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# Dose-Dependent Effects of Testosterone on Sexual Function, Mood, and Visuospatial Cognition in Older Men

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**Context:** The relationships between testosterone dose and its effects on sexual function, mood, and visuospatial cognition are poorly understood.

**Objective:** To elucidate testosterone dose-response relationships in older men, we examined the effects of graded testosterone doses on sexual function, mood, and visuospatial cognition in healthy, older men (age, 60–75 yr).

**Setting:** This study was performed at the General Clinical Research Center.

**Intervention/Methods:** Subjects each received a long-acting GnRH agonist to suppress endogenous testosterone production and were randomized to receive one of five doses (25, 50, 125, 300, and 600 mg) of testosterone enanthate weekly for 20 wk. Questionnaires were used to evaluate sexual function. Scores for overall sexual function as well as subcomponents of sexual function (libido, sexual activity, and erectile function) were calculated.

**Results:** Changes in overall sexual function ($P = 0.003$) and waking erections ($P = 0.024$) differed by dose. An interaction between libido and being sexually active was observed, such that libido changed by testosterone dose only among men who reported being sexually active at the beginning of the study ($P = 0.009$). Men's log-transformed free testosterone levels during treatment were positively correlated with overall sexual function ($P = 0.001$), waking erections ($P = 0.040$), spontaneous erections ($P = 0.047$), and libido ($P = 0.027$), but not with intercourse frequency ($P = 0.428$) or masturbation frequency ($P = 0.814$). No effects of testosterone dose were observed on two measures of mood: Hamilton's Depression Inventory ($P = 0.359$) and Young's Mania Scale ($P = 0.851$). The number of trials completed on a computer-based test of visuospatial cognition differed by dose ($P = 0.042$), but the number of squares correctly completed on this task did not differ by dose ($P = 0.159$).

**Conclusions:** Different aspects of male behavior respond differently to testosterone. When considered together with previous data from young men, these data indicate that testosterone dose-response relationships for sexual function and visuospatial cognition differ in older and young men. **(*J Clin Endocrinol Metab* 90: 3838–3846, 2005)**

SERUM TESTOSTERONE LEVELS decline with age; thus, older men have lower testosterone levels than younger men (1, 2). Some of the age-related changes in muscle mass, bone mineral density, fat mass, and sexual and cognitive functions resemble those observed in young, hypogonadal men. Consequently, the interest in treating older men with low testosterone levels with testosterone supplementation has grown rapidly. In older men, testosterone supplementation increases lean body mass, muscle strength, and hemoglobin levels and decreases whole body and visceral fat (3–7). One question of prime concern is how testosterone supplementation affects sexual function, mood, and cognition in older men.

Data linking the effects of testosterone interventions on sexual function, mood, and cognition have been obtained primarily from studies in young men. These data may not be extrapolated directly to older men. A handful of studies have examined the effects of testosterone supplementation on sexual function in older men (reviewed in Refs. 4, 8, and 9). In a recent review, Morley and Perry (4) found that testosterone supplementation in older men resulted in increased libido in seven of eight studies and improvement in erections in five of six studies. The studies reported in this review used only one or two testosterone replacement doses, limiting our understanding of the effects of a greater range of testosterone doses and concentrations on sexual function. Additional data are needed to elucidate whether older men receiving different doses, and thus achieving different concentrations of serum testosterone, experience changes in sexual function.

Several studies have investigated the effects of testosterone supplementation on mood and cognition in older men (reviewed in Refs. 10 and 11). Testosterone levels are lower among depressed, older men (12) than in age-matched controls, although testosterone supplementation in men with depression has produced inconsistent effects (13–15). Among younger men, administration of high doses of testosterone has been associated with increases in mania scores (16, 17), although the behavioral effects of testosterone supplementation have not been well studied among older men. Visuospatial cognition has been linked to variation in testosterone levels in older men, although the evidence is mixed (18, 19)

In this study we examine the effects of graded doses of testosterone on several domains of sexual function, mood, and visuospatial cognition in healthy, older men. The older men were treated with a long-acting GnRH agonist to sup-

