Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial

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Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, Braith RW, Beck DT, Martin JS, Morrow M, Roessner S, Beggs LA, McCoy SC, Cannady DF 2nd, Shuster JJ. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab 306: E433–E442, 2014. First published December 10, 2013; doi:10.1152/ajpendo.00592.2013.—Testosterone administration in older hypogonadal men: a randomized, controlled trial. Testosterone acts directly at androgen receptors and also exerts potent actions following 5α-reduction to dihydrotestosterone (DHT). Finasteride (type II 5α-reductase inhibitor) lowers DHT and is used to treat benign prostatic hyperplasia. However, it is unknown whether elevated DHT mediates either beneficial musculoskeletal effects or prostate enlargement resulting from higher-than-replacement doses of testosterone. Our purpose was to determine whether administration of testosterone plus finasteride to older hypogonadal men could produce musculoskeletal benefits without prostate enlargement. Sixty men aged 60 yr with a serum testosterone concentration of 300 ng/dl or bioavailable testosterone 70 ng/dl received 52 wk of treatment with testosterone enanthate (TE; 125 mg/wk) vs. vehicle, paired with finasteride (5 mg/day) vs. placebo using a 2 x 2 factorial design. Over the course of 12 mo, TE increased upper and lower body muscle strength by 8–14% (P = 0.015 to <0.001), fat-free mass 4.04 kg (P = 0.032), lumbar spine bone mineral density (BMD) 4.19% (P < 0.001), and total hip BMD 1.96% (P = 0.024) while reducing total body fat −3.87 kg (P < 0.001) and trunk fat −1.88 kg (P = 0.0051). In the first 3 mo, testosterone increased hematocrit 4.13% (P < 0.001). Co-administration of finasteride did not alter any of these effects. Over 12 mo, testosterone also increased prostate volume 11.4 cm3 (P = 0.0051), an effect that was completely prevented by finasteride (P = 0.0027). We conclude that a higher-than-replacement TE combined with finasteride significantly increases muscle strength and BMD and reduces body fat without causing prostate enlargement. These results demonstrate that elevated DHT mediates testosterone-induced prostate enlargement but is not required for benefits in musculoskeletal or adipose tissue.

testosterone; hypogonadal; prostate enlargement

SOME STUDIES OF TESTOSTERONE TREATMENT in older, hypogonadal men report substantial increases in muscle strength and bone mineral density (BMD) (12, 21), whereas others report only modest improvements (31, 41). Studies documenting substantial effects typically employed intramuscular (im) doses of 100 mg/wk im injection of long-acting testosterone esters (12, 21). In contrast, lower doses of testosterone that result from transdermal patch or gel administration produce only modest myotrophic effects (31, 32, 41). Meta-analysis data indicate that im testosterone produces a 4% increase in lumbar spine BMD, while transdermal testosterone has no effect (39). Unfortunately, higher doses of testosterone also increase the risk of adverse events, including three that have been confirmed by meta-analysis: polycythemia, a small reduction in HDL-cholesterol, and increased incidence of combined prostate-related events (16, 20, 25). Currently, many question whether the risk-to-benefit ratio is favorable enough to recommend higher-than-replacement testosterone therapy for the 20% of men aged over 60 yr who are at least moderately hypogonadal (27).

