Effect of Testosterone Supplementation on Functional Mobility, Cognition, and Other Parameters in Older Men: A Randomized Controlled Trial

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Effect of Testosterone Supplementation on Functional Mobility, Cognition, and Other Parameters in Older Men

A Randomized Controlled Trial

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Context Serum testosterone levels decline significantly with aging. Testosterone supplementation to older men might beneficially affect the aging processes.

Objective To investigate the effect of testosterone supplementation on functional mobility, cognitive function, bone mineral density, body composition, plasma lipids, quality of life, and safety parameters in older men with low normal testosterone levels.

Design, Setting, and Participants Double-blind, randomized, placebo-controlled trial of 237 healthy men between the ages of 60 and 80 years with a testosterone level lower than 13.7 nmol/L conducted from January 2004 to April 2005 at a university medical center in the Netherlands.

Intervention Participants were randomly assigned to receive 80 mg of testosterone undecenoate or a matching placebo twice daily for 6 months.

Main Outcome Measures Functional mobility (Stanford Health Assessment Questionnaire, timed get up and go test, isometric handgrip strength, isometric leg extensor strength), cognitive function (8 different cognitive instruments), bone mineral density of the hip and lumbar spine (dual-energy x-ray absorptiometry scanning), body composition (total body dual-energy x-ray absorptiometry and abdominal ultrasound of fat mass), metabolic risk factors (fasting plasma lipids, glucose, and insulin), quality of life (Short-Form Health 36 Survey and the Questions on Life Satisfaction Modules), and safety parameters (serum prostate-specific antigen level, ultrasonographic prostate volume, International Prostate Symptom score, serum levels of creatinine, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, hemoglobin, and hematocrit).

Results A total of 207 men completed the study. During the study, lean body mass increased and fat mass decreased in the testosterone group compared with the placebo group but these factors were not accompanied by an increase of functional mobility or muscle strength. Cognitive function and bone mineral density did not change. Insulin sensitivity improved but high-density lipoprotein cholesterol decreased; by the end of the study, 47.8% in the testosterone group vs 35.5% in the placebo group had the metabolic syndrome ($P = .07$). Quality-of-life measures were no different except for one hormone-related quality-of-life measure that improved. No negative effects on prostate safety were detected.

Conclusion Testosterone supplementation during 6 months to older men with a low normal testosterone concentration did not affect functional status or cognition but increased lean body mass and had mixed metabolic effects.

Trial Registration isrctn.org Identifier: ISRCTN23688581

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MALE AGING IS ASSOCIATED with a gradual but progressive decline in serum levels of testosterone,[1] occurring to a greater extent in some men than in others. Decline in testosterone is associated with many symptoms and signs of aging such as a decrease in muscle mass and muscle strength, cognitive decline, a decrease in bone mass, and an increase in (abdominal) fat mass. Despite the rapid increase in the population of people aged 60 years or older, little research on how to prevent or delay these age-related disabilities has been conducted. In recent years, the potential anti-aging effects of sex hormones, including testosterone, have become a focus of interest.

Clinical trials examining the effects of testosterone supplementation on aging have provided mixed findings.[2-5] These different findings likely reflect differences in study design, including age, gonadal status, and overall health status of the study population, the type and duration of treatment, and the instruments chosen to study aging. Im-

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portantly, most studies had only limited power to detect effects due to small sample sizes and have studied only 1 or 2 aspects of aging instead of the whole spectrum of aging. Additional data are needed to elucidate whether older men receiving testosterone supplementation experience benefits or adverse effects. For these reasons, the US Institute of Medicine's committee assessing the need for clinical trials of testosterone replacement therapy recommended in 2004 that short-term, randomized, placebo-controlled studies to examine the efficacy and safety of testosterone therapy in aging men should be conducted before embarking on long-term studies.[6]

We conducted a randomized, double-blind, placebo-controlled study to assess the effects of testosterone supplementation on functional mobility, cognition, bone mineral density, body composition, lipids, quality of life, and safety parameters in older men with low normal testosterone levels during a period of 6 months.

METHODS

This study had a randomized, double-blind, placebo-controlled design. Details of the study design, recruitment, and procedures have been published.[7] The institutional review board of the University Medical Center Utrecht approved the study protocol and all participants provided written informed consent. The study was conducted from January 2004 to April 2005.

Participants

Participants were recruited by a direct mailing to 8020 randomly selected men between the ages of 60 and 80 years whose addresses were obtained from the municipal register of the city of Utrecht, the Netherlands. We did not pay individuals for participation but we did reimburse their travel expenses.

Inclusion criteria included a testosterone level below the 50th percentile of the study population–based testosterone distribution and age between 60 and 80 years. The 50th percentile cutoff level of testosterone was determined to be 13.7 nmol/L (to convert to ng/dL, divide by 0.0347) after screening 50 candidates. This was comparable with the 50th percentile of the testosterone level obtained from screening potential participants throughout the study (13.8 nmol/L).

Exclusion criteria included myocardial infarction or cerebrovascular accident within the past 6 months; heart failure unless medically treated and not symptomatic; malignancy within the past 5 years except for non–melanoma skin cancer and history of hormone-dependent tumor; serious liver or renal diseases (>3 times the upper limit of normal); hematological abnormalities (hemoglobin ≤7.0 mmol/L [to convert to mg/dL, divide by 10] and hematocrit ≥0.50 [to convert to a percentage, divide by 0.01]), epilepsy or the use of antiepileptic medication, migraine more than once per month, diabetes mellitus, a fasting glucose level of 6.9 mmol/L or higher (to convert to mg/dL, divide by 0.0555), corticosteroid use (≥7.5 mg/d orally within the past 6 months with the exception of short bouts of prednisone use for ≤7 days or inhalation of ≥800 µg/d during the past 6 months), use of testosterone esters and similar substances within the past 60 days, history of prostate hyperplasia, and an elevated prostate-specific antigen (PSA) level (age of 60-69 years: ≥4.5 µg/L [to convert to ng/mL, divide by 1.0]; age of ≥70 years: ≥6.5 µg/L).

Following an initial telephone contact, 684 men were screened with medical history, laboratory testing, and digital rectal examination. A total of 237 men were eligible for entry into the study and agreed to participate.

Randomization and Blinding

After completing the baseline tests, participants were randomly assigned to the intervention or the placebo group. A randomization list without stratification using blocks of 6 was computer-generated by Organon NV (Oss, the Netherlands) using the Almedica Drug Labeling System (Almedica Technology Group Inc, Allendale, New Jersey). One box with active medication and 1 box with placebo medication were delivered to the University Medical Center Utrecht pharmacy with the randomization list. Pharmacy personnel labeled the jars for the participants and provided the study medication upon prescription by the trial physician. Randomization numbers were assigned to the participants in order of enrollment into the trial.

The key to the randomization numbers (ie, study drug allocation) was available 24 hours per day at the pharmacy department of the University Medical Center Utrecht only. Unblinding did not occur during the trial.

To assess the efficacy of blinding, the participants were asked at the end of intervention whether they thought they had been assigned to the placebo or the testosterone group.

Intervention

The intervention consisted of 2 capsules of 40-mg testosterone undecenoate (Andriol Testocaps, Organon NV) twice per day with breakfast and dinner (equaling a total dose of 160 mg/d of testosterone undecenoate), or matching placebo, for a total duration of 6 months. Adherence was monitored by capsule counting at each study visit.