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Abbreviation: DHT, Dihydrotestosterone.

press endogenous testosterone production and were randomized to receive one of five different doses of testosterone. This research design enables testing whether testosterone operates in a dose-response fashion, or whether, as some research has suggested, threshold levels of testosterone are sufficient to maintain sexual function. We have previously conducted a study using the same research design in young men and found that alterations in testosterone levels over a wide range, extending from slightly below the lower limit of normal for healthy, young men to supraphysiological levels, had no effect on sexual function, mood, or visuospatial cognition in healthy, young men (20). This study in older men was designed to determine whether the same testosterone regimens given to older men affect these outcomes differently than they do in younger men.

Because sexual function has several components, we investigated the effects of testosterone on overall sexual function as well as its three primary components: libido, overall sexual activity, and erectile function. The distinction between libido and sexual activity is commonly recognized (21). Due to the social constraints facing men, such as the availability of a partner, testosterone may modulate motivation without necessarily causing behavioral changes (22). Particularly in older men, testosterone may also affect erectile function (9, 23). Therefore, we evaluated these three components of sexual function separately to determine whether they are modulated by testosterone (24).

## Subjects and Methods

### *Human subjects review and informed consent*

The protocol was approved by the institutional review boards of Charles Drew University and Harbor-University of California-Los Angeles Research and Education Institute. All participants provided informed consent by signing an institutional review board-approved consent form.

### *Participants*

The study design and inclusion and exclusion criteria have been published previously (25). Briefly, the participants were healthy older men, 60–75 yr of age, with normal serum testosterone concentrations. Those with benign prostate hyperplasia, American Urology Association symptom score greater than 7, history of prostate cancer, prostate-specific antigen level greater than 4 ng/ml, hematocrit higher than 0.480 liter/liter, diabetes mellitus, congestive heart failure, or myocardial infarction in the preceding 6 months were excluded. Men who were taking androgenic steroids, GH, or anabolic steroids within the previous 12 months were excluded. We also excluded those who were participating in competitive sports, resistance training, or moderate to heavy endurance training. Subjects were required to be able to read and understand the informed consent, placing a lower limit on educational background needed to participate.

### *Study design*

Sixty eligible men, 60–75 yr of age, were treated for 20 wk with monthly injections of long-acting GnRH agonist to suppress endogenous testosterone production and weekly injections of one of five doses of testosterone enanthate (25, 50, 125, 300, and 600 mg). The GnRH agonist and testosterone treatments were started on d 1. The assignment of testosterone dose was based on a randomization table, using a block size of four. The General Clinical Research Center staff administered all testosterone and GnRH agonist injections. These 60 men were randomized to receive 25 (13 men), 50 (12 men), 125 (12 men), 300 (14 men), or 600 (10 men) mg testosterone. After the Data Safety Monitoring Board discontinued the 600-mg dose, subjects were randomized to one of the lower four doses (25). Of the 52 men who completed treatment, 44 completed questionnaires on sexual function and mood (Fig. 1).

### *Outcome measures*

Sexual function was assessed using a previously published instrument (26). This instrument contains items evaluating components of sexual activity, including erectile function, libido, and sexual activity. The questionnaire was given to subjects to complete daily over a 7-d period before testosterone treatment and during a 7-d period at the conclusion of testosterone treatment. Overall and subcomponent scores at the start and conclusion of the study were obtained by adding the scores for items from these 7-d periods. Higher scores on overall and subcomponent outcomes indicate higher levels of sexual function (*e.g.* a "yes" to reporting spontaneous erection upon waking received 1 point, and a "no" response received 0 points). All analyses reported in this study represent changes in overall and subcomponents of sexual function scores, subtracting starting scores from scores at the conclusion of the study.

