagus cancer, pulmonary embolism, heart failure, abdominal aneurysm, and constrictive pericarditis).

Discussion

This is the largest double-blind, placebo-controlled interventional study with T in elderly men to date, and the first to investigate its effects in intermediate-frail and frail elderly men. Our results showed that increasing low or borderline-low T concentrations to the middle of the normal range in elderly men for 6 months improved lower limb muscle strength (IME-PT) compared with placebo. In addition, T increased LBM and decreased FM along with

TABLE 2. Muscle strength, body composition, and QoL measures at baseline and 6 months in the placebo and T groups

	Placebo group (n = 132)			T group (n = 130)			Adjusted difference T − placebo (95% CI)	P^a
	Baseline	6 months	Change	Baseline	6 months	Change		
Muscle strength (Nm)								
PT								
IME	142 ± 39	137 ± 37	−4.7 ± 27.5	139 ± 41	144 ± 40	4.7 ± 31.0	8.6 (1.3–16.0)	0.04^b
IKE	98 ± 31	99.0 ± 29	1.9 ± 19.8	98 ± 29	103 ± 30	5.5 ± 20.7	3.6 (−1.6–8.7)	0.17^b
IMF	107 ± 34	110 ± 28	3.0 ± 24	106 ± 26	115 ± 25	8.8 ± 21.9	4.8 (−0.8–10.4)	0.14^b
IKF	60 ± 19	64 ± 21	3.6 ± 14.2	59 ± 19	66 ± 19.0	7.4 ± 13.4	3.6 (−0.3–7.4)	0.14^b
Grip strength (kg)	32 ± 8.2	33.4 ± 7.5	1.4 ± 5.3	30.9 ± 6.9	33.7 ± 7.0	2.8 ± 5.7	0.9 (−0.5–2.3)	0.21^b
Body composition								
LBM (kg)	51.2 ± 7.1	51.0 ± 7.3	−0.02 ± 1.5	51.6 ± 7.5	52.7 ± 7.6	1.08 ± 1.8	1.1 (0.6–1.5)	<0.001
FM (kg)	21.8 ± 7.7	21.5 ± 7.5	−0.3 ± 2.2	21.4 ± 7.6	20.6 ± 7.3	−0.9 ± 1.6	−0.6 (−1.1 to −0.1)	0.02
Physical function tests								
ALF score	23.1 ± 7.4	23.4 ± 10.1	0.29 ± 7.4	22.1 ± 6.2	21.4 ± 8.1	−0.7 ± 5.4	−0.04 (−0.09–0.008)	0.10
6MWT (m)	381 ± 96	390 ± 94	9.5 ± 53.0	385 ± 83	404 ± 78	194 ± 9.5	0.03 (−0.005–0.07)	0.09
Total PPT score	20.1 ± 4.5	20.1 ± 4.8	0.07 ± 2.7	21.3 ± 3.5	21.8 ± 3.2	0.5 ± 2.2	0.70 (−0.04–1.45)	0.06
Tinetti balance	14.0 ± 2.3	13.4 ± 2.3	−0.5 ± 1.5	14.1 ± 2.0	13.6 ± 2.3	−0.45 ± 1.7	−0.10 (−0.3–0.09)	0.29
Tinetti gait	11.1 ± 1.5	10.9 ± 1.5	−0.2 ± 0.8	11.4 ± 1.1	11.2 ± 1.3	−0.2 ± 1.01	−0.084 (−0.24–0.07)	0.28
PASE score	131 ± 61	142 ± 80	12 ± 68	148 ± 80	166 ± 92	18 ± 52	7 (13–27)	0.51
AMS								
Somatic subscale	15.8 ± 5.0	13.8 ± 4.7	−2.0 ± 4.6	16.3 ± 5.2	12.7 ± 4.3	−3.6 ± 4.1	−1.2 (−2.4 to −0.04)	0.04
Psychological subscale	8.5 ± 3.7	7.6 ± 3.2	−0.8 ± 3.4	9.7 ± 4.1	8.2 ± 3.5	−1.5 ± 3.0	−0.09 (−0.9–0.7)	0.83
Sexual subscale	13.8 ± 4.5	12.3 ± 4.6	−1.5 ± 4.3	13.7 ± 4.3	10.9 ± 4.5	−2.8 ± 3.9	−1.3 (−2.5 to −0.2)	0.02