Functional Mobility

The timed get up and go test was the time taken by an individual to rise from a standard chair, walk 3 meters, turn around, return, and sit down again. The individual was requested to sit with his back against the chair and arms resting on the chair and perform the test 3 times. The fastest time was recorded in seconds.[8]

The Stanford Health Assessment Questionnaire is a self-administered questionnaire to measure physical ability. We used a Dutch version of the health assessment questionnaire,[9] which consists of 24 questions about ordinary activities in 8 categories: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. All questions have 4 alternatives to choose from, ranging from

"without difficulty" (assigned a score of 0) to "unable to perform" (assigned a score of 3). Moreover, individuals can indicate whether they need aid or an assistance device. When a person indicates the need for aid or a device on a certain question, the corresponding category score is increased to 2 when that score was 0 or 1. The total score on the health assessment questionnaire is calculated by taking the highest score within each category and subsequently calculating the mean of the 8 category scores. Thus, the test can range from 0 (no disability) to 3 (completely disabled).

Isometric handgrip strength was measured using an adjustable hand dynamometer (JAMAR Technologies Inc, Horsham, Pennsylvania).[10] The size of the grip was set so that the participants felt comfortable. The participants were in the standing position and were instructed to keep their shoulders adducted and neutrally rotated, the arm was vertical and the wrist was in a neutral position. They squeezed the grip with maximal strength, alternating the left and right hand. Each test was repeated at least 5 times until no further improvements were seen. The best measure at each side, recorded in kilograms, was used for the analysis.

Maximal voluntary isometric knee leg strength was measured using the MicroFET hand-held dynamometer (Hoggan Health Industries Inc, West Jordan, Utah).[11] The participants were placed in a seated position at a mat table with the hip flexed to 90°, the knee stretched to 180°, and the legs dependent. The dynamometer was applied perpendicularly to each lower extremity just proximal to the malleoli. Participants were instructed to take a second or two to come to maximum effort and to then push as hard as possible during another 3 seconds, while the investigator was giving counterforce. Five maximal voluntary contractions were made at each side, and if the examiner was not confident that a maximal effort was reached, 2 more efforts were made. The best measure for each side, recorded in newton, was used for the analysis.

Cognitive Function

Participants were tested in a silenced room during the morning. Trained physicians administered identical versions of the test during baseline and at the end of the study, except for the Shepard Mental Rotation test, for which alternate versions were used.

The Dutch version of the Rey Auditory-Verbal Learning Test is a test for verbal episodic memory. In this test, the participants are asked to recall 15 words immediately (immediate recall) for 5 times consecutively (maximum score is 75) and after 15 minutes (delayed recall, maximum score is 15).[12]

The digit symbol substitution test, a subtest of the Wechsler Adult Intelligence Scale, measures cognitive and perceptual speed. The participant is given a code that pairs symbols with digits. The test consists of matching as many digits to their corresponding symbols as possible in 90 seconds.[13] Participants were scored a point for each correct response.

The trail-making test is a complex attention and mental flexibility task. In this test, pseudorandomly placed circles with numbers (A1), with letters (A2), and with both numbers and letters (B) have to be connected with a line as fast as possible in a fixed order. In the event of error, the participants were immediately informed and asked to restart from the point of error; this was done with the timer running. The time taken to complete the trail without error was recorded.[14]

The Benton Judgment of Line Orientation test measures basic perceptual processes contributing to extrapersonal spatial perception. The test requires the individual to identify which 2 of 11 lines presented in a semicircular array have the same orientation in 2-dimensional space as 2 target lines.[15] There are 30 items and participants get a point for each correct answer.

Visuospatial performance was assessed by the Vandenberg and Kuse adaptation of the 3-dimensional Shepard Mental Rotation test.[16] The test consists of 20 items in which the individual is presented with a 3-dimensional geometric target line drawing and 4 test drawings, and is required to indicate which 2 of 4 test drawings depict the target drawing in rotated positions. Two parallel test versions are made by taking the odd and even items on time 1 (baseline) and time 2 (after intervention), respectively, (10 items for each test). These parallel versions have been shown to correlate strongly with each other and to have a high reliability.[17] The test is scored by adding 1 point for each correct answer and subtracting a point for each incorrect answer, resulting in a range from –10 (no correct answer) to 10 (all of them correct). Individuals are instructed to "work as quickly as possible, but do not sacrifice accuracy for speed." They were allowed 10 minutes to complete the test.

Bone Mineral Density

Bone mineral density was measured using the Lunar prodigy dual-energy x-ray absorptiometry instrument (GE Healthcare, Waukesha, Wisconsin) at baseline and at the end of the 6-month intervention. Scanning was performed according to the instructions of the manufacturer. Bone mineral density was measured of lumbar vertebrae (L1-L4 individually and together) and proximal femur (femoral neck, trochanter, intertrochanter, Ward triangle and total hip, left or right if left not available). Quality assurance, including calibration, was performed routinely every morning for dual-energy x-ray absorptiometry using the standard provided by the manufacturer.

Anthropometry

Weight was measured, after taking off coat, sweaters, and shoes, to the nearest 0.5 kg and height was measured to the nearest 0.5 cm. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of midway the distance between the lower rib and the iliac crest after normal expiration without pressure on the skin. All measurements were performed in duplicate and the average of the readings was taken as the value for each circumference with results rounded to the nearest 0.1 cm.

Body Composition

Total body composition measurements were performed using the Lunar prodigy dual-energy x-ray absorptiometry instrument (GE Healthcare). Scanning was performed according to the instructions of the manufacturer. The participant was scanned in a horizontal position from dorsal to ventral. Legs and feet were endorotated and fixed to one another. Fat mass, fat-free mass, and lean body mass were calculated. Quality assurance including calibration was performed routinely every morning for dual-energy x-ray absorptiometry using the standard provided by the manufacturer.

Ultrasonography of fat mass was performed in all participants with an Ultramark 9 (Advanced Technology Laboratories, Bothell, Washington). The distances between the posterior edge of the abdominal muscles and the lumbar spine or psoas muscles were measured using electronic calipers. For all images, the transducer was placed on a straight line drawn between the left and right midpoint of the lower rib and iliac crest. A mark was made in the middle, 10 cm from the left and right side. Distances were measured from 3 different angles: medial, left, and right for intra-abdominal fat mass and medial for subcutaneous fat mass. Measurements were made at the end of quiet expiration, applying minimal pressure without displacement of intra-abdominal contents as observed by ultrasound image.

Laboratory

Fasting blood samples were obtained before the study drug was taken and between 8:00 and 11:00 AM to minimize diurnal variation. The serum levels of testosterone and sex hormone-binding globulin were measured with a solid-phase, competitive, chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, California) at baseline and at the end of the study. The levels of free testosterone and bioavailable testosterone were calculated from total testosterone, sex hormone-binding globulin, and albumin concentrations.[18]

Fasting glucose levels were assessed using a GlucoTouch reflectometer (LifeScan Inc, Beerse, Belgium), a reagent-strip glucose oxidase method. Venous whole blood was immediately applied to the test strip.

Fasting plasma insulin levels, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using commercially available assays at baseline and at the final visit. Low-density lipoprotein cholesterol was calculated with the Friedewald equation.[19]

To assess insulin sensitivity, we calculated the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI). HOMA-IR was calculated using HOMA-IR = [fasting insulin in mU/L × fasting glucose in mmol/L]/22.5. QUICKI was calculated using QUICKI = 1/[log (fasting insulin in mU/L) + log (fasting glucose in mg/dL)].