To investigate the effects on subcomponents of overall sexual function, items were selected that best evaluated the three subcomponents

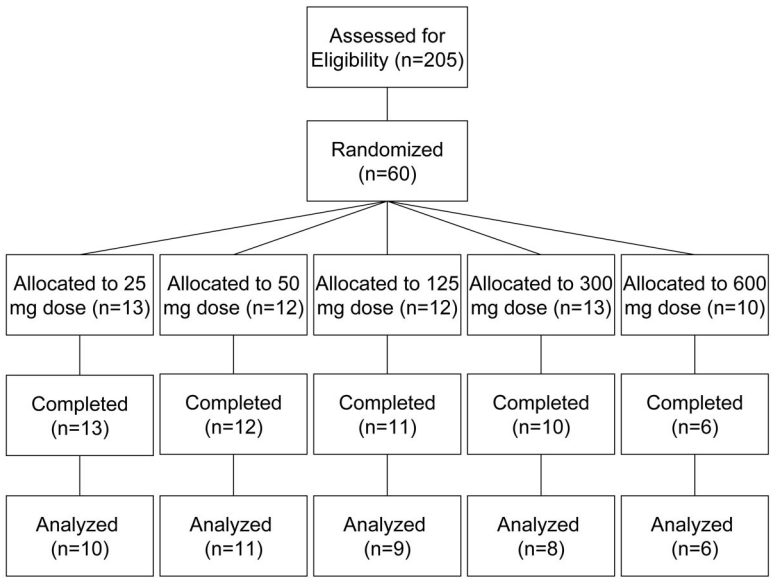


FIG. 1. Flow of subjects through different phases of the study.

of primary interest. Because nighttime and spontaneous erections have been shown to be testosterone dependent, two questions were used as measure of these aspects of erectile function: whether men reported (yes or no) erections upon waking ("Did you have an erection when you woke up this morning?"), and whether men reported spontaneous erections during the previous 24 h ["Did you have spontaneous erections during the past 24 h (not during intercourse or masturbation, not on awakening from sleep, and not while viewing erotic material)?"]. As a measure of libido, one question that allowed subjects to circle one of three ratings of their degree of sexual desire, from "no desire at all" to "some desire but not very strong" to "very intense sexual desire," was used. Masturbation (yes or no within the previous 24 h) was assessed (by the question "Did you masturbate during the past 24 h?"). Finally, sexual intercourse was coded as a yes/no response during the previous 24 h [to the question "In the past 24 h, did you have intercourse (penetration with or without orgasm)?"].

To determine whether testosterone intervention had effects on mood, we administered Hamilton's Depression Rating Scale (27) at baseline and during the last treatment week. Young's Mania Scale (28) was also used to determine whether testosterone resulted in an increase in mania. To examine whether testosterone intervention affected visuospatial cognition, we employed a computer-based checkerboard test (29). Two outcome measures from this checkerboard test were used: the number of trial levels (maximum of 10) that the subject reached before the test was terminated, and the number of checkerboard squares correctly marked across all trials.

### *Statistical analyses*

To investigate differences in sexual function outcomes by dose, one-way ANOVA was used. *Post hoc* Bonferroni tests were conducted where appropriate to control for multiple comparisons. To examine the interactions between sexual activity and libido, a two-factor ANOVA was used. In addition to examining dose effects of testosterone, total and free testosterone levels of men at the beginning and end of the study were log transformed to help normalize the data. These testosterone values were treated as continuous variables and were correlated with measures of sexual function using Pearson's correlation coefficient. All tests were two-sided, with an $\alpha$ set at 0.05.

### *Hormone analyses*

Serum total testosterone was measured by a previously validated RIA (20, 25) that has been validated against liquid chromatography-mass spectrometry/mass spectrometry. Free testosterone was separated by an equilibrium dialysis procedure and was measured by RIA (30). The sensitivity of the total testosterone assay was 0.02 nmol/liter (0.6 ng/dl), and the lower limit of the normal range was 9.5 nmol/liter (275 ng/dl). Intra- and interassay coefficients of variation were 8.2% and 13.2%, respectively. For free testosterone, the sensitivity was 0.76 pmol/liter (0.22 pg/ml); intra- and interassay coefficients of variation were 4.2% and 12.3%, respectively. The cross-reactivity of dihydrotestosterone (DHT) in the testosterone assay was less than 0.1%. Serum estradiol levels were measured by a previously described immunoassay with a sensitivity of 2.5 pg/ml (20). For measurement of serum DHT levels, the samples were extracted using an ethyl acetate/hexane mixture and were subjected to Celite chromatography. Fractions containing DHT were taken up in the assay buffer and analyzed by RIA.

