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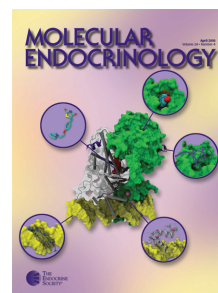
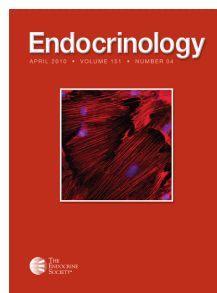
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Context: Short-term testosterone (T) treatment in frail elderly men improves muscle mass and strength. It is unclear whether these effects can be maintained post treatment.

Objective: To assess the durability of androgen effects in frail men.

Design and Setting: Single center, randomized, double-blind, placebo-controlled trial to investigate the effects of 6 months T (25–75 mg daily) on muscle strength, body composition, physical function, and quality of life (QoL). Participants were assessed at the end of treatment (6 months) and 6 months after treatment cessation (12 months).

Participants: 274 intermediate-frail and frail elderly men aged 65–90 years with low T levels.

Results: Mean T increased from 11.1 (3.1) nmol/liter at baseline to 18.4 (3.5) nmol/liter at 6 months, then declined to 10.5 (3.7) nmol/L at 12 months, in the T-treated group. Isometric knee extension peak torque increased in the T-treated group compared with placebo to give an adjusted mean difference (95% CI) between groups of 8.1 (–0.2 to 16.5) Nm at 6 months. Lean mass increased in the T-treated group giving a difference between groups of 1.2 (0.8 to 1.7) kg at 6 months. Somatic and sexual symptoms improved during treatment. None of these differences between groups remained at 12 months. Prostate specific antigen (PSA) levels and haematocrit increased slightly during treatment but returned to baseline by 12 months.

Conclusion: The effects of 6-month T treatment on muscle strength, lean mass, and QoL in frail men are not maintained at 6 months post treatment. (*J Clin Endocrinol Metab* 96: 454–458, 2011)

Frailty describes an age-related state of increased vulnerability, presaging adverse outcomes (1, 2). With the aging population, management of frailty is becoming an increasingly important healthcare issue. While resistance training may lead to functional improvements in the elderly (3, 4), this approach may be burdensome to frail elders. An alternative option is the use of pharmacological anabolic interventions (5). Testosterone (T) replacement in elderly men is among the first wave of these therapies.

T levels decline with aging (6, 7) and may contribute to the age-related physical deterioration in the elderly (8, 9). We recently reported an increase in lean body mass (LBM), muscle strength, and quality of life (QoL) in intermediate-frail and frail elderly men in response to 6 months T treatment in a randomized, placebo-controlled study (10).

The anabolic effects of T treatment on muscle mass in elderly men appear to peak after about 6 months; this increase in muscle mass can be maintained with continued treatment for up to 3 yr (11–13). It is unclear whether these effects can be maintained once treatment is withdrawn. Since the use of T in elderly men often raises concern regarding adverse effects (14, 15), it would be important to determine whether short-term treatment can lead to prolonged benefits beyond the duration of T exposure.

The effects of 12-week treatment with the anabolic-androgenic steroid, oxandrolone, on muscle mass and strength in healthy elderly men were shown to decline within 12 weeks of treatment cessation (16). However, the persistence of effects of physiological T treatment in frail elderly men has not previously been studied. Frail men may be undergoing a cycle of decline wherein a loss of muscle mass and strength leads to declines in physical function, energy levels, and physical activity, which further aggravate the deficits in muscle mass and function (2). Anabolic interventions like T may halt this frailty cycle, with improved strength allowing maintenance of function and activity thus preventing further decline. Frail men may therefore be more likely to experience prolonged benefits from anabolic interventions. This study sought to evaluate the post-treatment durability of effects at 6 months after the cessation of T treatment in intermediate-frail and frail elderly men.

Materials and Methods

This report focuses on the post-treatment follow-up phase of a 6-month trial of T treatment in intermediate-frail and frail elderly men. The detailed methods for this study, including the recruitment criteria, participants, interventions, outcome assessment, and safety monitoring were reported previously (10). Briefly, in a single-center, randomized, double-blind, placebo-controlled parallel group study, 274 men with low T levels (total T ≤ 12 nmol/liter or calculated free T ≤ 250 pmol/liter) and at

least 1 criterion for frailty (2) were randomized to receive either T gel (25–75 mg/d) or placebo for 6 months. The main outcome was knee extensor strength by isometric and isokinetic dynamometry; secondary outcomes included knee flexor strength, body composition (Dual-energy x-ray Absorptiometry), QoL [aging males' symptom scale (AMS)], and a range of functional assessments (10). Assessments were carried out at baseline, the end of treatment (6 months), and 6 months after treatment cessation (12 months).