We used HOMA-IR and QUICKI to measure insulin resistance and sensitivity. While the hyperinsulinemic euglycemic clamp is the criterion standard for measuring insulin resistance, all these measurements have been validated and proved to be strongly correlated with insulin resistance measured by clamp (correlation coefficients of –0.82 and 0.81, respectively).[20-22]

Blood Pressure, Metabolic Syndrome, and Quality of Life

Systolic and diastolic blood pressures were measured in duplicate at the left arm with the participant in the sitting position after 5 minutes of rest with an automated and calibrated oscillometric device (Omron Healthcare Europe, Hoofddorp, the Netherlands). Subsequently, the mean systolic and diastolic blood pressures were calculated.

The metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III[23] was defined as present when 3 or more of the following criteria were met: fasting plasma glucose of at least 6.1 mmol/L, serum triglycerides of at least 1.7 mmol/L, serum HDL cholesterol of less than 1.0 mmol/L, systolic/diastolic blood pressure of at least 130/85 mm Hg, or waist girth of more than 102 cm.

Quality of life was measured with the Short-Form 36 Health Survey (SF-36) as a generic quality-of-life questionnaire and the Questions on Life Satisfaction Modules as a hormone-specific questionnaire.

The SF-36 includes 9 measures of functioning relating to (1) physical functioning; (2) social functioning; (3) role limitations because of health problems (physical role); (4) role limitations due to emotional problems (emotional role); (5) mental health; (6) vitality; (7) bodily pain; (8) general health perception; and (9) reported health transition from the last month. Raw scores were transformed to a standardized scale ranging from 0 to 100, with the higher score representing better status.[24]

The Questions on Life Satisfaction Modules is a questionnaire translated from the *Fragen zur Lebenszufriedenheit* questionnaire according to the method described by Huber et al.[25] The questionnaire is extended with a module on hypopituarism[26] and divided in a general section, a health section, and a hormone section—the first 2 sections include 8 items and the last section includes 16 items (resilience or ability to tolerate stress, body shape, self-confidence, ability to become sexually aroused, concentration, physical stamina, initiative or drive, ability to cope with your own anger, ability to tolerate noise and disturbance, weight, body size, sleep, self-control, memory or clear thinking, ability to relax, social contacts). All items were recorded on a 5-point scale according to their individual importance (I) and degree of satisfaction (S). As effect measures, a combination of importance and satisfaction $(I-1)\times(S\times 2-5)$ was calculated and the sum of the combination values was calculated for each section. The scores from the general and health sections can

range from –96 to 160, while the scores from the hormone section can range from –192 to 320. The higher the scores, the better the quality-of-life status.

Safety

The safety of testosterone supplementation was assessed by measuring prostate, liver, and kidney function, and hematological parameters. Effects on the prostate were studied using serum PSA levels, rectal ultrasound of the prostate, and by the International Prostate Symptom score. Serum PSA levels were measured by an immunometric assay (Immulite 2000) at baseline, week 13, and at the end of the study. The intraassay and interassay coefficients of variation were 3.5% and 5.0%, respectively. Increases of 1.4 μg/L or more above baseline level on 2 consecutive measurements during 1 to 2 weeks prompted treatment discontinuation.

Biplanal transrectal ultrasonography of the prostate, using a 7-MHz transrectal probe (model 2101 Falcon, Brüel and Kjaer, Naerum, the Netherlands), was performed at entry and at the end of the study by an experienced urologist. For each participant, the volume of the total prostate was determined with a caliper-based method: height × width × length × π/6.[27] Furthermore, attention was placed on the presence of hypoechogenic lesions in the prostate. The sonographic criteria for prostate cancer described by Lee et al[28] were used. If abnormalities were found, patients were sent to the urology outpatient clinic for further evaluation.

The International Prostate Symptom score was developed by the American Urological Association and is composed of 7 questions regarding urological symptoms.[29] The questions are scored from 0 (no complaints) to 5 (almost always). The cumulative scores of all 7 questions are an indication of the severity of lower urinary tract symptoms. The maximum score is 35. The participants completed the International Prostate Symptom score at baseline, after 6 and 13 weeks, and at the end of the study.

Liver function (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase), kidney function (albumin and creatinine), and hematological parameters (hemoglobin and hematocrit) were measured in serum by standard autoanalyzer methods (Synchron LX, Beckman Coulter, Fullerton, California) at baseline, after 13 weeks, and at the end of the study. During the study, hemoglobin levels of 7 mmol/L or less, hematocrit levels of 0.50 or higher, liver function values more than 3 times the upper limit of normal (alanine aminotransferase: 10-50 U/L; alkaline phosphatase: 40-130 U/L; aspartate aminotransferase: 15-45 U/L; γ-glutamyltransferase: 15-70 U/L [to convert alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and γ-glutamyltransferase to μkat/L, multiply by 0.0167]), or creatinine levels of 180 μmol/L (to convert to mg/dL, divide by 88.4) or higher led to an extra blood check after a week. If the values were still too high, study participation was discontinued. All laboratory measurements were performed in the Sho Laboratory (Velp, the Netherlands).

Adverse Events

An adverse event was defined as any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the treatment. An adverse event could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medication whether or not it was considered related to the medication.

Information regarding adverse events was obtained by questioning or examining the individual. At each visit during the treatment period, all new complaints and symptoms (ie, those not existing before the treatment period) were recorded on the adverse event form. Preexisting complaints or symptoms that increased in intensity or frequency during the treatment period also were entered on the adverse event form.

A serious adverse event was defined as any medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization, or resulted in persistent or significant disability or incapacity. All serious adverse events were reported to the institutional review board and to Organon NV.

