Annals of Internal Medicine | ORIGINAL RESEARCH

Long-Term Effects of Dihydrotestosterone Treatment on Prostate Growth in Healthy, Middle-Aged Men Without Prostate Disease

A Randomized, Placebo-Controlled Trial

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Background: Benign prostatic hypertrophy increases with age and can result in substantially decreased quality of life for older men. Surgery is often required to control symptoms. It has been hypothesized that long-term administration of a nonamplifiable pure androgen might decrease prostate growth, thereby decreasing or delaying the need for surgical intervention.

Objective: To test the hypothesis that dihydrotestosterone (DHT), a nonamplifiable and nonaromatizable pure androgen, reduces late-life prostate growth in middle-aged men.

Design: Randomized, placebo-controlled, parallel-group trial. (Australian New Zealand Clinical Trials Registry number: ACTRN12605000358640)

Setting: Ambulatory care research center.

Participants: Healthy men (n = 114) older than 50 years without known prostate disease.

Intervention: Transdermal DHT (70 mg) or placebo gel daily for 2 years.

Measurements: Prostate volume was measured by ultrasonography; bone mineral density (BMD) and body composition were measured by dual-energy x-ray absorptiometry; and blood samples and questionnaires were collected every 6 months, with data analyzed by mixed-model analysis for repeated measures.

Results: Over 24 months, there was an increase in total (29% [95% CI, 23% to 34%]) and central (75% [CI, 64% to 86%]; $P < 0.01$) prostate volume and serum prostate-specific antigen level (15% [CI, 6% to 24%]) with time on study, but DHT had no effect ($P > 0.2$). Dihydrotestosterone treatment decreased spinal BMD (1.4% [CI, 0.6% to 2.3%]; $P < 0.001$) at 24 months but not hip BMD ($P > 0.2$) and increased serum aminoterminal propeptide of type I procollagen in the second year of the study compared with placebo. Dihydrotestosterone increased serum DHT levels and its metabolites (5α-androstane-3α,17β-diol and 5α-androstane-3β,17β-diol) and suppressed serum testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone levels. Dihydrotestosterone increased hemoglobin levels (7% [CI, 5% to 9%]), serum creatinine levels (9% [CI, 5% to 11%]), and lean mass (2.4% [CI, 1.6% to 3.1%) but decreased fat mass (5.2% [CI, 2.6% to 7.7%]) (P <0.001 for all). Protocol-specific discontinuations due to DHT were asymptomatic increased hematocrit (n = 8), which resolved after stopping treatment, and increased prostate-specific antigen levels (n = 3; none with prostate cancer) in the DHT group. No serious adverse effects due to DHT occurred.

Limitation: Negative findings on prostate growth cannot exclude adverse effects on the natural history of prostate cancer.

Conclusion: Dihydrotestosterone treatment for 24 months has no beneficial or adverse effect on prostate growth but causes a decrease in spinal but not hip BMD. These findings have important implications for the wider use of nonsteroidal pure androgens in older men.

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Benign prostate hyperplasia (BPH) is a frequent feature of male aging. Most men who live an average life expectancy develop nodular prostate enlargement (1); 50% develop lower urinary tract symptoms, and 25% ultimately require medical or surgical treatment (2). Symptomatic BPH diminishes the quality of life of older men and their carers, with annual costs for the average 14 million U.S. men affected exceeding $4 billion in direct health sector expenditure (3) and excluding private over-the-counter spending. Prostatectomy is among the most frequent operations for older men, constituting a major health and economic burden. Although the long latency and hormonal dependence of BPH is opportune for early detection and intervention, current medical therapy centers on α-blockers (4), which provide symptomatic benefit without modifying the natural history of disease (5, 6); however, prostatectomy is eventually required and involves hospitalization, risk for surgical complications, and recurrence in older men with several comorbid conditions (7, 8). Slowing BPH progression could reduce expensive and complication-prone surgery to improve quality of life and save health costs.

The prostate is a highly androgen-dependent tissue that strongly expresses the enzymes 5α-reductase type 2 (which converts testosterone to dihydrotestosterone [DHT], a 3- to

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Context

Benign prostatic hypertrophy (BPH) increases with age and can result in substantially decreased quality of life for older men. It has been hypothesized that long-term administration of nonamplifiable pure androgens might decrease prostate growth rate, decreasing or delaying the need for surgical intervention.

Contribution

In this randomized, placebo-controlled trial, participants received either placebo or transdermal dihydrotestosterone (DHT). Average prostate size increased over time in all men, with no significant difference between the DHT and placebo groups.

Caution

Men who received transdermal DHT had a small but statistically significant decrease in bone density in the spine but not in the hip. The study was not designed to assess the natural history of prostate cancer.

Implication

This trial does not support the use of nonamplifiable pure androgens to delay or prevent prostate growth and progression of presymptomatic BPH.

—The Editors

10-fold more potent androgen) and aromatase (which converts testosterone to estradiol, capable of acting on estrogen receptors). The prostate operates a powerful intraprostatic activation system that both amplifies and diversifies testosterone action before receptor interaction. Unlike testosterone, DHT is a potent, nonamplifiable, and nonaromatizable pure androgen, with a metabolite (3β-androstanediol-5α) that may inhibit prostate growth through interaction with estrogen receptor-β (9, 10). The rationale for our study was that administration of DHT would provide no direct amplifiable or aromatizable androgenic effects on the prostate, with a potential for growth inhibition through its metabolite, and would have indirect effects of reducing intraprostatic testosterone, DHT, and estradiol levels (all of which stimulate prostate growth) through negative feedback effects on endogenous gonadotropin and testosterone secretion. In concert, these effects might reduce the natural history of prostate growth in men without prostate disease (11). Previous studies found that 3-month treatment with DHT gel reduced the rate of prostate growth compared with placebo (12), but this was not confirmed in a 6-month study (13). If not due to chance, these disparities may be due to design differences, such as study duration, use of a single sonographer (12) versus several (13), or inclusion of healthy (12) versus symptomatic (13) older men. We aimed to test the hypothesis by measuring DHT effects on prostate growth in healthy men without prostate disease by using transdermal DHT or placebo gel for 24 months. We also aimed to examine secondary DHT effects on muscle, body composition, quality of life, and safety as well as bone, erythropoietic, and vascular end points. In addition, as a pure androgen, DHT is a prototype for the new class of specific androgen-receptor modulators, that is, nonsteroidal chemicals without more potent androgenic or estrogenic metabolites (14). Therefore, our study also provides the first insight into the long-term safety of pure androgens in otherwise healthy men.

METHODS

Design

Our study was a randomized, double-blind, placebo-controlled, parallel-group, single-center clinical trial involving 24 months of daily transdermal treatment with an active drug (DHT, 70 mg) or a matching placebo gel to determine whether DHT would reduce prostate growth. The primary efficacy end point was total prostate volume measured by transrectal ultrasonography at 6-month intervals over 2 years (15). The secondary efficacy end points included central prostate volume; serum prostate-specific antigen (PSA) levels; bone mineral density (BMD) (hip and spine) and body composition (lean and fat mass) by dual-energy x-ray absorptiometry (DXA); carotid artery intima–media thickness by ultrasonography; muscular strength by hand grip dynamometry; and quality-of-life questionnaires (Short Form-36 Health Survey [SF-36], International Prostate Symptom Score [IPSS], Physical Activity Scale for the Elderly [PASE], and Psychosexual Daily Questionnaire [PDQ]). Safety end points were vital signs, adverse events, and standard biochemical and hematologic profiles. Polycythemia was a morning fasting hematocrit of greater than 0.50 confirmed in the nonfasting state.