Testosterone exerts direct effects at androgen receptors (ARs) but also undergoes 5α-reduction to dihydrotestosterone (DHT), which mediates many of the developmental (42) and androgenic effects of testosterone (44). Both finasteride (type II 5α-reductase inhibitor) and dutasteride (types I and II 5α-reductase inhibitor) are used clinically to treat benign prostatic hyperplasia (BPH) and act by significantly reducing endogenous DHT (3). However, it remains unclear whether elevated DHT mediates the beneficial and/or adverse effects of administered testosterone. A single preliminary report indicates that 200 mg im testosterone enanthate (TE) biweekly plus 5 mg finasteride/day improved total body fat-free mass and lumbar spine and hip BMD and lessened the prostate enlargement resulting from TE alone in older hypogonadal men. However, this combination of TE plus finasteride failed to improve lower-extremity maximal strength over 3 yr (33). Others have reported that dutasteride (2.5 mg/day) does not limit the dose-dependent TE-induced improvements in lean mass or muscle function in younger eugonadal men who were administered a GnRH agonist to suppress endogenous testosterone, although dutasteride did not prevent TE-induced prostate enlargement in this study (11). As such, questions remain regarding the safety and efficacy of concomitant testosterone and steroid 5α-reductase inhibitors.
The primary purpose of this study was to determine whether coadministration of higher-than-replacement TE (125 mg/wk) and Proscar (5 mg finasteride/day) increases muscle strength, fat-free mass, and hematocrit in older hypogonadal men while limiting prostate enlargement. Secondary purposes were to determine whether coadministration of higher-than-replacement TE and finasteride improves BMD and body composition without adversely affecting blood lipids.

METHODS

Study Design

This study was approved by the Institutional Review Board of the University of Florida (UF). All participants gave written informed consent. Potential participants underwent screening to determine eligibility, including structured medical history, blood acquisition (performed twice between 8:00 and 10:00 AM, separated by at least 30 min) to determine complete blood count, complete metabolic profile, luteinizing hormone, lipid panel, total and bioavailable testosterone (BioT), hematocrit (Hct), PSA, and a physical exam that included prostate digital rectal examination (DRE) and transrectal ultrasound sizing (TRUS), and American Urological Association International Prostate Symptom Score (AUA/IPSS) (5). Participants were men aged ≥60 yr, with a serum total testosterone ≥300 ng/dl or BioT ≥70 ng/dl. Two blood samples were obtained during screening, because the Endocrine Society recommends repeated measurements to confirm low testosterone prior to initiating testosterone treatment (9).

We excluded individuals who failed the Mini-Cog test (13) or who had a history of prostate or breast cancer, severe BPH, AUA/IPSS score ≥25, class 3 or 4 congestive heart failure, sleep apnea, Hct >49%, PSA ≥2.6 ng/ml, BMI >35, orthopedic limitations precluding one-repetition maximum (1-RM) strength testing, or who had received testosterone within 4 wk, finasteride/dutasteride within 6 mo, or who were taking Coumadin. Participants were advised to maintain their current level of physical activity.

A randomization table was prepared with RanPro release 1.1 (Applied Logic Associates, Houston, TX) to assign each qualifying participant to one of four treatment groups: vehicle-placebo, TE-placebo, vehicle-finasteride, or TE-finasteride (Fig. 1), using a 2 × 2 factorial design. 40 participants completed 12 months of treatment. 9 participants dropped out for personal reasons, 5 were removed for adverse events unrelated to treatment, and 6 for adverse events that were probably related to treatment. Across all study groups, compliance was 98% for TE/placebo (as assessed by record of injection) and 95% for finasteride/placebo (as assessed by pill count).

Fig. 1. Flow of participants through the trial.
factorial design. Treatment lasted 12 mo and consisted of Proscar (5 mg/day po finasteride) or placebo and Delatestryl (125 mg/wk im TE) or vehicle. Proscar and matching placebo were donated by Merck, Delatestryl was donated by Novartis, and matching vehicle was prepared by WestLab Pharmacy (Gainesville, FL). Participants were not paid for participation other than receiving reimbursement for travel mileage. Study participants and investigators performing consenting, screening, drug administration, safety testing, and outcomes testing were blinded to treatment. The only unblinded team members were Research Pharmacy, the Laboratory Manager, who compared safety testing values to removal criteria, and the Study Physician, who assessed adverse events to determine participant removal criteria.

Protection from Risks

Participants underwent thorough health screenings every 3 mo throughout the study, including all baseline measures described above, with the exception of prostate TRUS (assessed every 6 mo). Participants were removed from the study if the following occurred: hematocrit ≥54%, serum PSA ≥4.0, increase in AUA/IPSS ≥7 points, or if gynecomastia or peripheral edema were noted at physical exam (Fig. 1).