## Results

### *Participant characteristics*

The baseline characteristics of all subjects are reported in Table 1; the five groups did not differ significantly in their baseline characteristics. Forty-four of the 52 men who completed the study completed the sexual function questionnaires; these 44 men did not differ in age ($P = 0.937$), height ($P = 0.752$), weight ($P = 0.829$), free testosterone ($P = 0.832$), or total testosterone ($P = 0.992$) at baseline compared with the entire pool of 52 subjects who completed the study.

### *Hormone data*

The hormone data in all subjects have been reported previously (25); presented in this manuscript are hormone data for the subjects who returned the questionnaires and whose data were used in this analysis. Baseline serum total and free testosterone levels in this sample of older men were significantly lower than baseline testosterone levels in younger men in our laboratory (data not shown) or younger men involved in a parallel study (20). During treatment, significant correlations were observed between testosterone dose and serum nadir total ($r = 0.94$; $P < 0.0001$) and free ($r = 0.87$; $P < 0.0001$) testosterone levels 7 d after the previous injection, and the changes from baseline in total ($r = 0.95$; $P < 0.0001$) and free ($r = 0.83$; $P < 0.0001$) testosterone levels. Serum total testosterone levels during treatment were lower than baseline in men receiving the 25-mg dose, but increased dose-dependently in men receiving the 125-, 300-, and 600-mg doses.

### *Sexual function data*

Baseline sexual function scores were not significantly correlated with log free testosterone levels ($r = 0.127$; $P = 0.413$; Table 2). Baseline log free testosterone levels were not significantly correlated with waking erections ($r = 0.291$; $P = 0.072$), spontaneous erections ($r = 0.074$; $P = 0.663$), libido ($r = 0.185$; $P = 0.280$), or coital ($r = -.131$; $P = 0.412$) or masturbation ($r = 0.288$; $P = 0.084$) frequencies.

Changes in overall sexual function scores differed by testosterone dose (Fig. 2 and Table 2; $P = 0.003$). *Post hoc* analyses revealed significant differences between men receiving 25 and 50 mg, on the one hand, and men receiving 300 mg, on the other ($P < 0.05$).

There were significant group differences in the change in waking erections (Table 2) ($P = 0.024$). *Post hoc* analyses showed significant differences between men receiving 25 mg

**TABLE 1.** Baseline characteristics of men

| Monthly GnRH agonist | + | + | + | + | + | + |
|---|---|---|---|---|---|---|
| Weekly testosterone dose (mg) | All men | 25 | 50 | 125 | 300 | 600 |
| Age (yr) | 65.5 (0.7) | 64.5 (0.7) | 64.7 (0.7) | 66.4 (1.0) | 67.3 (0.8) | 65.3 (2.1) |
| Height (cm) | 181.1 (3.7) | 182.9 (7.5) | 175.8 (4.3) | 179.8 (8.9) | 187.9 (9.7) | 181.1 (15.6) |
| Weight (kg) | 80.1 (0.4) | 80.4 (0.9) | 80.6 (0.7) | 80.2 (1.4) | 80.2 (0.6) | 78.4 (1.1) |
| Free testosterone (pg/ml) | 35.5 (1.5) | 33.2 (2.8) | 36.0 (3.6) | 41.1 (3.0) | 32.1 (3.2) | 34.2 (4.1) |
| Total testosterone (ng/dl) | 341.3 (13.7) | 349.6 (29.5) | 325.8 (14.8) | 366.9 (33.3) | 324.9 (34.8) | 339.3 (39.5) |
| No. of men | 44 | 10 | 11 | 9 | 8 | 6 |

Data are means (SE) for older men who were randomized into the study. By ANOVA, no differences in age ($P = 0.591$), height ($P = 0.887$), weight ($P = 0.614$), free testosterone ($P = 0.364$), or total testosterone ($P = 0.420$) were observed among testosterone treatment groups. To convert free testosterone levels to picomoles per liter, multiply by 3.467. To convert total testosterone levels to nanomoles per liter, multiply by 0.03467.