The Sydney South West Area Health Service Ethics Committee (Concord Hospital Sydney) within National Health and Medical Research Council guidelines (consistent with the Declaration of Helsinki) approved this study. We registered the study with the Australian New Zealand Clinical Trials Registry before commencing recruitment. An independent data safety and monitoring committee scheduled reviews of safety after completion of 12 months of drug treatment for the first 50 participants and at the end of the study.

Procedures

Men 50 years or older were eligible if they had no known prostate disease (cancer, disease requiring further treatment, or blood PSA level >4.0 μg/L). We excluded men who had any unstable, uncontrolled, or severe chronic medical disease (including infections or extensive bone or skin diseases) requiring treatment; polycythemia (hematocrit >0.50); a history of drug abuse or addiction; a history of mental illness requiring regular psychotropic medication; or used disallowed medication that interfered with sex steroid action or bone mass. Volunteers recruited through

advertising provided written, informed consent before undergoing screening. On entry, participants were given a unique, sequential study identifier and were randomly assigned (1:1) according to a randomization list with a balanced block size generated by pharmacy staff at Laboratoires Besins International (Montrouge, France) who was not involved in the Sydney study center. The study medication was produced with the full supply for each participant and was labeled with a study identifier number so that the sequence of treatments (DHT or placebo), by study identifier, was determined by the randomization list. The finished study drug sachets marked only with study identifier number were supplied to the Sydney study center. Eligible participants were enrolled in sequential order and assigned the next available study identifier number. Study identifiers were not reused. The active drug and placebo were formulated in hydroalcoholic gel with identical appearance, odor, and consistency, packed in identical sachets, and labeled according to the study identifier. All study staff and participants were unaware of treatment assignment throughout the study. The randomization code was broken only after the end of data collection and analyses. Participants received no payments.

We studied participants in the fasting state from 8:00 a.m. to 10:30 a.m. (before applying the daily gel dose) at baseline; during the study at 3, 6, 12, 18, and 24 (end of study) months; and at 3 months after cessation of treatment (recovery). Men who discontinued participation during the study were required to complete an end-of-study visit as soon as possible after withdrawal and recovery visits. At visits, participants were asked about adverse events, had a physical examination, provided blood and urine samples, completed questionnaires, had ultrasonography (prostate and carotid) and DXA (BMD and body composition), returned unused sachets (to estimate adherence), and were resupplied with sufficient sachets to last until the next scheduled visit. No dose adjustment occurred. Participants applied 2 sachets of gel daily on clean, dry skin on their trunk or thighs after their morning shower, allowing the application site to dry for 2 minutes before dressing.

Assays

Fasting serum and urine samples were stored frozen at −20 °C until analysis in a batch at the end of the study by laboratory staff unaware of treatment allocation. We quantified serum testosterone; DHT; 5α-androstane-3α,17β-diol (3α-diol); 5α-androstane-3β,17β-diol (3β-diol); and estradiol from 0.2-mL samples after acetonitrile extraction (16), followed by liquid chromatography, tandem mass spectrometry using positive atmospheric pressure photoionization as the ionization source for androgens (17), and negative electrospray ionization for estradiol (18). The assay limits of quantification and coefficients of variation were testoterone, 0.3 nmol/L (8.65 ng/mL) and 3% to 6%; DHT, 1.4 nmol/L and 8% to 14%; 3α-diol, 0.7 nmol/L and 6% to 9%; 3β-diol, 0.7 nmol/L and 7% to 9%; and estradiol, 15 pmol/L (4.09 pg/mL) and 3% to 6%. Serum luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were measured by automated immunoassays (Roche Diagnostics, Castle Hill, Australia); coefficients of variation were 1.0% to 2.0%. Serum concentration of the aminoterminal propeptide of type I procollagen was measured by an automated immunoassay (Roche Diagnostics; detection limit was 5 ng/mL and coefficient of variation was 2.3%). Urinary concentration of the aminoterminal cross-linked telopeptide of collagen type I was measured by a manual immunoassay (Osteomark, Ostex International, Seattle, Washington; detection limit was 20 nmol bone collagen equivalents and coefficient of variation was 4.6% to 6.9%) and adjusted for urinary creatinine (alkaline picrate method) excretion. Blood samples for biochemical and hematologic profiles were analyzed on the day of sampling by routine autoanalyzer methods.

Ultrasonography

Prostate volume was measured with a 7.5-MHz sector scanner (Seimens, Sydney, Australia) at 6-month intervals by using both transrectal and transperineal methods (15) to estimate the size of total prostate and its central zone (mL) by measuring the 3 maximal dimensions (mm) and using the ellipsoidal formula to calculate volume. Intima–media thickness of both carotid arteries was measured in duplicate by ultrasonography within 1 cm of the carotid artery bifurcation, as described (19). All ultrasonography measurements were done by a single highly experienced operator, and between-day coefficients of variation were 5% for total and 20% for central prostate volumes (15).

Bone Densitometry and Body Composition

Body composition (fat mass and lean tissue) and BMD at the femoral neck and lumbar spine (L2–4) were measured by DXA at baseline and at 6-month visits by using a Lunar Prodigy (Lunar, Madison, Wisconsin). Coefficients of variation ($n = 30$) were 2.1% for lumbar spine (L2–4), 1.4% for femoral neck BMD, 0.7% for lean tissue, and 1.5% for fat mass in body composition analysis. Bioelectrical impedance was measured with an IMP5 bioimpedance meter (ImpediMed, Brisbane, Australia). We measured whole-body resistance, reactance, and impedance from 4 electrodes (pisiform prominence of the wrist, distal metacarpal on the dorsal surface of the right hand, between the medial and lateral malleoli of the ankle, and distal metatarsal of the dorsal surface of the right foot) placed on fasting, supine participants. We calculated lean and fat mass from the Lukaski algorithm (20).

Anthropometry

We used a fixed stadiometer to measure height (nearest 0.1 cm) and calibrated scales for weight (nearest 0.1

kg). Participants wore a light gown and no shoes. Waist, hip, midarm, and midthigh circumferences were measured using a nonstretch measuring tape. We assessed skinfold thickness at right bicep, tricep, subscapular, and suprailiac positions with a Harpenden Skinfold Caliper (British Indicators, Bedfordshire, United Kingdom). Isometric hand grip strength was measured by using a Jamar hand grip dynamometer (JA Preston, Jackson, Mississippi), with duplicate measurements on dominant and nondominant hands (21).

Questionnaires

We administered 4 quality-of-life questionnaires at each visit. These comprised the SF-36 for health-related limitations (22); the IPSS questionnaire for lower urinary tract symptoms (23); the PASE for habitual physical activity (24); and the PDQ for psychosexual function, which included scoring for sexual desire, enjoyment, activity, and drive; number of erections; moods; and sex-life satisfaction on a daily basis (25).