Data Analysis

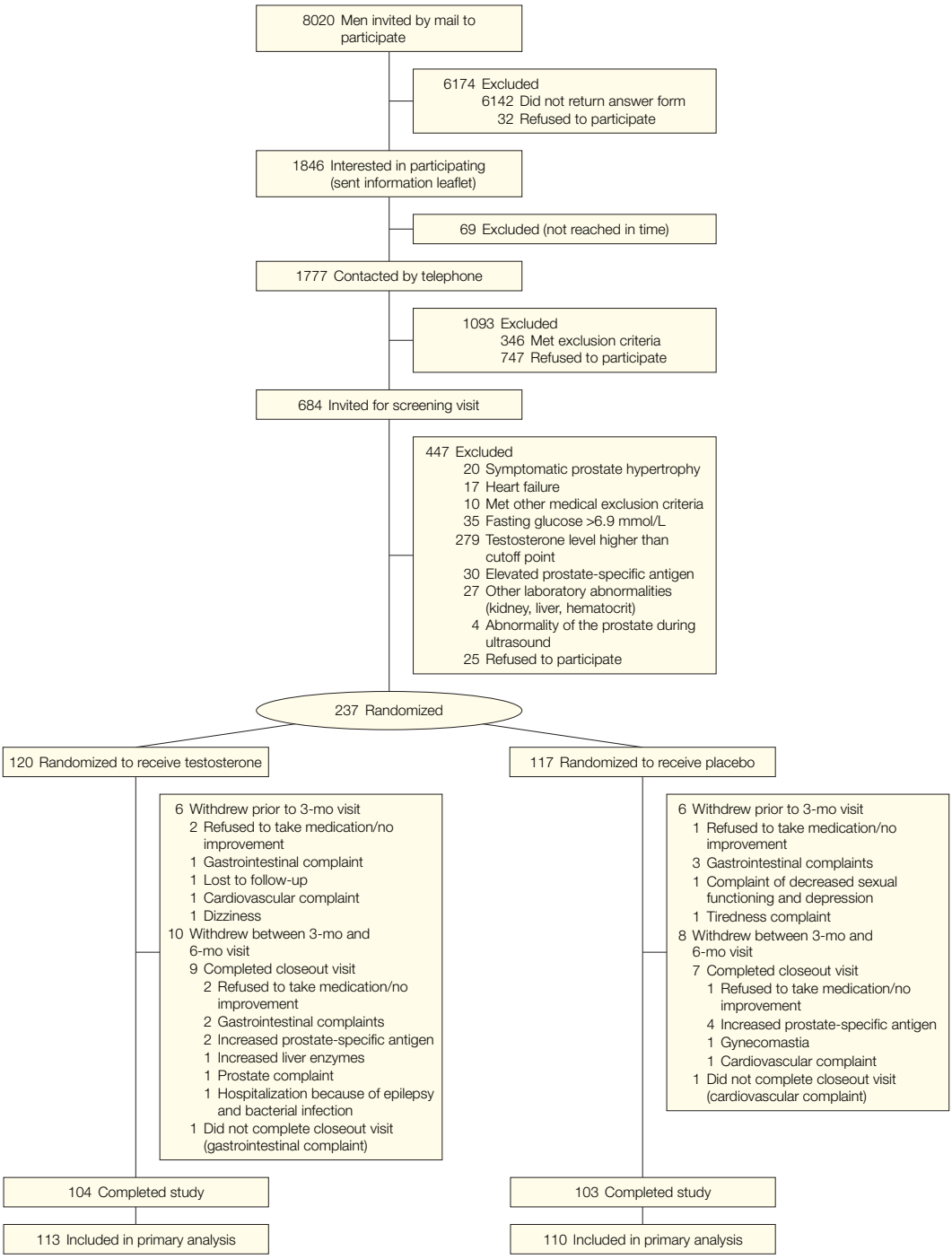
We performed power calculations based on the primary end point, the 15 Words test for cognitive function. The planned number of participants was 240 in total, 120 in each intervention group. This number was based on conventional assumptions of an α level of .05 and a β level of .20, withdrawal from intervention of 15%, and an improvement of 18% on the 15 Words test (equivalent to an improvement of 6 words).

Data were analyzed according to a modified intention-to-treat principle, including all those who had 2 measurements, including baseline, in the groups to which they were randomized. According to the protocol, a second visit was performed after 3 months and a final visit was performed after 6 months. When a participant remained in the study for less than 3 months, no second visit or closeout visit was performed because no benefit was anticipated in that time. When a participant dropped out between 3 and 6 months, a closeout visit was performed at the time of drop out.

Changes between the final visit and baseline for continuous measures were expressed as means and 95% confidence intervals (CIs); unpaired *t* tests were used for testing the difference in change between treatment groups. All comparisons were 2-tailed and the level of significance was set at a *P* value of less than .05. Because the percentage of missing data was very small (<3.6%), we did not use any specific strategies to handle this and the missing data were

treated as missing values in the analysis. In an alternate analysis, we imputed missing values using a regression-based imputation method. In addition, we performed an analysis adjusting the outcome variable difference for any possible baseline differences (testosterone level, age, smoking, alcohol, blood pressure, and body mass index). Repeated-measures analysis of variance was used to test the statistical significance of the effects of testosterone vs

Figure. Participant Flow Diagram



To convert fasting glucose to mg/dL, divide by 0.0555.

placebo for the safety parameters. All analyses were performed using SPSS statistical software version 11.0 (SPSS Inc, Chicago, Illinois).

RESULTS

The flow of study participants' recruitment and enrollment is shown in the FIGURE. Between January 2004 and October 2004, we randomized 237 men to the study, 120 to testosterone and 117 to placebo. There were 30 early withdrawals, 16 in the testosterone group and 14 in the placebo group. From the withdrawals, 7 had no follow-up in both groups. Therefore, the primary analysis included 113 in the testosterone group and 110 in the placebo group. The baseline characteristics of the 2 groups were similar (TABLE 1).

Table 1. Participant Characteristics at Baseline According to Randomization Group

	Testosterone (n = 113)	Placebo (n = 110)
	Mean (SD)	
Age, y	67.1 (5.0)	67.4 (4.9)
Testosterone, nmol/L	11.0 (1.9)	10.4 (1.9)
Serum hormone-binding globulin, nmol/L	33.0 (10.7)	32.8 (10.0)
Albumin, g/L	43.9 (2.3)	43.8 (2.4)
Free testosterone, nmol/L	0.22 (0.02)	0.21 (0)
Bioavailable testosterone, nmol/L	5.2 (1.1)	5.0 (1.2)
Body mass index[a]	27.4 (3.8)	27.3 (3.9)
Systolic blood pressure, mm Hg	155 (23.3)	151.4 (22.7)
Diastolic blood pressure, mm Hg	89.2 (12.0)	86.8 (11.7)
	No. (%)	
Smokers	21 (17.5)	15 (12.8)
Alcohol users	99 (82.5)	90 (76.9)
Prior cardiovascular disease[b]	35 (48.6)	37 (51.4)

SI conversion factors: To convert albumin to g/dL, divide by 10; testosterone to ng/dL, divide by 0.0347.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Includes myocardial infarction, angina, hypertension, or stroke.

Adherence, assessed by counting returned capsules, was good in both groups: more than 90% of participants used at least 80% of their medication. Blinding as to treatment group was effective; equal proportions of the 2 groups guessed they were receiving active treatment (χ^2 test $P = .98$).

At 6 months, total testosterone was unchanged from baseline in the testosterone group and increased slightly in the placebo group; the difference between the testosterone and placebo group at 6 months was −3.2 nmol/L (95% CI, −4.2 to −2.2; $P < .001$). Sex hormone-binding globulin levels declined from baseline in the testosterone group but did not decline in the placebo group (difference, −10.1 nmol/L [95% CI, −11.7 to −8.5]; $P < .001$). Also the between-group difference for free testosterone and bioavailable testosterone was statistically significant at month 6 (free testosterone difference, −0.03 [95% CI, −0.05 to 0]; $P = .04$ and bioavailable testosterone difference, −0.69 [95% CI, −1.24 to −0.13]; $P = .02$, respectively).

Individuals in the 2 groups had no significant change in score on the Stanford Hamilton Assessment Questionnaire; isometric grip strength, isometric leg extensor strength, and timed get up and go test were not affected by treatment with testosterone compared with placebo (TABLE 2). Both groups increased cognitive function scores on most of the tests at 6 months, but the differences were small and change in cognition did not differ between the groups. Neither the testosterone group nor the placebo group had significant changes in bone mineral density at any of the sites. Total body fat mass and the fat percentage of the body decreased significantly in the testosterone group, while the placebo group remained stable after treatment. Total body lean body mass in the testosterone group increased significantly relative to the placebo group. Body mass index and intra-abdominal fat mass measured by ultrasound did not differ significantly.

At the end of the study, both total cholesterol and HDL cholesterol decreased significantly in the testosterone group, resulting in a significant increase in the total cholesterol to HDL cholesterol ratio in the testosterone group compared with the placebo group (TABLE 3). Triglycerides and low-density lipoprotein cholesterol did not change significantly. Glucose and insulin concentration increased significantly in the placebo group compared with the testosterone group. The QUICKI index (insulin sensitivity) decreased and the HOMA-IR index (insulin resistance) increased significantly in the placebo group.