Statistical analyses

The analyses presented here are based throughout on the subset of participants completing the 12-month follow-up phase of the trial, so the 6-month data differ slightly from those presented previously (10). The outcome analysis was based on an analysis of covariance (ANCOVA) model for the effect of allocation on treatment outcome at 12 months, adjusting for baseline values. Baseline frailty status, 6 min walk time, and randomization number were included as covariates to account for recruitment trends in subject retention and frailty. Results are expressed as adjusted mean differences with 95% confidence intervals. Differences in safety parameters between groups were evaluated using Mann–Whitney tests.

Results

Subjects

Details of participant recruitment and retention during treatment were reported previously (10). This information is included here along with the retention during follow-up in the Supplemental Fig. 1, published on The Endocrine Society's Journals Online website at <http://jcem.endojournals.org>. Twenty-two men withdrew during the follow-up phase (6–12 months). One participant in the placebo group was excluded from analyses at 12 months after starting T treatment prescribed from his general practitioner. Baseline characteristics were well matched between groups and did not differ in the men completing the trial compared with the randomized cohort (Supplemental Table 1).

Hormones

Total T and free T levels that were raised during treatment in the T group had declined to baseline by 6 months post treatment (Table 1, Supplemental Figure 2). LH levels that were suppressed during treatment were slightly, but not significantly, elevated at 12 months (Table 1, Supplemental Figure 2).

Outcomes

This report focuses on the outcomes that changed with T treatment at 6 months (Table 1). Additional outcomes are included in Supplemental Table 2. The gain in isometric knee extension peak torque (IME-PT) in response to T at 6 months (adjusted difference between groups (95% CI) of 8.1 (–0.2 to 16.5) Nm) decreased to 4.0 (–3.9 to 11.9) Nm ($P = 0.32$) at 12 months. The increase in LBM in the T

TABLE 1. Main outcomes, hormones, and safety measures over 12 months

	Placebo			Testosterone			Adjusted difference testosterone-placebo (95% CI)		P
	Baseline	6 months	12 months	Baseline	6 months	12 months	6 months	12 months	
Main outcomes									
Isometric knee extension peak torque (Nm)	144.9 ± 41.5	140.0 ± 36.9	136.3 ± 36.1	142.7 ± 42.7	145.5 ± 42.5	137.4 ± 38.4	8.1 (−0.2 to 16.5)	4.0 (−3.9 to 11.9)	0.32
LBM (kg)	50.7 ± 7.6	50.7 ± 7.4	50.4 ± 7.9	51.6 ± 7.4	52.8 ± 7.4	51.7 ± 7.6	1.2 (0.8 to 1.7)	0.3 (−0.1 to 0.8)	0.12
Fat mass (kg)	21.0 ± 7.7	20.9 ± 7.5	20.7 ± 7.7	21.5 ± 7.6	20.7 ± 7.4	21.1 ± 7.2	−0.6 (−1.1 to −0.2)	0.0 (−0.6 to 0.6)	0.28
AMS somatic subscale	16.2 ± 5.2	13.6 ± 4.8	15.1 ± 5.4	16.3 ± 5.1	12.6 ± 4.1	14.1 ± 4.4	−1.0 (−2.2 to 0.2)	−1.1 (−2.3 to 0.1)	0.081
AMS sexual subscale	13.6 ± 4.4	12.3 ± 4.5	11.9 ± 5.0	14.0 ± 4.3	11.0 ± 4.4	12.6 ± 4.6	−1.3 (−2.5 to −0.1)	0.7 (−0.6 to 2.1)	0.28
Hormones									
Total testosterone (nmol/liter)	10.9 ± 3.1	10.8 ± 3.5	10.8 ± 3.7	11.1 ± 3.3	18.4 ± 9.3	10.5 ± 4.2	—	—	—
Free testosterone (pmol/liter)	176.4 ± 51.7	183.8 ± 59.0	184.0 ± 65.5	175.0 ± 49.9	365.7 ± 260.2	171.9 ± 66.0	—	—	—
Luteinising hormone (IU/liter)	8.0 ± 7.0	8.5 ± 8.5	8.7 ± 8.7	8.9 ± 8.2	2.2 ± 2.9	10.7 ± 9.3	—	—	—
Sex hormone binding globulin (nmol/liter)	47.2 ± 18.8	44.6 ± 17.6	45.7 ± 19.4	48.5 ± 19.7	43.1 ± 17.8	46.0 ± 21.1	—	—	—
Safety monitoring									
Prostate specific antigen (ng/dl)	1.5 ± 0.9	1.6 ± 1.0	1.6 ± 1.0	1.6 ± 0.9	2.0 ± 1.2	1.9 ± 1.6	—	—	0.97
Haematocrit (%)	41.9 ± 3.6	41.2 ± 3.8	40.6 ± 3.9	43.7 ± 3.2	45.4 ± 3.8	42.4 ± 3.7	—	—	0.002
HDL cholesterol (mmol/liter)	1.5 (1.2–1.8)	1.5 (1.2–1.8)	1.4 (1.2–1.8)	1.4 (1.3–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.7)	—	—	0.931