Statistical Analysis

The target sample size of 50 per group was based on previous data (12), which defined a 50% reduction in mean prostate growth rate (±SE) (4.8 ± 3.1 mL/y) as being a potentially clinically significant benefit, assuming a 25% withdrawal rate and power defined by a 2-sided α level of 0.05 and β level of 0.90. We analyzed data according to an intention-to-treat (ITT) analysis, which was defined as participants who were randomly assigned and received at least 1 dose of medication and had at least 1 efficacy value. Data were analyzed by using a linear mixed-model analysis for repeated measures that estimated effects of time with random (participants) and fixed (treatment) terms together with age (defined at entry to study to avoid collinearity with time receiving treatment) as a covariate in all models (NCSS, Kaysville, Utah). The linear model was fitted by restricted maximum likelihood methods using a Newton–Raphson search algorithm and utilizing an autoregressive variance–covariance error matrix with allowance for different variances between time points. Goodness of fit was evaluated for individual models by inspecting residuals between the fitted and observed values at each time point for systematic deviations and using the AIC (Akaike Information Criterion) or comparison of models. A DHT treatment effect was either a significant treatment main effect or treatment-by-time interaction. This analysis was robust to missing data from the ITT population by avoiding casewide deletion of participants for predictor variables missing at random for some time point or persons (26). Similarly, we expected no differential withdrawals (for efficacy reasons) because participants were all healthy, disease-free volunteers.

We did a sensitivity analysis for each end point to determine the effect of premature discontinuation as potentially nonignorable missing data on the findings. These sensitivity analyses comprised comparing models restricted to participants who completed the full study with those based on the full ITT population and a 2-stage selection model that involved first constructing a propensity (to withdraw) probability using logistic regression (forward stepping), selecting from all baseline variables, and then using the withdrawal probability as a covariate in reanalysis of study end points to adjust for the effect of missing data due to discontinuation (27). In evaluating why the hormone levels were different (reduced DHT metabolites and suppression of testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone) at the end-of-study time point compared with the stable levels throughout the active treatment period (including the 24-month time point), the linear mixed-model analysis was rerun using serum DHT as a covariate to determine whether the hormone changes were attributable to reduced serum DHT levels after cessation of DHT treatment. Reflecting the repeated measures design, data were analyzed and depicted as within-participant changes. Categorical data were analyzed by Fisher exact test (StatXact, version 9, Cytel Software, Cambridge, Massachusetts). Data were expressed as means (SDs) or 95% CIs.

Safety was evaluated by documentation and reporting adverse events and serious adverse events in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the European Agency for the Evaluation of Medicinal Products, and the U.S. Food and Drug Administration's Good Clinical Practice Guidelines. Study staff, unaware of treatment assignment, ascertained and recorded adverse events during personal interviews at every visit by using open-ended questions as well as by telephone between visits. We coded adverse events according to Medical Dictionary for Regulatory Activities, with causality determined according to standard definitions in the protocol. At completion of the study, findings were tabulated according to group. We included all participants who applied at least 1 dose of treatment in the safety analyses.

Role of the Funding Source

The study sponsor, BHR Pharma, provided funding support, including monitoring for the study, but had no influence on the study design, data analysis, interpretation of the findings, or decision to submit the manuscript for publication, all of which were solely the responsibility of the investigators. The authors designed the study, had unrestricted access to the data, performed and interpreted all data analysis, and wrote the manuscript independent of the sponsor.

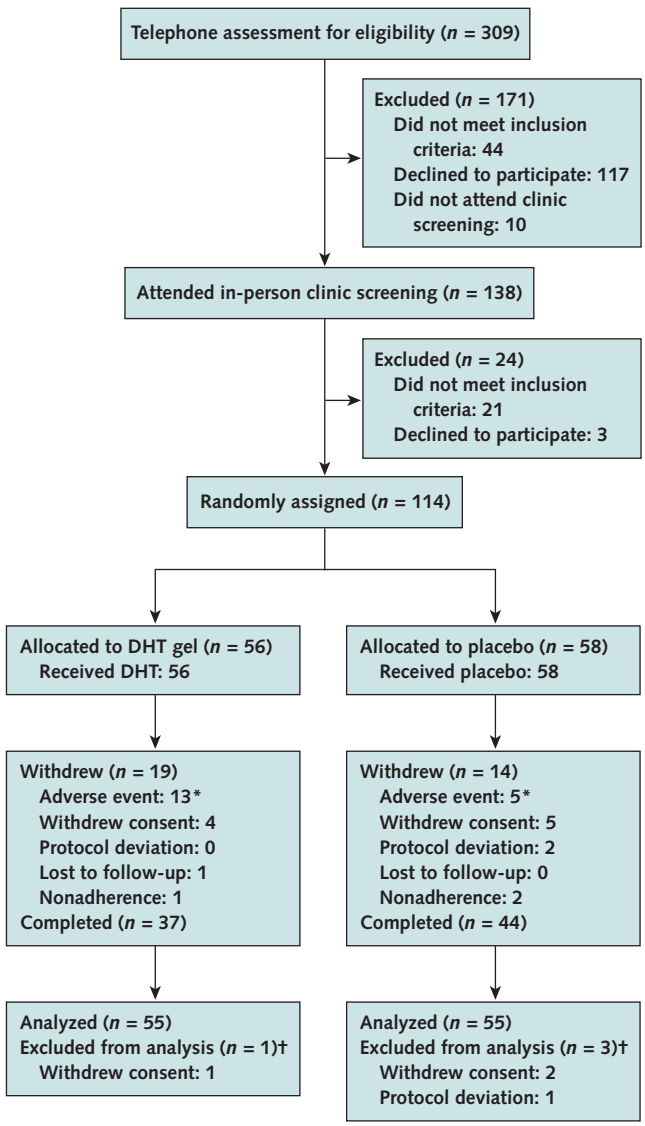
RESULTS

Participant Flow and Characteristics

Recruitment (August 2004 to March 2006) identified 309 volunteers. After excluding 44 ineligible persons, we