At the end of the study, metabolic syndrome increased more in the testosterone group (from 34.5% at baseline to 47.8% after 6 months) than in the placebo group but not significantly so ($P = .07$; Table 3). This increase was specifically due to the decrease in HDL cholesterol level in the testosterone group.

The SF-36 scores were not significantly changed in the testosterone group compared with the placebo group for any of the 9 sections of functioning (TABLE 4). The Questions on Life Satisfaction Modules also were similar in the 2 groups for the general and health-related quality of life. Only results from the hormone-related quality-of-life section differed significantly between the groups (results available on request from the authors).

Prostate volume and PSA were not significantly changed in the testosterone group compared with the placebo group. The numbers of lower urinary tract symptoms measured by the International Prostate Symptom score were similar in the 2 groups. During the study, 8 participants experienced an increase in PSA of 1.4 µg/L or more (3 in testosterone group and 5 in the placebo group; 6 during the

first 3 months and 2 at the end of the study), who had to discontinue the study. Four participants showed a hypoechogenic lesion at the end of study by prostate ultrasonography (2 in the testosterone group and 2 in the placebo group). One participant had a possible abnormality of the bladder in the placebo group at the end of the study. Further evaluation of these abnormalities revealed 2 carcinomas of the prostate in the placebo group. There were no significant differences in liver function but creatinine was higher in the testosterone group with borderline significance ($P=.05$). One participant in the testosterone group discontinued study medication because of liver function values of more than 3 times the upper limit of normal. After discontinuation of the medication, the liver functions normalized. Both hemoglobin levels and hematocrit increased significantly in the testosterone group compared with the placebo group. This increase occurred during the first 3 months and remained stable after that (data available on request). Two participants developed red cell parameters just above the normal range at the end of the study; the others did not reach predetermined hemoglobin and hematocrit levels for discontinuation of study medication (TABLE 5).

A total of 129 participants (54.3%) experienced 1 or more adverse events (TABLE 6). The mean number of adverse events per participant was 0.87 in the testosterone group and 0.90 in the placebo group. The most frequent adverse events were gastrointestinal, cardiovascular, and urological. Types of adverse events did not differ significantly between the groups.

Table 2. Functional Mobility, Cognitive Function, Bone Mineral Density, and Body Composition Outcomes by Treatment Group

	Mean (SD)					
	Baseline		Final Visit			
	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Change Difference (95% CI)	*P* Value
Functional Mobility						
Health Assessment Questionnaire score (0-3)	0.02 (0.1)	0.06 (0.2)	0.05 (0.1)	0.07 (0.2)	0.01 (–0.02 to 0.04)	.61
Isometric grip strength, kg						
Left	43.0 (9.7)	44.4 (11.6)	42.3 (8.8)	42.7 (8.2)	0.7 (–1.6 to 3.0)	.54
Right	44.6 (8.7)	46.5 (9.5)	43.0 (7.5)	43.4 (7.7)	1.3 (–0.5 to 3.2)	.16
Isometric leg extension strength, N						
Left	78.8 (29.4)	84.5 (36.3)	73.3 (25.0)	75.2 (24.8)	3.5 (–6.4 to 13.5)	.83
Right	79.8 (29.0)	84.3 (35.9)	73.2 (24.3)	77.0 (26.0)	1.1 (–8.6 to 10.7)	.48
Timed get up and go test, s	4.24 (0.9)	4.24 (1.0)	4.27 (0.7)	4.34 (1.0)	–0.04 (–0.02 to 0.04)	.70
Cognitive Function						
Benton Judgment of Line Orientation (maximum score of 30)	25.6 (3.7)	25.8 (3.7)	25.9 (3.2)	26.1 (2.9)	0 (–0.7 to 0.7)	.86
Digit symbol substitution, score number of symbols	44.8 (10.9)	46.0 (10.4)	47.0 (11.0)	47.9 (10.5)	0.4 (–0.9 to 1.7)	.57
Shepard Mental Rotation (maximum score of 10)	4.8 (7.1)	5.9 (6.4)	6.3 (6.2)	7.5 (6.7)	–0.1 (–1.6 to 1.5)	.93
Rey auditory verbal learning test						
Immediate recall (maximum score of 75)	35.5 (9.5)	34.9 (9.6)	37.8 (10.2)	36.6 (8.3)	0.5 (–1.3 to 2.3)	.57
Delayed recall (maximum score of 15)	7.1 (2.6)	6.9 (2.8)	7.8 (2.8)	7.5 (2.5)	0.1 (–0.5 to 0.7)	.69
Trail-making test, s						
A1	47 (18)	48 (16)	44 (16)	43 (13)	1.3 (–2.3 to 4.9)	.50
A2	53 (33)	55 (34)	49 (28)	47 (22)	2.5 (–3.0 to 8.0)	.45
B	108 (51)	101 (43)	107 (66)	95 (43)	5.4 (–7.2 to 17.9)	.40
Bone Mineral Density						
Total hip, g/cm^2	1.03 (0.1)	1.03 (0.2)	1.02 (0.2)	1.03 (0.2)	0 (0 to 0)	.77
Lumbar spine, g/cm^2	1.22 (0.2)	1.21 (0.2)	1.23 (0.2)	1.23 (0.2)	0 (0 to 0)	.47
Body Composition						
Body mass index[b]	27.4 (3.8)	27.3 (3.9)	27.5 (3.8)	27.4 (3.9)	0 (–0.2 to 0.3)	.76
Total mass, kg						
Fat	23.2 (7.9)	22.9 (7.2)	22.2 (8.1)	22.8 (7.1)	–1.3 (–1.8 to –0.8)	<.001
Lean mass	58.9 (6.8)	58.3 (7.6)	60.0 (6.6)	58.0 (7.5)	1.2 (0.7 to 1.7)	<.001
Fat mass percentage, %	27.7 (6.0)	27.8 (5.4)	26.4 (6.2)	27.8 (5.4)	–1.7 (–2.1 to –1.1)	<.001
Fat ultrasound, cm						
Intra-abdominal	8.3 (2.3)	8.2 (2.0)	8.6 (2.5)	8.5 (2.1)	0 (–0.4 to 0.4)	.98
Subcutaneous	2.6 (0.8)	3.5 (0.8)	2.5 (0.8)	2.7 (0.8)	0.7 (–0.8 to 2.4)	.34

Abbreviation: CI, confidence interval.
[a]Some data were missing for participants, but the percentage of missing values never exceeded 3.6%.
[b]Calculated as weight in kilograms divided by height in meters squared.

During the study, there were 15 serious adverse events, 5 in the testosterone group and 10 in the placebo group; 13 were hospitalizations, of which 5 were planned before the study started. The hospitalizations were not related to the study medication. The other 2 serious adverse events were the 2 prostate carcinomas in the placebo group we described above.