Data are presented as mean ± SD or median (25–75 interquartile range).

P values are from ANCOVA comparing adjusted mean difference between placebo and testosterone groups at 12 months; adjusted for corresponding baseline value, frailty criteria, walk time, and randomization number and from Mann–Whitney tests comparing difference between groups at 12 months for safety measures.

group, adjusted difference of 1.2 (0.8 to 1.7) kg at 6 months declined to 0.3 (−0.1 to 0.8) kg ($P = 0.12$) at 12 months (Table 1). Similarly, the decrease in fat mass in the treatment group at 6 months was not maintained at 12 months; 0.0 (−0.6 to 0.6) kg ($P = 0.68$) (Table 1). Symptom scores for the somatic and sexual scales of the AMS decreased

during treatment (improved quality of life) to a greater extent in the T group compared with placebo. No difference between groups for either scale remained at 12 months (Table 1). The percentage changes in IME-PT, LBM, AMS somatic and sexual symptoms are summarized in Figure 1 (A–D).

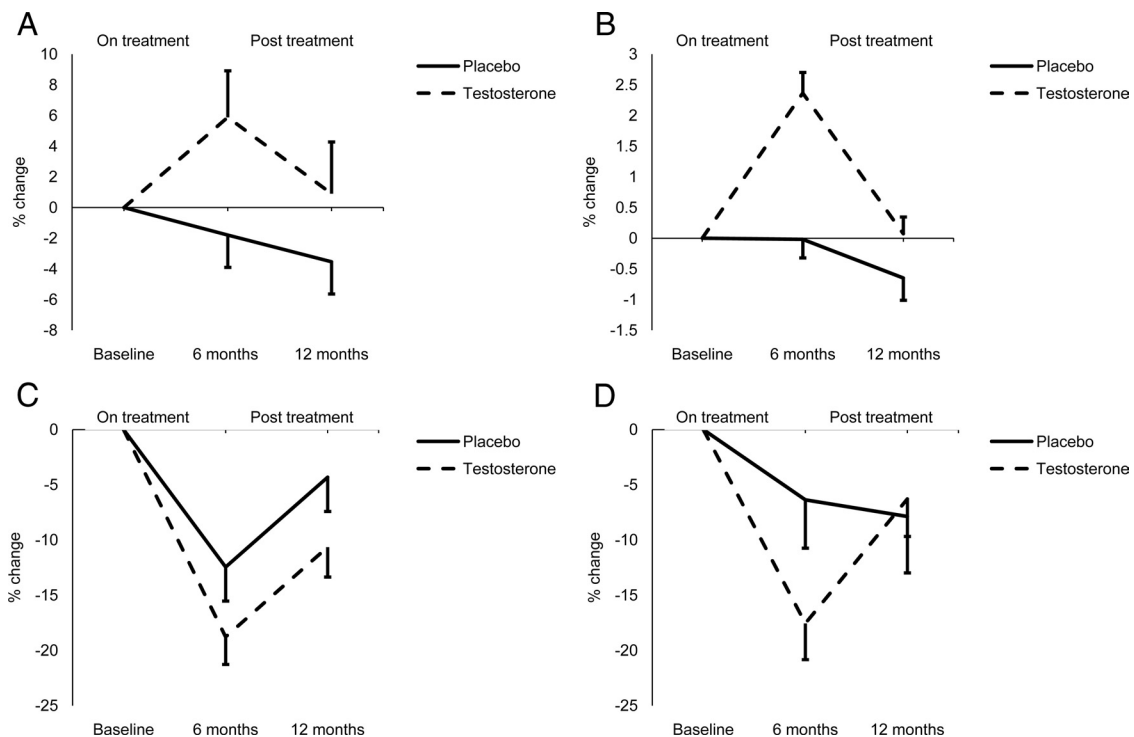


FIG. 1. Percentage (mean ± SEM) changes over 12 months for knee extensor strength (A), LBM (B), AMS somatic symptoms (C), and (D) AMS sexual symptoms. Solid line, Placebo; dashed line, testosterone.