screened 138 men; 117 declined to participate after receiving the study information, and 10 did not attend the screening visit (**Figure 1**). After we excluded 24 men because of prostate disease (1 with cancer and 10 with elevated PSA levels); polycythemia (5 men); disallowed medications (3 men); alcohol abuse (1 man); and inability to consent (1 man); and 3 withdrew after screening, we randomly assigned 114 men (mean [±SE] age, 60.5 ± 0.7 years; height, 176.5 ± 0.6 cm, and weight, 84.8 ± 1.2 kg) to DHT (n = 56) or placebo (n = 58). The groups were well matched for baseline characteristics (**Table**). Participants were of European background, apart from 8 Asian men and 1 man of Pacific Islander/Aboriginal origin. In total, 81 of 114 persons (71.1%) completed the 24-month treatment period of the study (37 [66.1%] received DHT and 44 [75.9%] received placebo). Most men who discontinued completed the end-of-study (109 of 114) and recovery (105 of 114) visits. Discontinuations were due to adverse effects (13 DHT, 5 placebo), withdrawal (4 DHT, 5 placebo), protocol violation (2 placebo), loss to follow-up (1 DHT), and nonadherence with medication (1 DHT, 2 placebo). For men who discontinued, the last visit completed was baseline (n = 4), 3 months (n = 11), 6 months (n = 7), 12 months (n = 7), and 18 months (n = 4) without any difference in distribution between groups (P = 0.13, extended Fisher test). The ITT population comprised 55 (98.2%) men in the DHT group and 55 (94.8%) men in the placebo group. The study treatment period (November 2004 to July 2008) achieved a median duration of 99% of scheduled time for both groups (median time on study, 722 days for DHT and 725 days for placebo). Adherence (percentage of sachets dispensed that were returned and used) was high (95% DHT, 94% placebo), with more than 95% of the ITT population having an adherence rate from 80% and 120%. There was no difference in adherence rates by treatment group. At the end of the study, significantly more participants guessed correctly whether they had received the active drug or placebo (64 of 106; 60% [95% CI, 50% to 70%]; P = 0.05), with no difference between groups (55% DHT vs. 66% placebo [CI, −29% to 7%]).

Figure 1. **Study flow diagram.**



DHT = dihydrotestosterone.
* For details of adverse events, see the Results section.
† Participants excluded from the intention-to-treat analysis received the randomly allocated intervention but did not provide any efficacy end point data.

Hormones

Dihydrotestosterone treatment produced a marked (about 10-fold) increase in serum DHT and its 2 metabolites, serum 3α-diol and 3β-diol, which were sustained during the study (**Figure 2** and **Appendix Figure 1**, available at www.annals.org). Serum testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone were markedly suppressed to castrate levels (**Figure 2** and **Appendix Figure 1**) throughout the treatment period, whereas serum sex hormone–binding globulin was unchanged (P >0.10) by DHT treatment. No hormone variables were changed by placebo treatment. The end-of-study data comprised the last measurements during the treatment phase, representing the scheduled 24-month visit for the 81 (71%) men completing the study, with the last measurements before entry into the recovery period for the 31 men who discontinued prematurely. At the end-of-study visit, the men who discontinued prematurely had not been applying gel treatment for a median of 31 days (range, 1 to 180 days). Median serum DHT (±SE) was 5.2 ± 7.6 nmol/L in men who received DHT and 25.8 ± 17.7 nmol/L in men who completed the study at 24 months. By using a covariance analysis, the decrease in serum DHT levels at the end-of-study visit accounted for the changes in

Table. **Baseline and Observed Changes During 24 Months***

Variable	Baseline†		Changes at 24 Months‡		Difference
Prostate	**DHT**	**Placebo**	**DHT**	**Placebo**	
Total volume, *mL*	28.6 (10.4)	29.3 (16.2)	9.5 (7.2)	9.7 (9.4)	−0.2 (−4.0 to 3.6)
Central volume, *mL*	4.1 (2.2)	5.4 (8.4)	4.4 (2.6)	3.6 (287)	0.8 (−0.4 to 2.0)
Serum PSA level, *μg/L*	1.6 (1.1)	1.5 (1.1)	0.2 (0.6)	0.3 (0.7)	−0.06 (−0.3 to 0.2)
IPSS score	5.4 (4.2)	6.2 (5.0)	1.0 (3)	0.4 (3)	1 (−1 to 2)
Hormone levels					
DHT, *nmol/L*	2.2 (2.1)	1.8 (1.2)	23 (15)	−0.2 (0.9)	24 (19 to 28)
Testosterone, *nmol/L*	17.1 (6.1)	17.5 (6.4)	−14.7 (6.2)	−0.3 (4.2)	−14 (−17 to −12)
Estradiol, *pmol/L*	64 (45)	58 (31)	−57 (38)	−5 (32)	−51 (−67 to −36)
3α-diol, *nmol/L*	0	0	15 (12)	0	15 (11 to 19)
3β-diol, *nmol/L*	0	0	1.5 (1.3)	0	1.0 (0.7 to 1.4)
LH, *IU/L*	4.5 (2.7)	4.3 (2.5)	−2.6 (4.5)	0.2 (1.7)	−2.8 (−4.2 to 1.3)
FSH, *IU/L*	5.6 (4.2)	5.4 (3.8)	−3.2 (3.4)	0.4 (1.5)	−3.6 (−4.7 to −2.4)
SHBG, *nmol/L*	43 (23)	44 (20)	−4 (18)	0.7 (132)	−5 (−11 to 2)
Hemoglobin, *g/L*	150 (9)	150 (9)	11 (10)	−2 (8)	15 (12 to 19)
Creatinine, *μmol/L*	86 (12)	88 (13)	8 (8)	−2 (8)	9 (6 to 13)
Urea, *mmol/L*	6.3 (0.2)	6.5 (0.2)	0.09 (1.1)	0.17 (1.2)	−0.08 (−0.6 to 0.4)
Bone, fat, and muscle					
Lumbar spine (L2–4) BMD, g/cm^2	1.309 (0.198)	1.258 (0.199)	−0.023 (0.045)	0.005 (0.037)	−0.028 (−0.046 to −0.009)
Femoral neck BMD, g/cm^2	1.016 (0.149)	1.000 (0.150)	−0.020 (0.035)	−0.020 (0.064)	0 (−0.023 to 0.024)
Serum PINP level, *μg/L*	43 (27)	41 (16)	7 (27)	0.2 (12)	7 (−2 to 16)
Urinary NTX level, *nmol/BCE*	50 (54)	53 (34)	−4 (61)	−5 (30)	1 (−20 to 22)
Fat mass, *kg*	23.6 (7.1)	22.2 (7.8)	−1.1 (2.4)	0.8 (2.3)	−2.8 (−2.9 to 0.8)
Lean mass, *kg*	58.5 (6.9)	56.9 (6.2)	1.5 (1.8)	−0.03 (1.4)	1.6 (0.9 to 2.3)
Grip strength, *lb*	44 (9)	43 (8)	0.9 (5)	0.2 (5)	0.4 (−1.4 to 2.2)
Cardiovascular					
BMI, kg/m^2	27.2 (3.3)	27.0 (3.7)	0 (0.8)	0.3 (1.8)	−0.3 (−1.0 to 0.3)
Pulse, *beats/min*	67 (9)	70 (11)	3 (8)	−1 (10)	4 (−6 to 8)
Systolic BP, *mm Hg*	128 (17)	128 (14)	6 (19)	0 (17)	6 (−2 to 14)
Diastolic BP, *mm Hg*	83 (9)	83 (8)	4 (10)	2 (8)	2 (−2 to 6)
Right carotid IMT, *mm*	0.76 (0.15)	0.71 (0.18)	0.02 (0.08)	0.02 (0.07)	0 (−0.3 to 0.4)
Total cholesterol level, *mmol/L*	5.0 (1.0)	5.2 (0.9)	0.1 (0.8)	0.05 (0.8)	0.09 (−0.3 to 0.5)
HDL cholesterol level, *mmol/L*	1.4 (0.3)	1.5 (0.7)	−0.09 (0.2)	−0.12 (0.7)	0.03 (−0.2 to 0.3)
LDL cholesterol level, *mmol/L*	3.0 (0.9)	3.1 (0.8)	0.2 (0.8)	0.2 (0.8)	0.07 (−0.3 to 0.4)
Fasting glucose level, *mmol/L*	5.3 (0.8)	5.1 (0.9)	0.01 (0.6)	0.05 (0.5)	−0.06 (−0.3 to 0.2)
Fasting insulin level, *IU/L*	63 (29)	61 (37)	−12 (27)	−13 (23)	1 (−10 to 12)