Adjusting outcome variable differences for baseline differences did not

Table 3. Glucose, Insulin, Plasma Lipids, and Metabolic Syndrome Outcomes by Treatment Group

	Mean (SD)					
	Baseline		Final Visit			
	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Change Difference (95% CI)	*P* Value
Glucose, Insulin, and Plasma Lipids						
Glucose, mmol/L	5.6 (0.6)	5.5 (0.6)	5.6 (0.7)	5.7 (0.8)	–0.2 (–0.4 to –0.1)	.007
Insulin, μIU/L	10.1 (9.8)	8.9 (5.5)	10.2 (7.6)	11.5 (11.8)	–3.2 (–6.2 to –0.1)	.04
Insulin sensitivity-Quicky	0.3 (0)	0.4 (0)	0.3 (0)	0.3 (0)	0 (0 to 0)	.03
Insulin resistence-HOMA-IR	2.6 (2.6)	2.3 (1.5)	2.6 (2.0)	2.9 (2.9)	–0.9 (–1.7 to –0.1)	.02
Total cholesterol, mmol/L	5.6 (1.0)	5.5 (1.0)	5.4 (1.0)	5.4 (1.0)	–0.2 (–0.4 to 0)	.03
HDL cholesterol, mmol/L	1.2 (0.3)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	–0.1 (–0.2 to –0.1)	<.001
Triglycerides, mmol/L	1.6 (1.0)	1.5 (1.1)	1.5 (0.8)	1.6 (0.9)	–0.1 (–0.2 to 0.1)	.33
LDL cholesterol, mmol/L	3.9 (0.9)	3.8 (0.9)	3.8 (1.0)	3.7 (0.9)	0 (–0.2 to 0.1)	.83
Ratio total cholesterol/HDL cholesterol	5.1 (1.3)	5.0 (1.2)	5.5 (1.4)	5.0 (1.2)	0.4 (0.2 to 0.6)	<.001
	Metabolic Syndrome[b]					
	No. (%)				Odds Ratio (95% CI)	
Waist circumference	37 (32.7)	31 (28.2)	36 (31.9)	29 (26.4)	1.3 (0.7 to 2.3)	.74
Glucose	28 (24.8)	21 (19.1)	25 (22.3)	30 (27.2)	0.8 (0.4 to 1.4)	.10
Blood pressure	100 (88.5)	92 (83.6)	105 (92.9)	93 (84.5)	2.4 (1.0 to 5.9)	.08
HDL cholesterol	41 (36.2)	43 (39.1)	63 (56.6)	46 (41.8)	1.8 (1.0 to 3.0)	.003
Triglycerides	38 (33.6)	32 (29.1)	45 (40.7)	36 (32.7)	1.4 (0.8 to 2.4)	.46
Metabolic syndrome	39 (34.5)	34 (30.9)	54 (47.8)	39 (35.5)	1.7 (0.97 to 2.8)	.07

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert glucose from mmol/L to mg/dL divide by 0.0555; total cholesterol, HDL cholesterol, and LDL cholesterol from mmol/L to mg/dL divide by 0.0259; triglycerides from mmol/L to mg/dL divide by 0.0113.
[a] Some data were missing for participants, but the percentage of missing values never exceeded 3.6%.
[b] Percentage of participants who met the component criteria (waist circumference, glucose, blood pressure, HDL cholesterol, triglycerides) for the metabolic syndrome.

Table 4. Quality-of-Life Outcomes by Treatment Group

	Mean (SD)					
	Baseline		Final Visit			
	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Change Difference (95% CI)	*P* Value
Short-Form 36 Health Survey						
Physical functioning	89.8 (12.2)	86.8 (16.2)	89.6 (10.9)	86.1 (17.0)	0.7 (–2.0 to 3.5)	.61
Social functioning	92.0 (13.2)	91.0 (15.3)	91.9 (13.1)	89.8 (16.0)	1.5 (–2.2 to 5.2)	.42
Physical role	91.9 (21.4)	86.8 (29.1)	86.3 (28.7)	86.1 (29.5)	–4.5 (–12.0 to 3.0)	.24
Emotional role	90.6 (24.8)	89.4 (29.0)	93.8 (20.5)	89.5 (27.3)	3.3 (–4.4 to 11.0)	.41
Mental health	81.7 (13.0)	81.5 (15.9)	81.7 (12.8)	81.6 (14.8)	0.2 (–2.3 to 2.8)	.86
Vitality	75.0 (14.6)	73.7 (16.5)	75.8 (14.8)	72.5 (16.1)	2.4 (–0.4 to 5.3)	.10
Bodily pain	87.7 (16.3)	84.9 (17.6)	87.1 (15.2)	85.5 (17.9)	–1.5 (–5.5 to 2.5)	.47
General health perception	70.7 (16.2)	70.8 (16.0)	70.2 (16.0)	72.6 (16.2)	–2.3 (–5.8 to 1.2)	.19
Health transition	50.9 (12.6)	52.5 (13.9)	50.6 (12.1)	51.2 (11.0)	0.9 (–3.1 to 5.0)	.65
Herschbach questionnaire						
General	73.9 (25.4)	79.8 (25.2)	74.4 (26.5)	79.5 (26.8)	1.3 (–3.7 to 6.3)	.62
Health	80.9 (28.2)	78.3 (34.2)	75.9 (28.7)	77.7 (30.7)	–3.8 (–9.9 to 2.3)	.22
Hormones	107.6 (56.8)	113.6 (63.1)	112.4 (56.9)	106.8 (58.2)	13.6 (–3.6 to 23.5)	.008

Abbreviation: CI, confidence interval.
[a] Some data were missing for participants, but the percentage of missing values never exceeded 3.6%. When data were imputed, the *P* value for Herschbach questionnaire on hormones became .03.

Table 5. Safety Outcomes by Treatment Group

	Mean (SD)							
	Testosterone			Placebo			Change Difference in Final Visit vs Baseline (95% CI)	*P* Value[b]
	Baseline	(n = 113)[a] 13 wk	Final Visit	Baseline	(n = 110)[a] 13 wk	Final Visit		
Prostate-specific antigen, µg/L	1.6 (1.1)	1.6 (1.1)	1.6 (1.1)	1.7 (1.1)	1.8 (1.6)	1.7 (1.3)	0.1 (–0.1 to 0.2)	.58
Prostate volume, cm^3	28.3 (12.6)	[c]	30.7 (13.1)	28.0 (9.9)	[c]	29.2 (10.4)	1.0 (–1.6 to 3.7)	.43
International Prostate Symptom score	6.3 (5.1)	6.4 (4.8)	6.6 (4.8)	6.7 (4.9)	6.1 (4.3)	6.8 (4.6)	0.2 (–0.8 to 1.2)	.94
Creatinine, µmol/L	93.7 (18.2)	99.8 (21.6)	101.5 (18.3)	93.1 (15.2)	94.0 (16.3)	94.9 (15.9)	6.0 (3.7 to 8.3)	.05
Aspartate aminotransferase, U/L	22.8 (7.3)	22.5 (6.4)	23.0 (7.0)	24.2 (12.5)	23.2 (8.5)	24.0 (8.7)	0.6 (–1.4 to 2.5)	.31
Alanine aminotransferase, U/L	26.1 (11.1)	24.9 (11.9)	25.3 (11.1)	27.0 (13.9)	27.2 (12.6)	27.9 (12.2)	–1.8 (–4.1 to 0.6)	.17
Alkaline phosphatase, U/L	71.8 (19.5)	68.2 (20.7)	70.3 (19.5)	70.1 (18.2)	70.8 (17.7)	73.0 (19.5)	–4.7 (–8.1 to –1.4)	.74
γ-Glutamyltransferase, U/L	29.3 (15.8)	32.1 (26.4)	31.5 (14.7)	30.3 (19.8)	30.0 (18.2)	31.5 (18.0)	1.0 (–1.9 to 3.9)	.82
Hemoglobin, mmol/L	9.2 (0.5)	9.35 (0.6)	9.5 (0.6)	9.1 (0.6)	9.1 (0.6)	9.2 (0.6)	0.2 (–0.1 to 0.3)	.02
Hematocrit, %	0.45 (0.02)	0.46 (0.03)	0.46 (0.03)	0.45 (0.03)	0.45 (0.03)	0.45 (0.03)	0.01 (0 to 0.02)	.009

Abbreviation: CI, confidence interval.
SI conversion factors: To convert alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase to µkat/L, multiply by 0.0167; creatinine to mg/dL, divide by 88.4; hematocrit, multiply by 0.01; hemoglobin to mg/dL, divide by 10; prostate-specific antigen to ng/mL, divide by 1.0.
[a] Some data were missing for participants, but the percentage of missing values never exceeded 3.6%.
[b] *P* value is for repeated-measures analysis of variance over all 3 time points.
[c] Prostate volume was not measured at 13 weeks.