Outcomes

Outcome measures were performed at baseline and at 3-mo intervals thereafter except dual X-ray absorptiometry (baseline and 12 mo only) and prostate TRUS (every 6 mo).

Prostate DRE and TRUS. DRE and TRUS were performed by the Urology Service, Malcom Randall VA Medical Center (VAMC), Gainesville, FL. TRUS was performed using the General Electric LOGIQ P5 scanning system with the highest sector transrectal probe/transducer of 7 MHz. The GE LOGIQc has built-in software for electronically calculating prostate volume (height × length × width × 0.52). The same operator performed testing for all participants.

1-RM strength testing. 1-RM strength testing was performed on Cybex (Medway, MA) leg press, knee flexion, knee extension, chest press, and triceps extension selectorized resistance exercise machines. A 5-min warm-up preceded testing, and weights were gradually increased to 1-RM. Testing was repeated within 2–7 days, and the highest load completed was utilized.

Grip strength. Grip strength of the right hand was assessed using a Jaymar hand-held dynamometer (Sammons Preston Roylan, Bolingbrook, IL).

Urinary symptoms. Urinary symptoms were assessed using the AUA/IPSS questionnaire (5).

Hormone Assays

Serum samples were obtained 1 wk after TE/vehicle injection. Clinical laboratory values, including total testosterone, were assessed in the Clinical Laboratory, Malcom Randall VAMC. Testosterone was assayed by Cobas electrochemoluminescence immunoassay. Separate serum samples were stored at −80°C and analyzed in duplicate in a single assay for CTX-1 and osteocalcin by ELISA (Immunodiagnostic Systems, Fountain Hills, AZ). Estradiol (E2) was assessed by ELISA (American Laboratory Products, Salem NH). BioT and BioE2 were assessed by ammonium sulfate precipitation of samples spiked with [3H]testosterone or [3H]estradiol (40). DHT was assessed by LC-MS-MS at Laboratory Corp of America (Calabasas Hills, CA).

Body Composition and Lumbar Spine and Hip BMD

These were assessed using a fan-bean densitometer (Lunar Prodigy; GE Medical Systems, Little Chalfont, Buckinghamshire, UK), calibrated daily.

Statistical Methods

Descriptive methods are given as means with standard deviations (SD) or as means with 95% confidence intervals (CI), as appropriate. P values < 0.05 (two-sided) were considered statistically significant. Repeated-measures dependent variables were analyzed as linear mixed models with participants as random effects, and time (3, 6, 9, or 12 mo), testosterone, finasteride, interaction, and baseline value of the dependent measures as fixed effects. We utilized an autoregressive correlational structure, allowing measures closer in time to have higher within-subject correlations than when farther apart. Missing at random was presumed for our analyses, and we chose not to use imputation, because it results in greater bias. For variables collected only at baseline and 12 mo, we used a fixed-effects ANOVA model with dependent variable as 12-mo minus baseline difference with the same treatment-related independent variables as above. This coding yields valid interpretable main effects even if interactions are present. The main effect of testosterone, for example, represents the average effect of testosterone under placebo and finasteride (weighted 50–50). In comparison, the interaction addresses whether or not the difference between the means for treatment factors (e.g., testosterone vs. vehicle) differ quantitatively according to the level of other treatment factors (e.g., finasteride vs. placebo). The changes from baseline to 12 mo are presented, but they estimate a different outcome than the mixed model, which measures an average effect over the times after baseline. The mixed model has two additional advantages over the simple 0- to 12-mo difference comparisons: 1) It uses all of the data, and 2) it is more sensitive than the 0- to 12-mo comparison for effects that increase early and decrease over time.