3α-diol = 5α-androstane-3α,17β-diol; 3β-diol = 5α-androstane-3β,17β-diol; BCE = bone collagen equivalent; BMD = bone mineral density; BMI = body mass index; BP = blood pressure; DHT = dihydrotestosterone; FSH = follicle-stimulating hormone; HDL = high-density lipoprotein; IMT = intima–media thickness; IPSS = International Prostate Symptom Score; LDL = low-density lipoprotein; LH = luteinizing hormone; NTX = aminoterminal cross-linked telopeptide of collagen type I; PINP = aminoterminal propeptide of type I procollagen; PSA = prostate-specific antigen; SHBG = sex hormone–binding globulin.

* Baseline and observed changes (expressed as means [SDs]) during 24 mo, with difference (expressed as DHT treatment minus placebo effect) and 95% CI. To convert testosterone values to ng/dL, divide by 0.0347. To convert estradiol values to pg/mL, divide by 3.671. To convert creatinine, cholesterol, and glucose values to mg/dL, divide by 88.4, 0.0259, and 0.0555, respectively.

† Total participants varied from 55 to 56 in the DHT group and 57 to 58 in the placebo group per variable.

‡ Total participants included 37 in the DHT group and varied from 43 to 44 in the placebo group per variable.

serum DHT metabolite, testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone levels.

Hemoglobin was increased by 10 to 15 g/L consistently during DHT treatment, with return to baseline at 3 months after cessation of treatment. Placebo had no effect on hemoglobin levels (**Appendix Figure 2**, available at www.annals.org).

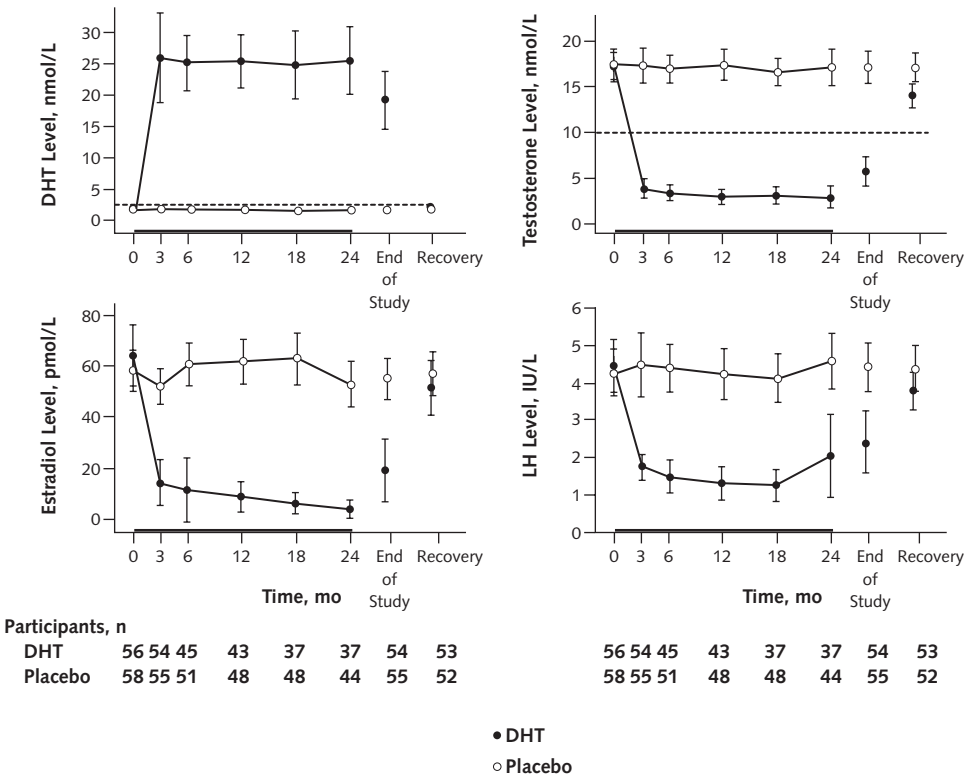
Prostate

Total and central prostate volumes (**Figure 3**) ($P < 0.001$ for both) and serum PSA levels (**Appendix Figure 2**) ($P = 0.011$) increased during the study, but there was no significant effect of DHT ($P > 0.2$ for all). There was no change in total IPSS score (**Table**) over time ($P = 0.40$) or due to DHT treatment ($P = 0.31$).

Bone

Lumbar spine BMD decreased progressively during DHT treatment (1.4% [CI, 0.6% to 2.3%] at 24 months; $P < 0.001$) but not placebo treatment (**Figure 4**). Femoral neck BMD decreased with time during the study (**Figure 4**) but without any difference due to DHT treatment ($P > 0.2$) (**Table 1**). Serum aminoterminal propeptide of type I procollagen was increased markedly by DHT but not placebo during the second year of the study; however, urine aminoterminal cross-linked telopeptide of collagen

Figure 2. **Serum DHT, testosterone, estradiol, and LH levels during the study.**



Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. The dashed line indicates the reference range (upper limit for serum DHT level and lower limit for serum testosterone level). To convert estradiol values to pg/mL, divide by 3.671. To convert testosterone values to ng/dL, divide by 0.0347. DHT = dihydrotestosterone; LH = luteinizing hormone.

type I was not significantly changed by time or treatment (**Appendix Figure 3**, available at www.annals.org).

Body Composition

In DXA analysis, lean mass was increased and fat mass was decreased each by 1.0 to 1.5 kg with DHT but not placebo treatment (**Appendix Figure 2**). We observed similar body composition changes using bioimpedance analysis and derived from skin-fold thickness (data not shown). Muscle strength measured by hand grip dynamometry was increased by DHT for both dominant ($P = 0.064$) and nondominant ($P = 0.032$) hands (**Table**). No significant change was found in abdominal or hip girth or midarm or midthigh circumference (data not shown).

Vascular

Right carotid intima–media thickness increased nonsignificantly during the study without any significant DHT effect ($P > 0.25$). Dihydrotestosterone produced a small but significant increase in pulse and systolic, but not diastolic, blood pressure (**Table**). Total and low-density lipoprotein cholesterol levels increased, whereas high-density lipoprotein cholesterol levels decreased during the study but without any significant effect of DHT.