Table 6. Adverse Events by Treatment Group

	No. (%) of Adverse Events		
	Testosterone (n = 113)	Placebo (n = 110)	*P* Value
Gastrointestinal complaints	10 (9)	9 (8)	.86
Cardiovascular complaints	7 (6)	3 (3)	.21
Gynecomastia/breast tenderness	1 (<1)	2 (2)	.55
Urological complaints	11 (10)	10 (9)	.98
Skin problems	7 (6)	7 (7)	.17
Musculoskeletal complaints	11 (10)	9 (8)	.35
Lung problems	12 (11)	5 (5)	.26
Neoplasms (benign/malignant)	2 (2)	3 (3)	.63
Edema	1 (<1)	0	.32
Neurological complaints	4 (4)	1 (<1)	.18
Other complaints	38 (34)	56 (51)	.19
Total	**104**	**105**	

affect the results (available on request). Imputing missing variables resulted in 2 substantive changes in *P* values: the *P* value for the difference in bioavailable testosterone changed from .02 to .12 and the *P* value for the difference in the Herschbach questionnaire on hormones changed from .008 to .03.

COMMENT

In this large double-blind, placebo-controlled, randomized trial, we found that supplementation with 80 mg of testosterone undecenoate twice daily administered orally during 6 months to older men with low normal circulating testosterone levels increased lean body mass and decreased fat mass, but did not improve functional mobility or muscle strength. There were no beneficial effects on cognition or bone mineral density. Decreased fat mass was accompanied by decreased total and HDL cholesterol, resulting in an increase in total cholesterol to HDL cholesterol ratio. The decrease in fat mass also was accompanied by a decrease of the glucose level together with an increase of the insulin sensitivity. Quality-of-life measures did not differ aside from hormone-related quality of life in the testosterone group. Adverse events were not significantly different in the 2 groups.

To fully appreciate these results, some issues need to be addressed. First, the testosterone levels in this study population were low to low normal. Seventy-one percent of the men had a testosterone level below 12.0 nmol/L and are considered possibly testosterone deficient according to conventional standards.[30] The testosterone levels were comparable with other studies that found beneficial short-term effects of testosterone supplementation.[31,32]

The men in this trial were selected on the basis of their androgen status and not on the basis of their health status or symptoms that might indicate reduced testosterone levels; most of the participants were healthy and had no important preexisting health problems.

Six months is a relatively short period for supplementation. However, other studies with a shorter interven-

tion period have shown treatment effects.[31,33,34] Moreover, for the end points chosen, effects, if any, should have been reached within 6 months, with the exception of bone mineral density, for which longer treatment may be necessary.

The total daily dose of 160 mg of testosterone undecenoate orally used in this study has been used in clinical practice and in other studies.[35,36] The lack of increase in serum testosterone levels at the end of the study in the testosterone treatment group is a known effect of oral supplementation of testosterone undecenoate capsules, and is consistent with other studies.[35,36] Due to the pharmacokinetic profile of oral testosterone undecenoate, the testosterone level as measured in a single blood sample is highly dependent on the time of sampling relative to the time of ingestion of the capsules. Although the final testosterone level was not increased, various studies have shown that the pharmacological profile of testosterone undecenoate yields increased testosterone levels during most of the 24 hours,[37,38] so the circulating hormone level is changed and significant physiological alterations occur. Unfortunately we were not able to measure a postdose level, which undoubtedly would have been higher. We attribute the increase in testosterone in the placebo group largely to regression to the mean because we only measured testosterone levels once. More or larger effects of testosterone may have occurred with higher doses, but the risks involved are unknown. Moreover, this study did show the same statistically significant biochemical (increased hematocrit) and physical (decreased fat mass and increased lean body mass) effects as studies reporting an increase of the serum testosterone concentration with the use of intramuscular or transdermal testosterone. Finally, when this study was designed, patches and gels that provide more steady testosterone levels were not available in the Netherlands.

Medication adherence is always a concern. However, based on pill counts, more than 90% of participants completing the study used at least 80% of their medication, and these numbers did not differ between treatment groups. Finally, some data were missing but imputing them made no substantive difference in the overall results.

The levels of free testosterone and bioavailable testosterone were calculated from total testosterone, sex hormone-binding globulin, and albumin concentrations. This appears to be a rapid, affordable, simple, and reliable method, and suitable for clinical practice, although not ideal compared with equilibrium dialysis.

The increase in lean body mass and the decrease in fat mass in this study are comparable with those reported in most other testosterone supplementation studies in hypogonadal men.[39] There were no effects of testosterone on body mass index, waist circumference, and subcutaneous and intra-abdominal fat mass measured with ultrasound, probably because these measurements are not sensitive enough to detect small changes. In this study, the increase in lean body mass was not accompanied by an increase in muscle strength or functional mobility. Muscle strength is a key factor in maintaining independence in older people, while decreased muscle strength is a risk factor for falls, frailty, and disability.[40,41] Observational epidemiological studies have shown an association not only between testosterone levels and muscle mass and strength, but also between testosterone levels and physical performance and fall risk.[42,43] Still, in other studies with testosterone supplementation, the effects of the increase in lean body mass on muscle strength are inconsistent. The majority of studies show a discrepancy between changes in lean body mass and muscle performance.[2-5,39] A recent meta-analysis[44] suggests that testosterone supplementation in healthy older men might produce a moderate increase in muscle strength, but the mean effect size was strongly influenced by 1 study. Few previous studies have evaluated the effects of testosterone supplementation on functional mobility.[3,45]

The decrease in fat mass was also accompanied by a decrease in plasma glucose concentration and an increase in insulin resistance. Other studies with testosterone supplementation also have shown a decrease in blood glucose concentrations, plasma insulin levels, and mean glycated hemoglobin and an increase in insulin sensitivity, but these were mainly based on individuals with type 2 diabetes or abdominal obesity.[46,47] There are almost no well-designed studies on the effects of testosterone supplementation on insulin resistance in healthy older men similar to the participants in this study.