**TABLE 2.** Sexual function descriptive data

| Variable | 25 mg | 50 mg | 125 mg | 300 mg | 600 mg |
|---|---|---|---|---|---|
| Sexual function score | | | | | |
| Baseline | 5.9 (1.0) | 6.3 (1.0) | 7.3 (1.2) | 5.0 (1.0) | 7.2 (1.4) |
| Wk 20 | 3.8 (1.0) | 6.4 (1.0) | 9.0 (1.4) | 9.5 (1.4) | 9.8 (2.6) |
| Change[a] | −2.1 (1.2) | 0.1 (1.0) | 1.7 (0.4) | 5.2 (1.0) | 2.2 (2.6) |
| Waking erection frequency | | | | | |
| Baseline | 3.7 (0.7) | 2.6 (0.6) | 3.1 (0.8) | 2.3 (0.9) | 4.0 (1.1) |
| Wk 20 | 1.6 (0.6) | 2.9 (0.9) | 4.9 (1.0) | 4.9 (0.9) | 3.5 (1.2) |
| Change[b] | −2.2 (1.1) | 0.1 (0.7) | 0.9 (0.6) | 2.6 (1.0) | −0.6 (1.6) |
| Spontaneous erection frequency | | | | | |
| Baseline | 1.3 (0.7) | 1.9 (0.7) | 1.2 (0.6) | 0.1 (0.1) | 0.4 (0.2) |
| Wk 20 | 1.3 (0.9) | 2.4 (1.0) | 1.3 (0.8) | 2.3 (0.8) | 3.2 (1.3) |
| Change | 0.2 (1.5) | 0.3 (0.8) | −0.1 (1.0) | 1.7 (0.7) | 3.0 (1.6) |
| Intercourse frequency | | | | | |
| Baseline | 1.3 (0.4) | 0.3 (0.4) | 0.8 (0.6) | 0.6 (0.3) | 2.2 (0.6) |
| Wk 20 | 0.0 (0.6) | 0.4 (0.4) | 1.1 (0.8) | 1.1 (1.1) | 1.8 (1.5) |
| Change | −1.5 (0.6) | 0.4 (0.2) | 0.3 (0.6) | −0.1 (0.8) | 0.0 (1.3) |
| Masturbation frequency | | | | | |
| Baseline | 0.4 (0.3) | 0.8 (0.6) | 2.3 (0.8) | 0.0 (0.0) | 1.2 (1.2) |
| Wk 20 | 0.1 (0.1) | 1.0 (0.7) | 2.1 (0.7) | 1.1 (0.6) | 0.2 (0.3) |
| Change | −0.3 (0.3) | 0.0 (0.4) | 0.2 (0.5) | 1.3 (0.7) | −1.2 (1.5) |
| Libido | | | | | |
| Baseline | 12.9 (1.3) | 14.0 (1.0) | 15.1 (0.8) | 12.3 (0.9) | 14.2 (0.8) |
| Wk 20 | 11.0 (0.9) | 14.3 (1.6) | 15.2 (0.9) | 16.3 (1.0) | 15.8 (1.7) |
| Change | −2.2 (2.0) | 0.3 (0.8) | 0.1 (1.0) | 2.7 (1.0) | 1.8 (2.4) |

Data are means (SE). Baseline values refer to baseline scores, wk 20 values refer to scores at wk 20, and change scores refer to baseline scores subtracted from wk 20 scores. All frequencies refer to the average number of days a behavior occurred during a 7-d period. By ANOVA, no differences in baseline sexual function scores ($P = 0.423$), waking erections ($P = 0.535$), spontaneous erections ($P = 0.268$), intercourse frequency ($P = 0.113$), masturbation frequency ($P = 0.230$), or libido ($P = 0.513$) were observed among testosterone treatment groups.

[a]Overall ANOVA $P = 0.003$.

[b]Overall ANOVA $P = 0.024$.

and men receiving 300 mg. The changes in spontaneous erections did not differ across testosterone groups ($P = 0.380$).