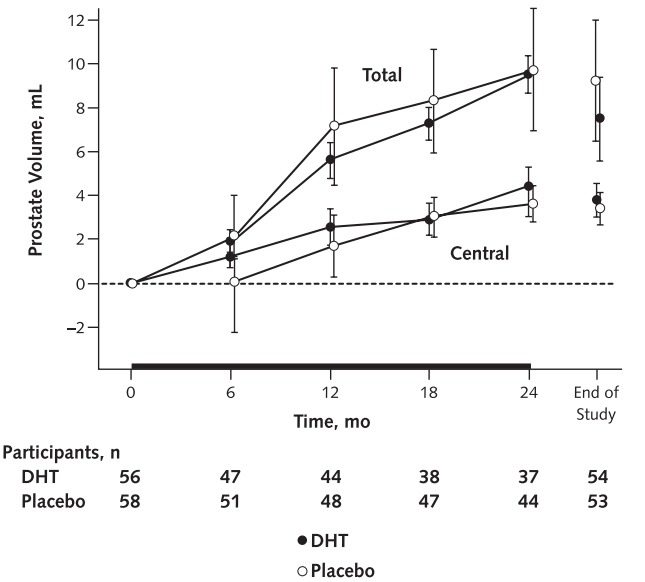
Quality of Life

No significant difference was found in any of the 8 subdomains of the SF-36 scale, habitual physical activity (total PASE score), or psychosexual function (positive mood, negative mood, activity score, recent erections, libido, PDQ scale) over time or due to DHT treatment (data not shown).

Sensitivity Analysis

We developed a withdrawal probability scoring for the selection model by using logistic regression. The final model predicting withdrawal (80% correct prediction) included 3 variables: hip BMD (odds ratio [OR], 0.0017 [CI, 0.0024 to 0.1262]); blood alanine transaminase (OR, 1.040 [CI, 1.022 to 1.057]); and blood total cholesterol level (OR, 0.628 [CI, 0.483 to 0.816]) but excluded treatment; time on study; and baseline anthropometric, prostate (total or central prostate volume), BMD (lumbar spine and hip), or any other biochemical variables. By using the withdrawal probability as a covariate, sensitivity analyses

Figure 3. **Total and central prostate volumes during the study.**



Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. The dashed line indicates no change from baseline. DHT = dihydrotestosterone.

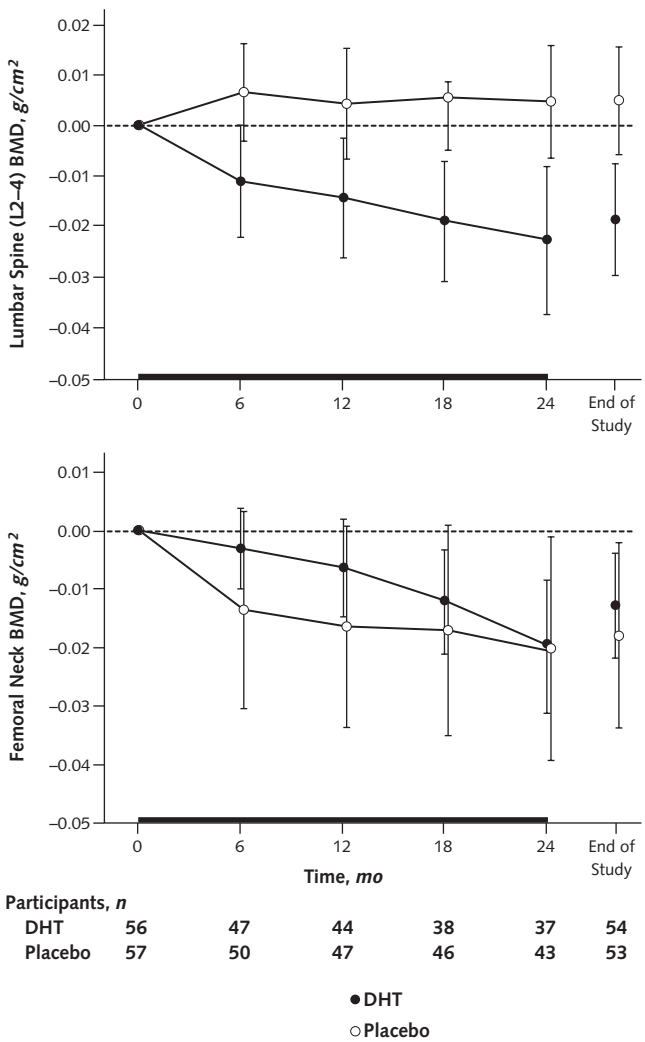
confirmed that the findings for total (covariate $P = 0.51$) and central ($P = 0.57$) prostate volumes; lumbar spine ($P = 0.59$) and hip ($P = 0.47$) BMD; lean ($P = 0.30$) and fat ($P = 0.90$) mass; hemoglobin level ($P = 0.78$); and serum hormone levels (DHT [$P = 0.24$], testosterone [$P = 0.45$], and estradiol [$P = 0.95$]) were robust, with respect to missing data from discontinuing participants because the patterns were unchanged when adjusted by the withdrawal probability as a covariate. In addition, the findings for the subset of men who completed the full study ($n = 81$ [71%]) confirmed the original analyses of the full ITT population.

Safety

A total of 13 men in the DHT group and 5 in the placebo group discontinued treatment. Men who had protocol-specific discontinuation were all in the DHT group (8 had polycythemia and 3 had an increased PSA level >4.0 μg/mL). No men who discontinued for polycythemia (persistent, nonfasting hematocrit >0.50) were symptomatic or required treatment. Men who became polycythemic had significantly elevated mean (±SE) pretreatment hemoglobin levels of 162 ± 5 g/L versus 149 ± 3 g/L; $P < 0.001$. Compared with other participants and the magnitude of the hematologic response to DHT, mean (±SE) hematocrit (47.1 ± 1.3 vs. 43.4 ± 0; $P < 0.001$) was the same in men who did or did not become polycythemic.

The study urologist reviewed the 3 men who discontinued because of an increased PSA level. Serum PSA levels decreased in all 3 men; 1 had a course of antibiotics, and none had a biopsy or prostate cancer diagnosis during ongoing follow-up. Discontinuation for adverse events (other than protocol-specific) occurred once in the DHT group (adverse events for exacerbation of a stress-related condition) and 4 times in placebo group (serious adverse events due to hospitalization for cervical vertebral fracture, acute myocardial infarction, and transurethral resection of the prostate; an adverse event for retinal venous occlusion). In addition, 1 participant in each group discontinued because of starting disallowed medication (bisphosphonates) for osteopenia. Eight (14.3%) men in the DHT group reported

Figure 4. **Lumbar (L2–4) spine and femoral neck BMD during the study.**



Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. The dashed line indicates no change from baseline. BMD = bone mineral density; DHT = dihydrotestosterone.

serious adverse events (pericarditis and atrial fibrillation, Crohn disease, rib fracture, pulmonary embolism, vocal cord cyst, elective surgery for intervertebral disc, inguinal hernia repair, and deep venous thrombosis). Eleven (18.9%) men in the placebo group reported hospitalizations for cholecystectomy, wrist fracture ($n = 2$), bone grant, hernia repair, angioplasty, trabulectomy and transurethral resection of prostate, cellulitis, pneumonia, and spinal fracture, but none of the events was considered to be caused by study treatment. Numbers of total adverse events were similar in each group (224 in DHT and 227 in placebo), with 53 in each group (95% DHT and 91% placebo) reporting at least 1 nonserious adverse event. The scheduled interim and final data safety and monitoring committee reviews recommended no changes to the study.