Data are presented as mean ± SD. 6MWT, Tinetti gait and balance, and ALF test scores represent untransformed data; they were log transformed for the purpose of analysis.

[a] ANCOVA *P* comparing adjusted mean difference between placebo and T groups, adjusted for corresponding baseline value, frailty criteria, walk time, and randomization number.

[b] *P* values adjusted for multiple testing using the Holm-Sidak method.

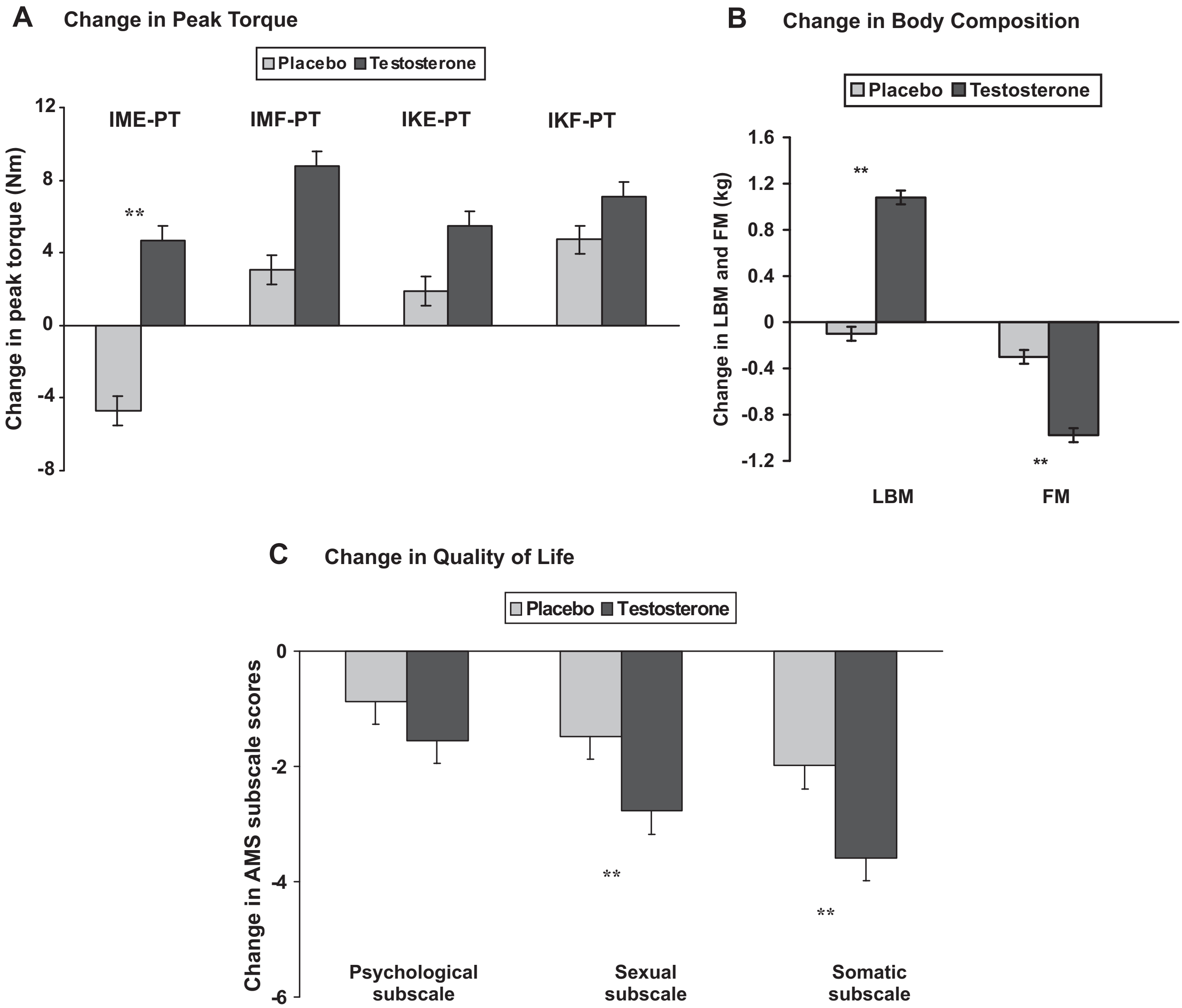

FIG. 3. A, Change in IME-, IMF-, IKE-, and IKF-PT in the placebo and T groups at 6 months; B, change in LBM and FM at 6 months compared with baseline in the placebo and T groups; C, change in AMS subscale scores at 6 months compared with baseline in the placebo and T groups. **, Significant difference between groups (ANCOVA, comparing adjusted mean difference between placebo and T groups).

improvement of somatic and sexual symptoms (AMS questionnaire). T treatment also improved physical function among older (≥75 yr) and frailer (at least two frailty criteria) men.

It is noteworthy that the between-group difference in IME-PT reflected an increase in the T group compared with a decrease in the placebo group, suggesting that intervention ameliorated age-associated deterioration in muscle strength. It is well known that muscle strength decreases with age, at approximately 1% per year, even in physically active men (28). Furthermore, there is evidence that age-related loss of physical function preferentially affects knee extensor muscle groups (29, 30). It is likely that this explains the decrease of IME-PT in the placebo group. The improvement in IME-PT we observed is recognized as functionally significant; an increase in knee extension PT of around 5 Nm has been shown to be associated with improvements in physical function (31). Furthermore, the increment in IME-PT in the current study was corroborated by improvements in LBM and physical symptoms. The trend of all muscle strength endpoints (except IME-PT) to improve from baseline in both groups may have resulted from a learning effect. However, some of the apparent improvement may be due to a significant placebo effect known to be substantial in objective measures of physical parameters (32, 33).

Most previous T interventional studies on healthy elderly men did not measure (6, 34) or were unable to demonstrate (7, 8, 11, 35) improvements in lower limb strength. Only Clague *et al.* (10) and Nair *et al.* (36) previously assessed the effects of T using IME-PT; they were,

TABLE 3. Subgroup analysis: selected outcome measures at 6 months in older and frailer men