The decrease in fat mass also was accompanied by a decrease in total cholesterol, mainly because of a decrease in HDL cholesterol. Exogenous testosterone increases the activity of hepatic lipoprotein lipase, an enzyme involved in HDL catabolism.[48] This should reduce HDL levels but available data are controversial. Two recent meta-analyses have shown different results, one in which intramuscular administration of testosterone to hypogonadal men resulted in a small, dosage-dependent decrease in HDL cholesterol and concomitant declines in total cholesterol and low-density lipoprotein cholesterol[49] and the other in which total cholesterol declined after supplementation of testosterone (oral, intramuscular, or transdermal) to agonadal or hypogonadal men. However, HDL cholesterol was reduced only in studies with higher pretreatment testosterone concentrations[39] and the effects on HDL cholesterol were smaller in studies using intramuscular testosterone esters than in studies using oral and transdermal testosterone. This agrees with our study and could reflect higher serum levels of estradiol achieved with intramuscular testosterone injections, which are important in maintaining HDL cholesterol concentrations in men to counteract the ef-

fects of testosterone on lipoprotein lipase activity.[48]

The metabolic syndrome is a strong risk factor for cardiovascular disease and type 2 diabetes mellitus[50,51] and epidemiological studies have shown an association with low androgen levels.[52-54] However, no studies have evaluated the effects of testosterone supplementation on the metabolic syndrome. We found a nonsignificant increase in the percentage of men who met the criteria of the metabolic syndrome, mainly caused by the decrease in HDL cholesterol levels. The effects of these changes on risk of cardiovascular disease and type 2 diabetes are still unknown.

With advancing age, men lose bone mineral density, which increases risk for fractures. Up to 20% of men with vertebral fractures[55] and 50% of men with hip fractures[56] have biochemical evidence of hypogonadism, suggesting a potential role of testosterone supplementation for prevention. Testosterone supplementation did not affect bone mineral density in this study, although the intervention period was relatively short for detecting bone turnover changes. Two meta-analyses have shown that testosterone supplementation, particularly intramuscular testosterone, moderately increased lumbar bone density in men after a minimum of 12 to 36 months of treatment, but the results on femoral neck bone are inconclusive.[39,57] However, none of these studies showed a decreased rate of fractures with testosterone therapy.

The prevalence of age-associated cognitive decline in the general older population is estimated to be between 20% and 35%.[58] Cognitive decline can precede dementia and subsequent institutionalization. Epidemiological studies have reported a positive association between testosterone level and cognition[59-62] and between testosterone level and the incidence of Alzheimer disease.[60,63,64] Furthermore, on the basis of basic research and animal studies, testosterone is suggested to exert a protective effect on cognitive function.[65-67] However, testosterone supplementation did not affect cognitive function in this study, and other studies found similar results.[2,31,33,68] Even visuospatial abilities, tested using a sensitive and widely used visuospatial test (mental rotation performance), had no change with testosterone supplementation. However, we could only exclude an effect larger than approximately 0.2 standard deviations of the baseline distribution of the visuospatial test; if smaller effects are considered clinically relevant, larger studies are necessary.

Most of the participants in this study had no preexisting cognitive abnormalities, but the participants scored between the 50th and 70th percentile for all cognitive tests, suggesting that there was no ceiling effect. Moreover, even studies with testosterone supplementation in men who have mild cognitive impairment or Alzheimer disease have shown mixed findings.[34,69,70]

Age-related decline in testosterone levels in men has been suggested to adversely affect quality of life.[71] However, most studies that assessed health-related perception of quality of life using the SF-36 have not shown any benefit,[45,72] including our study, and might be due to the fact that this questionnaire is not sensitive enough. In our study, we also used a questionnaire developed to measure hormone deficiency–dependent quality of life, and we found modest beneficial results in one portion of the survey, especially on the item "resilience or ability to tolerate stress." Even with this significant difference, the multiple comparisons involved do not support a large effect on quality of life.

There is serious concern that men receiving hormone replacement may be vulnerable to increased health risks. Known adverse effects of androgen supplementation are gynecomastia, edema, and an increase in hematocrit. However, the most important concern of androgen supplementation in old age is the risk of the development and/or progression of prostate disease such as benign prostate hyperplasia and prostate carcinoma. Two recent studies[73,74] have found no increase in prostate-related health problems, but several case reports have suggested that testosterone therapy may convert occult prostate cancer into a clinically symptomatic lesion.[75,76] In this study, there were no indications that testosterone would stimulate an occult prostate carcinoma. A systematic review found that testosterone replacement in men with hypogonadism increased PSA levels an average of 0.30 ng/mL in young men and 0.43 ng/mL in older men.[77] We found no overall effect on serum PSA, prostate volume, and voiding symptoms in this trial. A stimulatory effect of testosterone on erythropoiesis has been documented in several studies.[73] This effect was confirmed in our study, but without apparent clinical consequences. Liver function and (serious) adverse events did not differ significantly between groups, although creatinine did increase with borderline statistical significance. However, the study duration was only 6 months and a larger trial would be needed to establish safety.

This study is, as far as we know, the largest study of testosterone supplementation with the most end points and a randomized, double-blind design. Adherence was high and the dropout rate was low. We found a change in body composition that was accompanied by different effects on metabolic risk factors and no beneficial effects on functional mobility, bone mineral density, or cognitive function. One subset of the hormone-related quality-of-life survey was improved in the testosterone group. The findings in this study do not support a net benefit on several indicators of health and functional and cognitive performance with 6 months of modest testosterone supplementation in healthy men with circulating testosterone levels in the lower range.

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The scientist is not content to stop at the obvious.
—Charles H. Mayo (1865-1939)

vances.[1] I also agree that the influence of education on health and socioeconomic status probably exceeds that of income. But income is hardly irrelevant; it has independent effects on health status and is interconnected with education as both a mediator and by-product. For example, economic hardship makes learning difficult for students; preoccupies parents and families with concerns other than their children's study habits; makes tuition unaffordable; and chokes off tax revenue and other resources for schools, teachers, and infrastructure. Income is also a by-product of education: it boosts earnings and provides the means to purchase the commodities of good health (eg, insurance coverage, health care, nutritious foods).

Muennig is certainly correct that boosting household incomes, by itself, will not eradicate health disparities. Neither will diplomas. Health disparities reflect multiple causes, and no singular strategy could be expected to fully solve the problem. Disparities also reflect other individual-level characteristics, some of which are modifiable (eg, smoking, obesity, seeking care for warning symptoms) and some of which are not (eg, race). Apart from individual factors, health is influenced by environmental conditions that individuals cannot directly control, such as pollution, safety, advertising, and the built environment. Finally, health is affected by access to health care and its quality. All of these variables are heavily interrelated, and their associations with health status are vulnerable to confounding.

A comprehensive approach to ameliorating health disparities therefore requires attention to each of these domains and, as Muennig advocates, the pursuit of evidence-based strategies that improve outcomes.[2] Work is under way in many of these areas, such as improving schools, helping the uninsured, and making cities safer. Amid these high-profile initiatives, however, it is easy to disregard income, in part because the policy solutions are so politically intimidating but perhaps also because the scale of the problem—the stagnated income of much of the population and the rise in poverty rates—is not widely appreciated.

I agree with Muennig that other factors matter more, but I doubt that income plays no role. Failing to address that piece of the puzzle can undermine the other population-based and clinical efforts to reduce disease. Providing schooling and low-cost health care and social services holds less promise if the clientele cannot afford the basic expenses on which the effectiveness of these programs depends (eg, bus fare and pharmacy bills). Moreover, the ripple effects of financial hardship extend beyond the health sector: it disrupts lives and families, destabilizes communities, lowers workforce productivity, and stifles economic growth.[3] Education and other strategies that help the larger population make ends meet are important for public health and the economy.

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