Changes in libido did not differ significantly by group ($P = 0.215$). However, when libido was entered in a two-way ANOVA along with men's reported sexual activity (sexually active or not at the start of the study), the results showed a significant overall testosterone effect ($P = 0.002$). In this two-way ANOVA, a significant interaction effect between being sexually active at the start of the study and testosterone dose was observed ($P = 0.009$).

Masturbation rates did not differ across testosterone groups ($P = 0.166$). Changes in coital activity also did not differ across groups ($P = 0.356$).

Log free testosterone levels during treatment were significantly correlated with changes in overall sexual function ($r = 0.473$; $P = 0.001$), waking erections ($r = 0.349$; $P = 0.040$), spontaneous erections ($r = 0.338$; $P = 0.047$), and libido ($r = 0.391$; $P = 0.027$; Fig. 3). However, free testosterone levels were not correlated with changes in measures of sexual activity: intercourse frequency ($r = 0.139$; $P = 0.428$) or masturbation frequency ($r = 0.042$; $P = 0.814$). Results were similar if log total testosterone levels were used in place of free testosterone levels; total testosterone levels were significantly correlated with changes in overall sexual function ($r = 0.524$; $P < 0.0005$), waking erections ($r = 0.365$; $P = 0.031$), and libido ($r = 0.458$; $P = 0.008$). Total testosterone levels were not significantly correlated with changes in spontaneous erections ($r = 0.316$; $P = 0.064$), intercourse frequency ($r = 0.119$; $P = 0.498$), or masturbation frequency ($r = -0.022$; $P = 0.902$).

### *Mood and visuospatial cognition data*

Baseline depression ($r = -0.069$; $P = 0.627$) and mania ($r = -0.001$; $P = 0.946$) scores were not correlated with log free testosterone levels (Table 3). Changes in mood during the study did not differ by group (Fig. 4; depression, $P = 0.359$; mania, $P = 0.851$) and were not significantly correlated with free or total testosterone levels.

With respect to visuospatial cognition, the number of trials reached before tests terminated was not correlated with baseline log free testosterone levels ($r = -0.149$; $P = 0.324$). However, the number of squares correctly marked in all trials was significantly, and negatively, correlated with baseline log free testosterone levels ($r = -0.353$; $P = 0.016$). Changes in the number of visuospatial trials reached before tests were terminated differed across groups ($P = 0.042$). *Post hoc* tests revealed significant differences in the number of visuospatial trials completed between men receiving 600 mg testosterone weekly and men receiving 25 mg weekly. Changes in the number of squares correctly marked in all trials did not differ by group ($P = 0.159$).

Log free testosterone levels during treatment were not significantly correlated with the number of squares correctly marked on visuospatial tests ($r = 0.186$; $P = 0.222$). Changes in the number of trials completed on the visuospatial tests ($r = 0.303$; $P = 0.043$) were significantly correlated with log free testosterone levels near the end of treatment. Results were similar if log total testosterone levels were examined in relationship to changes in these same outcomes; log total testosterone levels were significantly correlated with changes in the number of trials completed on the visuospatial tests ($r = 0.362$; $P = 0.015$), but not with changes in the number of squares correctly marked on visuospatial tests ($r = 0.154$; $P = 0.312$)

As secondary analyses, we performed correlations between changes in the sexual function, mood, and visuospatial outcome variables and the log-transformed estradiol levels during the treatment period. These analyses revealed positive correlations (all $P < 0.05$) between log-transformed estradiol levels during treatment and overall sexual function, libido, and the number of trials completed on the checkerboard tests. However, serum estradiol levels were highly correlated with serum testosterone levels. Therefore, we additionally performed partial correlations between changes in outcome measures and log estradiol levels, controlling for log-transformed free testosterone levels during treatment. These analyses revealed no significant correlations between changes in outcome measures and estradiol levels (all $P > 0.227$) after controlling for log free testosterone levels.