	Placebo			T			Adjusted difference (95% CI)	P^a	P^b
	Baseline	6 months	Change	Baseline	6 months	Change			
Men ≥75 yr (n = 106: 56 placebo; 50 T)									
LBM (kg)	48.8 ± 6.1	48.8 ± 6.2	0.05 ± 1.4	50.8 ± 7.2	51.0 ± 76.8	1.2 ± 2.1	1.1 (0.3–1.8)	0.007	0.09
IME-PT (Nm)	123 ± 35.8	121 ± 32.5	−5 ± 25.8	125 ± 30.4	122 ± 28.0	0 ± 24.8	2.76 (−6.90–12.43)	0.57	0.06
AMS somatic subscale	16 ± 4.5	14 ± 5.1	1 ± 3.2	16 ± 4.7	13 ± 4.6	−4 ± 2.6	−3.53 (−5.25 to −1.82)	<0.001	0.03
AMS psychological subscale	7 ± 2.6	8 ± 3.9	0 ± 2.2	9 ± 3.6	8 ± 3.1	−1 ± 3.4	−1.42 (−3.01–0.16)	0.08	0.38
AMS sexual subscale	13 ± 4.7	13 ± 4.6	0 ± 4.4	14 ± 4.3	12 ± 4.8	−3 ± 4.3	−1.93 (−3.91–0.04)	0.05	0.41
ALF score	26.7 ± 9.4	26.5 ± 9.7	0.5 ± 4.0	24.7 ± 7.9	23.2 ± 7.4	−0.9 ± 4.5	−1.3 (−3.2–0.5)	0.07	0.39
6MWT (m)	341 ± 87	341 ± 82	−0.3 ± 44	349 ± 77	376 ± 67	26 ± 46	25.4 (4.8–45.9)	0.02	0.12
Total PPT score	17.9 ± 4.8	17.9 ± 4.9	−0.5 ± 3.1	19.1 ± 3.9	20.6 ± 3.4	0.9 ± 2.2	1.9 (0.6–3.2)	0.004	0.005
Tinetti balance	12.9 ± 2.7	12.3 ± 2.5	−0.7 ± 2.0	13.4 ± 2.3	13.1 ± 2.4	0.0 ± 1.6	0.70 (−0.12–1.52)	0.03	0.15
Tinetti gait	10.5 ± 1.8	10.2 ± 1.8	−0.3 ± 1.0	11.0 ± 1.5	11.0 ± 1.3	−0.1 ± 1.3	0.29 (−0.17–0.76)	0.19	0.03
≥2 frailty criteria (n = 100: 53 placebo, 47 T)									
LBM (kg)	51.0 ± 7.3	51.2 ± 7.3	−0.1 ± 1.5	50.0 ± 8.1	51.6 ± 8.67	1.5 ± 2.1	1.6 (0.8–2.4)	<0.001	0.33
IME-PT (Nm)	128 ± 38.6	131 ± 39.7	−1 ± 29.8	119 ± 45.4	134 ± 43.7	11 ± 35.1	9.48 (−4.05–23.02)	0.17	0.68
AMS Somatic subscale	19 ± 5.1	17 ± 5.3	−1 ± 6.1	18 ± 4.7	13 ± 4.2	−4 ± 3.6	−2.76 (−5.18 to −0.34)	0.03	0.03
AMS psychological subscale	10 ± 5.0	10 ± 4.1	−1 ± 4.5	11 ± 4.0	8 ± 3.7	−3 ± 3.6	−1.61 (−3.47–0.24)	0.09	0.001
AMS sexual subscale	15 ± 4.6	14 ± 4.5	−1 ± 4.4	15 ± 4.4	11 ± 4.4	−4 ± 4.5	−3.03 (−4.87 to −1.20)	0.002	0.02
ALF score	27.2 ± 9.7	28.3 ± 13.7	1.9 ± 11.4	24.9 ± 8.2	22.3 ± 9.9	−1.0 ± 8.1	−3.66 (−8.52–1.20)	0.04	0.004
6MWT (m)	323 ± 94.7	340 ± 88	8.3 ± 60	338 ± 81	374 ± 72	31.9 ± 65	28.0 (1.5–54.5)	0.05	0.20
Total PPT score	18.2 ± 4.5	17.9 ± 5.2	−0.6 ± 2.8	19.0 ± 3.8	20.7 ± 2.7	0.6 ± 2.8	1.65 (0.11–3.20)	0.04	0.01
Tinetti balance	13.2 ± 2.9	12.6 ± 3.0	−0.6 ± 1.7	13.6 ± 2.3	12.8 ± 3.0	−0.6 ± 2.2	0.06 (−0.89–1.01)	0.33	0.86
Tinetti gait	10.6 ± 1.9	10.3 ± 1.9	−0.3 ± 0.9	11.0 ± 1.3	10.8 ± 1.6	−0.2 ± 1.4	0.10 (−0.38–0.57)	0.34	0.67

Data are presented as mean ± SD. The 6MWT, Tinetti gait and balance, and ALF test scores represent untransformed data; they were log transformed for the purpose of analysis.