The study was powered around four end points: fat-free mass, 1-RM leg press, hematocrit, and prostate volume, although a wide range of variables were evaluated due to the systemic nature of androgen-AR interactions and to ensure participant safety. We intended to obtain 12 completers in each of the four arms. Allowing for a 20% dropout rate, the goal was 60 randomized participants. Bhasin et al. (1) reported that older men experience a ≥2σ (σ = SD) increase in fat-free mass (4.2 ± 0.6 SE, n = 12) and hematocrit (0.07 ± 0.01 SE, n = 12) and 1.18x increase in 1-RM strength (28.0 ± 6.8 SE, n = 12) after 20 wk of 125 mg/wk TE, whereas Zitzmann et al. (46) reported that testosterone replacement increased prostate volume 1.85x per year (6.1 ± 3.3 SD). For each variable, a 2 × 2 factorial study has 80% power to detect a 0.87σ difference at P < 0.05 (two-sided), and 80% power to detect a 1.0σ difference at P = 0.0125 (0.05/4). Importantly, 1-RM strength, fat-free mass, and hematocrit were powered using data from changes occurring over a 20-wk period of testosterone administration, whereas our study duration was 52 wk. As such, we powered to achieve significance in the aforementioned outcomes at the 6-mo time point of our study, which protects against the adverse effects of an unexpectedly high participant dropout rate on statistical power.

RESULTS

Primary Outcomes

Baseline values are reported in Table 1 and treatment effects in Tables 2–4 and Fig. 2. TE progressively increased 1-RM strength over 12 mo (Table 2) by 12.9 kg for leg press, an 11.4% increase (P < 0.001; Table 2 and Fig. 2H), 6.00 kg for knee extension (8.1%, P = 0.012), 5.42 kg for knee flexion (12.5%, P = 0.0023), 6.47 kg for chest press (14.5%, P < 0.001), 5.32 kg for triceps extension (9.5%, P < 0.001), and 0.77 kg for grip (11.3%, P = 0.015). TE also increased total body fat-free mass 4.04 kg (P = 0.032; Table 3 and Fig. 2G) and HCT 4.13% (P < 0.001; Table 2 and Fig. 2C), with most of the Hct increase occurring in the first 3 mo of treatment. Finasteride did not significantly affect muscle strength, fat-free
mass, or Hct. Additionally, TE increased prostate volume 5.33 cm³ (Table 2; main effect, \( P = 0.0051 \)), and finasteride reduced prostate volume by \(-5.79\) cm³ (main effect, \( P = 0.0027 \)). These changes resulted in progressive prostate enlargement of 11.4 cm³ (\( P = 0.0051 \)) within the TE group, an increase that was fully prevented by coadministration of finasteride (\( P = 0.0027 \); Fig. 2D). Prostate volume remained similar between TE-finasteride, vehicle-finasteride, and vehicle-placebo treatments.

### Demographic and Blood Values

TE elevated nadir testosterone and BioT, representing 1.8-fold and 2.2-fold increases over baseline, respectively (Table 2 and Fig. 2A). Finasteride did not affect those increases. TE elevated serum DHT, and finasteride lowered DHT (Table 2 and Fig. 2B). TE reduced LH to near-zero concentrations, whereas finasteride modestly increased LH (Table 3). TE elevated E₂ 1.7-fold and BioE₂ 2.2-fold (\( P < 0.001 \)), whereas finasteride had no effect (Table 4). TE elevated hemoglobin with a time course similar to that of Hct (Table 4), whereas finasteride had no significant effects on hemoglobin. TE lowered HDL-cholesterol and triglycerides while increasing LDL-cholesterol (Table 4). Finasteride significantly reduced LDL-cholesterol while increasing triglycerides (Table 4). Neither treatment altered total cholesterol. TE significantly decreased CTX-1 but did not affect osteocalcin (Table 4). All clinical values remained within normal reference ranges throughout the study (Table 4).

### Body Composition

TE increased lumbar spine BMD 4.19% (\( P < 0.001 \); Table 3 and Fig. 2E), lumbar spine BMC 3.94% (\( P = 0.0032 \)), and total hip BMD 1.96% (\( P = 0.024 \)); BMC was not affected in other regions. TE also reduced total body fat mass 3.87 kg (\( P < 0.001 \); Table 3 and Fig. 2F), trunk fat 1.88 kg (\( P = 0.0051 \); data not shown), and android fat mass 0.42 kg (\( P < 0.001 \); data not shown). Finasteride did not affect the above measurements.