DISCUSSION

Our study shows that 24-month daily treatment with 70-mg DHT transdermal gel causes a small, nonsignificant decrease in total prostate growth rate compared with placebo gel in middle-aged men without known prostate disease. Because DHT has 3 to 10 times greater androgenic potency than testosterone (28–30), the large increase in circulating DHT outweighs the suppression of serum testosterone to castrate levels. However, the sustained increase in net androgen exposure does not increase prostate growth, dispelling long-held concerns about supraphysiologic androgen levels on prostate size (31, 32).

The failure to confirm our primary hypothesis cannot be due to insufficient DHT dosage. Our DHT treatment represents a high net androgen dose, as indicated by not only the large (about 10-fold) increase in serum DHT and its metabolites (3α- and 3β-diol) but the prominent androgenic effects, including complete suppression of serum luteinizing hormone; follicle-stimulating hormone; testosterone; and estradiol (through negative hypothalamic feedback), increased hemoglobin levels, a cumulative 14% incidence of polycythemia, increased muscle, and decreased fat mass. Our findings can be extrapolated to other pure androgens, such as nandrolone analogues (33–36), as well as newer nonsteroidal androgens, which are also inherently nonamplifiable and nonaromatizable (14). Our findings are consistent with studies of relatively low-dose testosterone administration for at least 6 months in older men in which no prostate enlargement was observed (37, 38). Furthermore, the sensitivity analyses confirm that the findings are robust, with respect to missing data from premature discontinuation.

The strengths of this study include its randomized, placebo-controlled, well-powered design to test the effects of a pure androgen administered for a prolonged period to otherwise healthy older men without known prostate disease. The design featuring repeated measurements of key end points allowed for sensitive analysis of within-participant changes and was strengthened by having all ultrasonographies done by a single experienced sonographer (15); removing the nullifying effect of measurement error due to inexperience and between-observer variability (39); and measuring serum steroids by liquid chromatography, tandem mass spectrometry to overcome the nonspecificity and inaccuracy of direct serum testosterone, and estradiol immunoassays (40–44).

Our study has limitations. Negative findings on prostate growth cannot exclude other important adverse effects, such as the natural history of prostate cancer, which requires evaluation by large-scale, prolonged, prospective studies. The slowly progressive increase in prostate size equally in both groups over time reflects an age effect that such late-life prostate growth is primarily a manifestation of underlying but undiagnosed BPH present in most men at this age (1, 45). This finding reinforces the interpretation that age has a greater effect on late-life prostate growth in healthy men than androgen exposure (46–49) does. Neither central prostate volume growth nor serum PSA level was significantly increased by DHT treatment, although both increased with study treatment duration, which we presume is also an age effect of evolving undiagnosed BPH.

Dihydrotestosterone treatment substantially reduced lumbar spine BMD by 1.5% during 24 months but had no significant effect on the age-related decrease in femoral neck BMD, which was comparable with healthy Australian men of similar age (50). The DHT-induced loss of spinal BMD reflects the net effect between the anabolic effects of the high circulating DHT, which were overcome by the catabolic effect of the reduced intraprostatic testosterone and estradiol levels. This finding is consistent with the recognition that estrogen action is important for bone development in male mice and men with congenital estrogen deficiency (51). Furthermore, our study extends this to the maintenance of normally developed mature bone in the face of adult-onset functional estrogen deficiency, whereas previous studies were able to examine only short-term biochemical effects on bone markers (52, 53). The marked decrease in serum estradiol levels is presumably due to substrate limitation because testosterone is the immediate steroidogenic precursor of estradiol for the aromatase enzyme (54). It is less likely that DHT inhibits aromatase because androgens upregulate aromatase activity in tissues, such as the brain, where aromatization is an important mediator of testosterone action (55). The striking increase in serum aminoterminal propeptide of type I procollagen in the second year of the study is presumably a compensatory response to spinal cancellous bone loss similar to the effects of acute estrogen withdrawal in women (56); however, the failure of urinary aminoterminal cross-linked telopeptide of collagen type I to increase coordinately is unexplained, given the usual tight coupling between bone formation and resorption (57).

Dihydrotestosterone displayed modest, sustained, but reversible effects of increasing muscle mass and (marginal)

strength and circulating hemoglobin and serum creatinine levels while reducing fat mass, as expected from any androgen at sufficient dosage, even in eugonadal older men (58–61). The lack of improvement in quality-of-life measures in our study is due to the ceiling effects in the healthy functional state of participants required for entry. Consequently, these findings do not exclude the possibility that functional gains in quality of life for frail, older men or those with cognitive impairment may occur with DHT treatment in suitably selected populations. If a pure androgen can safely achieve similar gains in muscle function in frail, older men or show other benefits of androgen therapy in men with chronic diseases, the new generation of nonsteroidal androgens (specific androgen-receptor modulators) may have benefits for alleviating comorbid conditions and promoting healthy aging in older men (14). However, our findings reveal that they should avoid gonadotropin suppression if possible. Our study suggests no risk for accelerating BPH progression in older men from even relatively high androgen dosage for at least 2 years, although the long-term effects on prostate cancer progression remain to be better defined. Another limitation is that reduced spinal but not hip BMD should be anticipated with prolonged treatment with any pure androgen.

Our findings are also relevant to the growing use of testosterone as an antiaging treatment for older men without pathologically based hypogonadism (62). Although our findings alleviate concern about androgen therapy slowing BPH progression for up to 2 years, concerns remain about the risks for prostate cancer, cardiovascular disease, or idiosyncratic adverse effects of androgens (sleep apnea, polycythemia, or behavior) with long-term use of testosterone therapy.

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Reproducible Research Statement: *Study protocol and data set*: Available from Dr. Handelsman (e-mail, djh@anzac.edu.au). *Statistical code*: Not available.