[a] ANCOVA *P* comparing adjusted mean difference between placebo and T groups, adjusted for corresponding baseline value, frailty criteria, walk time, and randomization number.

[b] Interaction test for a difference in treatment response between older and younger participants or frailty groups as indicated.

TABLE 4. Safety monitoring and adverse events

	Placebo group (n = 132)	T group (n = 130)
Total T (nmol/liter)	10.7 ± 3.5	18.4 ± 9.2
Free T (pmol/liter)	180 ± 60	360 ± 26
SHBG (nmol/liter)	44.8 ± 17.4	43.2 ± 17.0
PSA (ng/ml)	1.5 ± 0.9	2.0 ± 1.4
IPSS	6.3 ± 5.0	6.8 ± 5.5
Total cholesterol (mmol/liter)	4.4 (3.8–5.1)	4.2 (3.6–4.8)
LDL cholesterol (mmol/liter)	2.1 (1.5–2.7)	2.2 (1.4–2.6)
HDL cholesterol (mmol/liter)	1.5 (1.2–1.9)	1.3 (1.1–1.6)
Triglycerides (mmol/liter)	1.2 (0.9–1.7)	1.4 (1.0–2.0)
Hemoglobin (g/dl)	13.9 ± 1.4	15.3 ± 1.4
Hematocrit (%)	41 ± 4.0	45 ± 4.0
Skin rash, n (%)	14 (10.6)	11 (8.5)
Hospitalization, n (%)	8 (6.0)	8 (6.0)
Falls, n (%)	16 (12.1)	11 (8.5)
Mild to moderate adverse events, n (%)	7 (5.3)	10 (7.7)
Serious adverse events, n (%)	3 (2.3)	6 (4.6)

Data are presented as mean ± SD, median (25–75, interquartile range), or number (%). HDL, High-density lipoprotein; LDL, low-density lipoprotein.

however, unable to demonstrate any beneficial effects on lower limb muscle strength. Several studies of T on grip strength yielded negative results, as in the present study (6–11, 16), probably reflecting the large intra-individual variability. The use of healthy men, small sample size, lack of significant rise in T levels with treatment, and absence of practice sessions may have contributed to such negative findings. Only Crawford *et al.* (15), treating elderly men on glucocorticoids with T and nandrolone decanoate, demonstrated improvements in lower limb muscle strength measured by dynamometry (IKE and IKF). It is well recognized that dynamometry is effort dependent and affected by motivation, mood, and fatigue (37). The greater inherent variability associated with dynamometry (38) may limit its ability to detect relatively small improvements in muscle strength (8, 10, 11). Ferrando *et al.* (39) and Sattler *et al.* (13) reported improvement in lower limb muscle strength of over 200 and 23%, respectively, using one-repetition maximum (1-RM). Bhasin and co-workers (5) reported improvement in leg press strength of around 10% using 1-RM in elderly gonadotropin-suppressed men who received physiological replacement doses of T. Because 1-RM and dynamometry assess different aspects of muscle function, it would not be appropriate to compare the relative improvements in muscle strength assessed by these methods.

Treatment with GH and T (40) and recombinant human chorionic gonadotropin (41) in healthy elderly men showed no improvement in muscle strength measured by dynamometry. Fiatarone *et al.* (42) and Onambélé *et al.* (43) demonstrated strength gains among elderly men after resistance training. In general, high-resistance weight training produces greater improvement in muscle strength than pharmacological intervention. However, the role of T in improving muscle strength remains attractive given that resistance training usually requires three sessions per week of intense exercise over several months.

Our results corroborate studies that have demonstrated increased LBM and decreased FM with T in healthy (7, 8, 11, 13) and in elderly men with chronic illness (14, 15, 44). The increase in LBM in the current study was associated with improvements in physical function only among older and frailer men, but not the entire T-treated group. It is reasonable to speculate that beneficial effects of T on well-being, tiredness, and exhaustion (AMS somatic subscale) may have contributed to the improvement in physical function to a greater extent in frailer men.