### Prostate-Related Measures

TE elevated serum PSA, and finasteride reduced PSA (Table 2). The AUA/IPPS was not altered by treatment. Two participants received prostate biopsies, prompted by DRE findings (one each from the TE-placebo and TE-finasteride groups); both were negative.

### DISCUSSION

Testosterone exerts direct effects at ARs and can also induce indirect effects at ARs and/or estrogen receptors (ERs) following the 5α-reduction to DHT (44) or the aromatization to E₂ (28), respectively. However, the role of DHT in mediating beneficial and/or adverse effects of administered testosterone has received little focus in the literature. We report that 12-mo administration of higher-than-replacement TE (alone) or TE plus finasteride increased fat-free mass, muscle strength, Hct, and lumbar spine and hip BMD while reducing fat mass in older hypogonadal men. TE (alone) also elevated PSA and prostate volume, whereas coadministration of a clinically relevant dose of finasteride completely prevented TE-induced increases in PSA and prostate volume.

In young and older men, testosterone dose-dependently augments lean mass with high-dose TE (600 mg/wk for 10 wk) increasing quadriceps area 7% and muscle strength 10–12% (10). In contrast, low-dose testosterone (5 mg/day for 2 yr) increased femoral neck BMD but did not alter muscle strength in older men (31), suggesting that higher doses of testosterone may be required for improvements in muscle function (41). In support of this contention, moderate-dose TE (200 mg bi-weekly) improved lumbar spine and hip BMD, physical performance, and grip strength but did not increase leg strength.
over 3 yr of treatment (4, 33). Importantly, equivalent results were observed whether TE was administered alone or in combination with finasteride (14, 23), indicating that elevated DHT is not required for the beneficial skeletal responses to testosterone in adults. We report similar findings, in that TE were observed whether TE was administered alone or in combination with dutasteride (4, 33). Dutasteride inhibited TE-induced improvements in muscle mass and strength in older hypogonadal men. One difference between these studies is that Page et al. (33) measured isokinetic strength, whereas we measured 1-RM strength. Interestingly, type I 5α-reductase expression appears essential for normal musculoskeletal development, as demonstrated by male 5α-reductase type I knockout (srd5a1−/−) mice that exhibit reduced bone mass and muscle force despite normal circulating androgen concentrations (42). However, 5α-reductase type I activity is not essential for testosterone-induced myotrophic effects in adult men. As evidence, Bhasin et al. (11) reported that dutasteride did not inhibit TE-induced improvements in lean mass or muscle function in young eugonadal men administrated...
istered GnRH agonists to suppress testosterone despite a near-complete ablation of circulating DHT. Preclinical findings also indicate that high-dose TE plus MK-434 (types I and II 5α-reductase inhibitor) (14, 15) and trenbolone [a highly potent non-5α-reducible and nonaromatizable testosterone analog (15, 30, 43)] protect against orchitectomy-induced muscle and bone loss, although no clinical study has examined the skeletal responses to TE plus dutasteride.

We also observed that TE treatment significantly elevated serum E2 and BioE2. In this regard, recent evidence indicates that the lipolytic (but not the muscular) effects of testosterone may be influenced by the aromatization of testosterone to E2 (22). Additionally, E2 is a more potent bone antiresorptive agent than testosterone in older men undergoing experimental sex steroid deficiency (at least when administered in doses that result in physiological serum concentrations) (19). As such, the possibility exists that the lipolytic and bone-protective effects that we observed were, in part, mediated by elevated E2. However, this certainly does not preclude the possibility that androgens influence bone and adipose tissue through direct AR-mediated mechanisms. In support of this contention, trenbolone (a highly potent nonaromatizable and non-5α-reducible testosterone analog) reduces adiposity and preserves bone mass in several animal models of sex steroid deficiency (30, 43). Additionally, human preadipocytes and mature adipocytes express ARs (35) and nonaromatizable androgens inhibit adipogenesis in human adipose tissue (17). Human osteoblasts also express ARs at sites of bone formation (1), and physiological testosterone replacement maintains bone formation in older men undergoing experimental sex steroid deficiency (19). Re-
regardless of the mechanism, the biological significance of our findings is profound given that we have demonstrated that the desirable musculoskeletal and lipolytic effects of higher-thanreplacement testosterone can be obtained without deleterious effects on prostate mass, which significantly improves the safety profile of this clinically relevant treatment.