Safety

Hematocrit and PSA were raised and HDL-cholesterol slightly reduced during treatment in the T-treated group compared with placebo. None of these changes persisted at 12 months (Table 1). No other safety parameters were significantly affected by treatment (Supplemental Table 2). Details of adverse events during this treatment follow up period are given in Supplemental Table 3.

Discussion

The main finding of this study was that the increased LBM, muscle strength, and QoL after 6-month T treatment in intermediate-frail and frail elderly men were not maintained 6 months post treatment. Our results also indicate that any potentially adverse changes in safety parameters of T treatment did not persist post treatment.

While lower limb muscle strength assessed by IME-PT declined progressively over 12 months in the placebo group, it increased by around 6% with T treatment but then declined to the baseline after treatment by 12 months (Figure 1). Similar trends were seen for the other outcomes (Figure 1). The different trajectories between the T and placebo groups highlight the clear, albeit unsustained, effects of short-term intervention. This suggests that the observed effects of our intervention were due to the direct influence of changing T levels and not to any secondary treatment-related factor. This is consistent with a previous study (16) showing that the anabolic effects of oxandrolone did not persist post-treatment in healthy older men.

The decline in muscle mass and strength post treatment suggests that treatment for 6 months may not be sufficient to interrupt the progression of frailty in this heterogeneous cohort of intermediate-frail and frail elderly men. The potential for any intervention to produce prolonged benefits in this population may be related to the size of the treatment effect, and particularly how this affects functional ability. It is possible that greater gains in strength with more potent anabolic stimuli administered over a longer period may produce more sustained functional benefits. The effect of increasing T within the physiological range for 6 months may have been too small or too brief to meaningfully affect the functional ability and lifestyle and to influence the cycle of frailty in these subjects. On the other hand, the majority of the study cohort consisted of intermediate-frail (rather than frail) men whose baseline functional impairment may not be severe enough for a small effect of T to engender substantial improvements.

At present, the optimal duration of anabolic hormonal intervention to produce sustained benefits is unknown. Resistance training can produce substantial gains in

strength and function even in the very elderly (3, 4). The use of T or other anabolic agents may augment the effects of exercise (17). This underscores the importance of a multi-disciplinary interventional approach including resistance exercise, diet, and other lifestyle options, in conjunction with pharmacological agents in the elderly to interrupt the downward spiral into frailty.

There have been concerns about the health risks associated with the use of T in the elderly (14, 18). In this study, the effects on traditional safety parameters were small during treatment and they returned to baseline after treatment within 6 months. Unlike studies using high doses of T in elderly men (14), the current study reported few and no increase in cardiovascular or other adverse events compared with placebo. The favorable safety profile in our study may be related to: 1) lower doses of T (2.5–7.5 mg daily), 2) careful dose adjustments to ensure physiological levels of T are achieved and maintained during treatment, and 3) the exclusion of men with symptomatic ischemic heart disease. These are important points to note for designing future T interventional studies in elderly men.

The results presented here were based on the subset of men that completed assessments at 12 months to allow clear comparison of the 6-month and 12-month data. In this subset, some results reported previously (10), did not reach statistical significance, but the magnitude of the effects were virtually identical to that reported for the entire cohort (10), and the loss of formal significance simply reflects the smaller numbers analyzed.

A limitation in the design of this follow-up phase was the lack of interim measurements between 6 and 12 months. It was therefore not possible to evaluate the decay time course of the offset of treatment effects in this study. It is possible that some benefits may have remained for a short time post treatment. Furthermore, it is possible that any delay in recovery from suppressed endogenous T secretion resulting in transient T deficiency could have accelerated the decay of treatment effects in the initial post treatment phase.

In summary, the effects of T treatment on body composition, muscle strength, and QoL did not persist by 6 months after treatment withdrawal in intermediate-frail and frail elderly men. This suggests that any benefits of short-term T exposure on these parameters are entirely hormone-dependent and do not propagate secondary derivative pathways that might help break a cycle of frailty in the elderly.

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