The lack of demonstrable improvement of physical function in the entire cohort could result from several factors, including use of tests with a floor and ceiling effect, day-to-day and intra-individual variation in performance of these tests and the lack of instruments suitable for a heterogeneous cohort. The fact that the majority of participants in this study had only one or two frailty criteria may have skewed the observed changes in physical function downward. Physical function tests also tend to be confounded, especially in frailer men, by the presence of neuropathy, vascular disease, visual and hearing impairment, loss of confidence, cognitive impairment, and arthritis, which are unlikely to be responsive to T intervention. Indeed, most previous studies (8, 9, 36, 41, 45) among healthy men have not demonstrated improvements in physical function with T treatment.

We demonstrated improvements in QoL using a validated health-related instrument (AMS questionnaire). The improvement in the somatic domain of this instrument reflects improvement in symptoms such as muscular strength, tiredness, and general well-being. Many previous studies have been unable to report improvement in QoL (9, 41). Svartberg *et al.* (46) reported a nonsignificant mean change in AMS somatic and sexual subscales of −0.4 and −1.5, respectively, in elderly men after im T undecanoate treatment for 1 yr. The participants in our study had higher baseline scores of somatic and sexual symptoms, and the magnitude of improvement in the somatic subscale was greater than the aforementioned study. In a small study (15) of elderly men on glucocorticoids, treated with T, only the total QoL score of the Qualeffo-41 questionnaire improved, not individual domains. Snyder *et al.* (8) reported improvement in perception of physical functioning but not other domains of Short Form 36 among elderly men. The improvement in sexual symptoms such as libido, sexual performance, and morning erections in the current study was expected from results of previous studies (34, 47).

The consistency of the positive changes across various objective and subjective assessments at 6 months leads us to suggest that these T-induced changes are functionally linked and, although modest, may be clinically meaningful. The absence of any treatment effect in the AMS in the psychological score would suggest that it is unlikely that psychological factors contributed to improvement in physical outcomes. Although the physical function results are based on *post hoc* analyses, these subgroups are of clinical interest, and the data in these groups will assist in the design of future studies. Longer-term studies are required to provide further evidence that the type and extent of improvements we have demonstrated will lead to reduced falls and improved mobility.

There are some limitations to this study. We used a single serum T measurement to determine eligibility. Although there is significant intra-individual variation in T levels, suggesting that more than one measurement should be included at baseline (48), this tends to be less marked among the elderly (49), and our placebo group results confirmed that T levels were stable over time (Fig. 2, A and B). Diet and physical activities of the participants were not standardized. However, the PASE data confirmed that self-reported physical activity did not differ between groups. Due to unavoidable logistical issues, there was a time gap between randomization and baseline assessment. Twelve randomized men withdrew before baseline assessment and before they received the allocated treatment; they were not included in the analyses because they provided no data. The formal dropout rate (12%) was as expected. Although we found no evidence that missing data led to any bias, the possibility of frailty-related missing data and consequent bias (in either direction) cannot be completely eliminated. The small increases in hematocrit and PSA within normal range with unchanged IPSS score and lipid profiles during T treatment are also consistent with previous studies (6, 8, 9, 11, 15) and reassuring.

In summary, our study provides evidence that short-term T treatment of intermediate-frail and frail elderly men with low to borderline-low circulating T levels prevents deterioration in muscle strength and improves body composition and symptom-related QoL. Additionally, treatment is associated with improved physical function in older and frailer men, highlighting possible functional consequences of small changes in physical performance. These encouraging preliminary results should be confirmed by further studies of longer treatment duration in larger numbers of older men, defined by specific components of the frailty syndrome using assessments optimized for this population.

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