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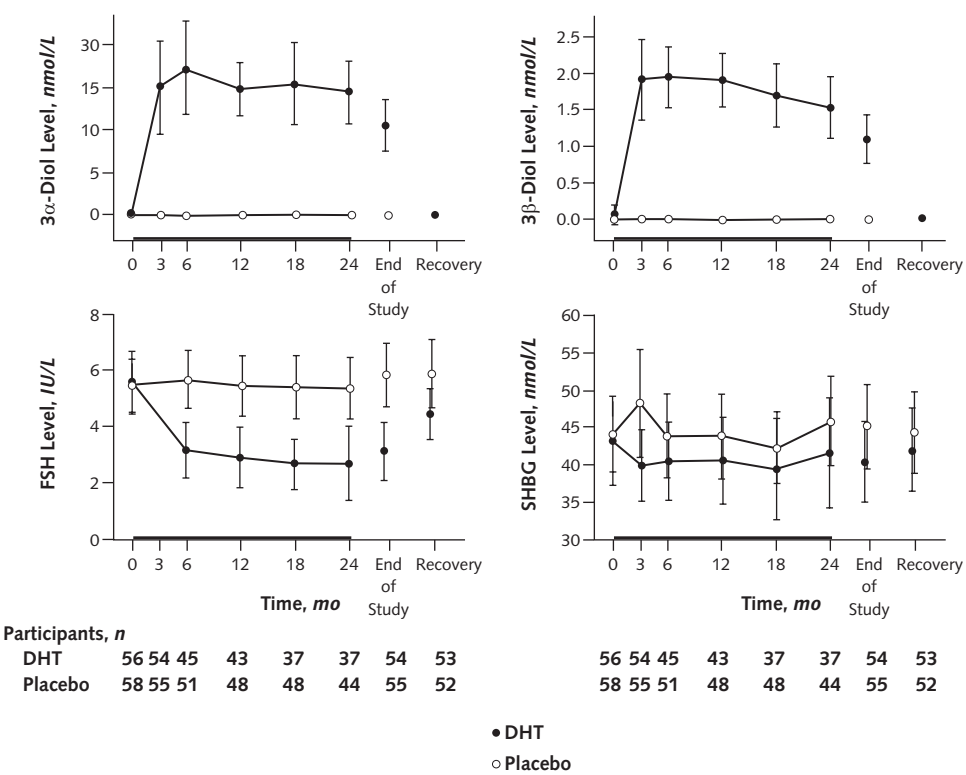
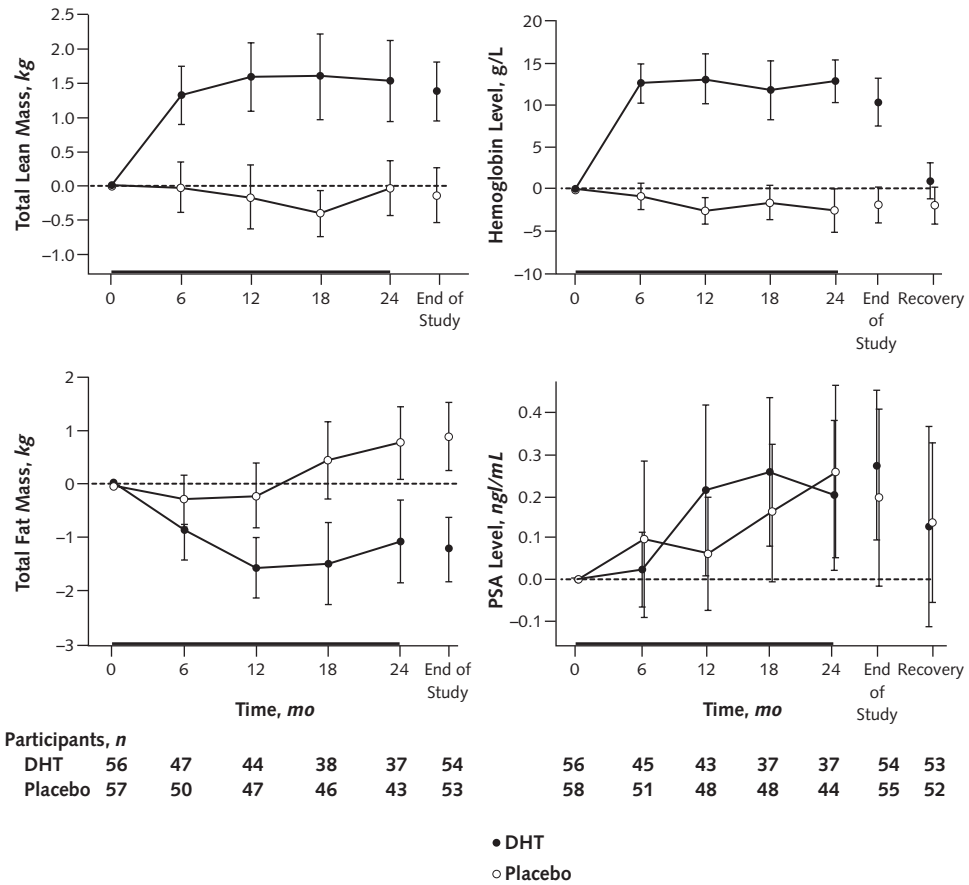
Appendix Figure 1. **Serum 3α-diol, 3β-diol, FSH, and SHBG levels during the study.**



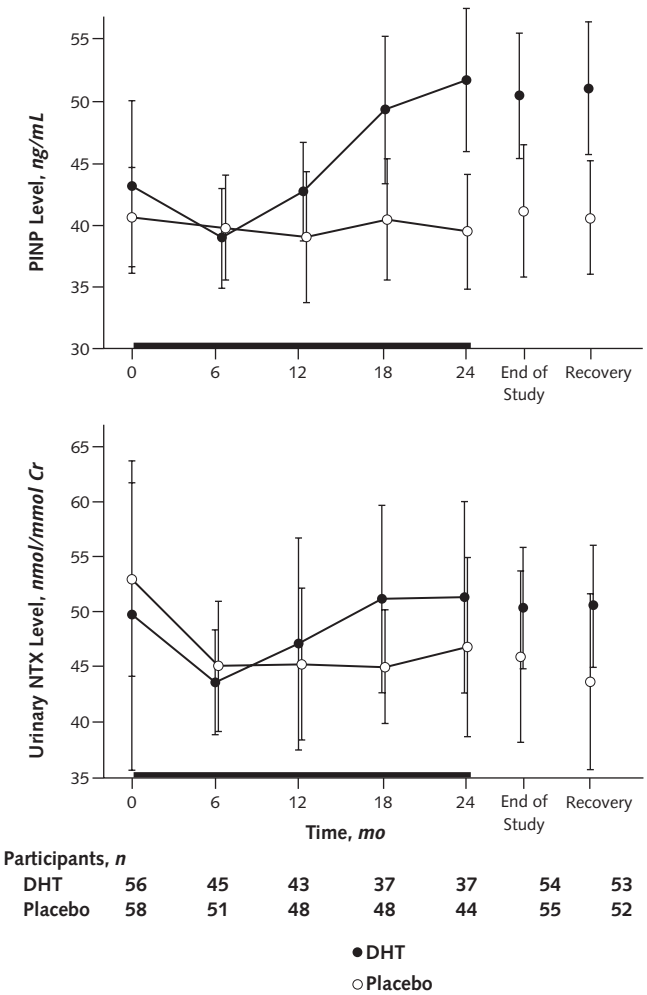
Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. 3α-diol = 5α-androstane-3α,17β-diol; 3β-diol = 5α-androstane-3β,17β-diol; DHT = dihydrotestosterone; FSH = follicle-stimulating hormone; SHBG = sex hormone–binding globulin.

Appendix Figure 2. **Total lean mass, hemoglobin level, total fat mass, and serum PSA level during the study.**



Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. The dashed line indicates no change from baseline. DHT = dihydrotestosterone; PSA = prostate-specific antigen.

Appendix Figure 3. **Serum PINP and urinary NTX levels during the study.**



Data are expressed as means and 95% CIs of changes from pretreatment baseline for men who received DHT and placebo. Treatment period is indicated by the thick line along the *x*-axis. Total participants are indicated at each time point. DHT = dihydrotestosterone; NTX = aminoterminal cross-linked telopeptide of collagen type I; PINP = aminoterminal propeptide of type I procollagen.