DHT mediates many of the androgenic effects of testosterone, including prostate enlargement, and may worsen prostate cancer risk (29). Both finasteride and dutasteride are used clinically to treat BPH due to their ability to reduce circulating DHT (38). However, only two previous clinical studies (4, 11) have examined whether elevated DHT mediates prostate enlargement following testosterone administration, with somewhat conflicting results. Bhasin et al. (11) reported that graded doses of TE (ranging from 50 to 600 mg/wk) increased prostate volume 2.5 cm³ over 20 wk in young men and that dutasteride did not prevent this enlargement. Conversely, Amory et al. (4) reported that TE (200 mg biweekly) increased prostate volume 14 cm³ over 3 yr in older hypogonadal men and that finasteride coadministration limited prostate enlargement to only 5 cm³. Others reported that men receiving testosterone by patch, gel, or injection experienced prostate volume increases of 4.9 cm³/yr of treatment (46) and that coadministration of transdermal testosterone (1% T gel) and dutasteride reduced prostate size in older men with BPH (34). Similarly, we report that the main effect of 125 mg/wk TE on prostate volume was 5.3 cm³ when administered to hypogonadal older men; however, this underestimates the actual 12-mo change in the TE-placebo group (11.4 cm³), because finasteride coadministration completely prevented TE-induced prostate enlargement.

Testosterone dose-dependently increases hemoglobin and hematocrit, possibly independently of erythropoietin, and this effect is greater in older men compared with younger (18). We observed a 4–5 point Hct increase following administration of either TE or TE plus finasteride; suggesting that elevated DHT does not mediate this change. The Hct increase that occurs in most older men receiving testosterone is not considered detrimental and may be beneficial (37), although this must be weighed against the risk of polycythemia (25) and associated cardiovascular risks (23).

Several meta-analyses (16, 25) have identified polycythemia, combined incidence of prostate events (including elevated PSA, increased urinary symptoms, number of prostate biopsies, and prostate cancer), and a modest reduction in HDL-cholesterol as the three proven adverse events resulting from testosterone administration. Rates of adverse events were similar between groups in our study, although we observed that TE lowered HDL by ~10%, an effect not altered by finasteride. TE also increased LDL 29% and reduced triglycerides. Conversely, finasteride coadministration reduced LDL-cholesterol but did not alter triglycerides. The clinical ramifications of these blood lipid changes remains unknown (36). Additionally, several putative adverse events are associated with testosterone administration, including worsening of sleep apnea, edema, gynecomastia, increased incidence of cardiovascular events, acceleration of underlying prostate cancer, and liver-related side effects (6, 7, 25). In this regard, coadministration of testosterone plus finasteride has some advantages, including lessening of androgen-induced prostate enlargement, and some potential disadvantages compared with treatment with testosterone alone, including altering the clinical usefulness of PSA measurements (29). However, the value of PSA testing has come into question, especially in men aged ≥70 yr (8).

Testosterone administration combined with 5α-reductase inhibition may also alter prostate cancer risk or severity, given that finasteride alone reduces the incidence of prostate cancer while increasing the number of prostate cancers with Gleason scores of 7–10 (38). Similarly, testosterone-stimulated prostate cancer growth in culture is ablated by dutasteride (2), perhaps through mechanisms involving upregulation of testosterone-sensitive tumor suppressors (24).

Table 3. Treatment effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0–12 mo Change</th>
<th>Main Effect of TE</th>
<th>Main Effect of F</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, ng/dl</td>
<td>Vehicle-Placebo</td>
<td>15 (−48 to 78)</td>
<td>479 (374 to 584)</td>
<td>45 (−59 to 152)</td>
<td>28 (−182 to 238)</td>
</tr>
<tr>
<td>DHT, ng/dl</td>
<td>Vehicle-Placebo</td>
<td>7.2 (−11 to 25)</td>
<td>148 (114 to 184)</td>
<td>25 (−30 to 38)</td>
<td>−6.7 (−30 to 64)</td>
</tr>
<tr>
<td>BioT, ng/dl</td>
<td>Vehicle-Placebo</td>
<td>7.0 (−13 to 15)</td>
<td>12.3 (−59 to 28.2)</td>
<td>−11.6 (−26.2 to 3.05)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LH, U/l</td>
<td>Vehicle-Placebo</td>
<td>−0.29 (−2.41 to 1.83)</td>
<td>−7.40 (−9.38 to −5.42)</td>
<td>2.73 (0.74 to 4.72)</td>
<td>−0.47 (−4.52 to 3.58)</td>
</tr>
<tr>
<td>Osteocalcin, ng/ml</td>
<td>Vehicle-Placebo</td>
<td>−0.29 (−2.41 to 1.83)</td>
<td>−7.40 (−9.38 to −5.42)</td>
<td>2.73 (0.74 to 4.72)</td>
<td>−0.47 (−4.52 to 3.58)</td>
</tr>
</tbody>
</table>

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As with all studies, several limitations exist with our data set, including a relatively small sample size and a slightly higher than expected non-completion rate. In this regard, the 2 × 2 factorial design that we utilized is the most powerful study design to detect outcomes resulting from a combination pharmacological therapy and allows for adequate power with smaller sample sizes. To ensure an appropriate sample size, we powered to detect differences in three of four primary outcomes (i.e., 1-RM strength, fat-free mass, and Hct) at the 6-mo time point despite the 12-mo duration of our study. In this regard, we met our expected non-completion rate of 20% at 6 mo, whereas the 12-mo noncompletion rate in our study (i.e., 33%) was slightly higher than anticipated. Importantly, non-completion was similar among all groups (χ² P value = 0.48, indicating no differences) and was comparable to the non-completion rates of 27–29% in other long-term testosterone studies (4, 11, 26). Additionally, our non-completion rate was not exceedingly high, given that once-weekly visits to the hospital were required for 52 consecutive weeks and that we observed a significant main effect for testosterone in each of our primary and secondary outcomes and a significant interaction for prostate volume (the only primary outcome powered on 12-mo data), as hypothesized. Indeed, we detected all a priori hypotheses for primary and secondary outcomes. However, it remains theoretically possible that we did not observe significant interactions (at the 12-mo time point) because our noncompliance rate resulted in a slightly lower than expected power to detect such outcomes. We believe this to be highly unlikely given that the 0- to 12-mo changes and point estimates (i.e., 95% CI) for the vast majority of our data were directionally similar and of a comparable magnitude in the I) testosterone-placebo and testosterone-finasteride groups and 2) vehicle-placebo and vehicle-finasteride groups. Regardless, when one is interpreting our data, nonsignificant interactions should not be used to infer that an interaction was not present. In addition to the above mentioned limitations, some nonsignificant differences also existed between groups at baseline. To account for this random variability, baseline values were included in our statistical model as fixed effects. Additionally we examined the baseline characteristics of the randomized cohort (n = 60) and of the completers (n = 40) and observed no differences between cohorts, indicating that completers were representative of the overall randomized cohort. Irrespective of these limitations, we report significance in each of our primary and secondary outcomes, demonstrating the robustness of our data and that our study achieved appropriate power to detect all desired outcomes.

In conclusion, our results add to the growing number of preclinical (24–26) and clinical trials (4, 11, 33) reporting that musculoskeletal and lipolytic improvement can be obtained.
without prostate enlargement when higher-than-replacement testosterone is coadministered with finasteride (an inhibitor of the type II 5α-reductase enzyme). These findings indicate that elevated DHT is not required for the benefits of exogenous testosterone and support the contention that finasteride ablates prostate enlargement associated with higher-than-replacement TE administration. As such, our findings provide a rationale for larger and more comprehensive clinical trials examining the safety and efficacy of higher-than-replacement testosterone plus finasteride/dutasteride treatment in hypogonadal elderly men.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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