Similarly, log-transformed DHT levels during treatment were correlated significantly with overall sexual function scores ($r = 0.398$; $P = 0.010$). Correlations of serum DHT levels with all other subcomponents of sexual function were

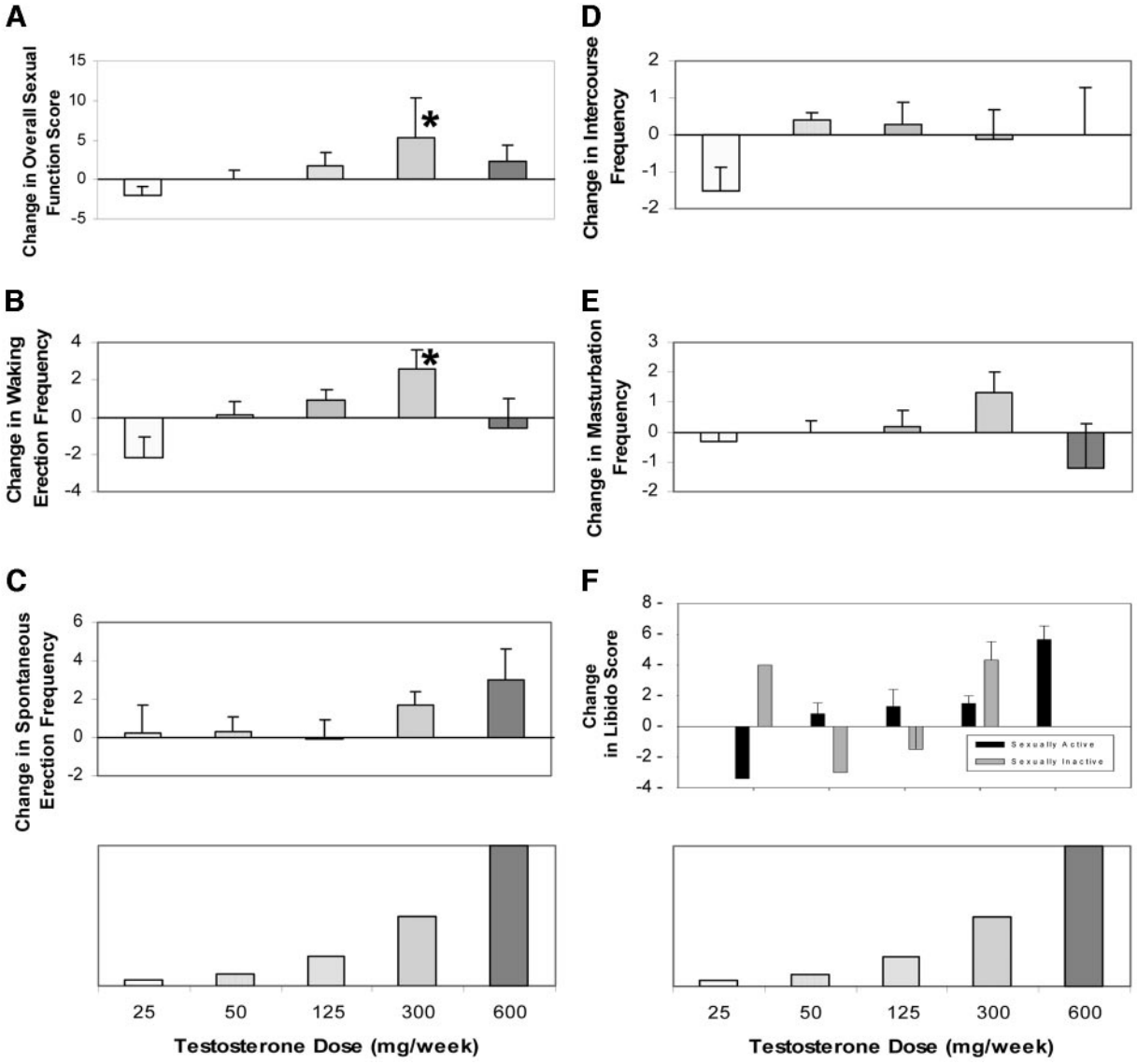


FIG. 2. Change in overall sexual function (A), waking erections (B), spontaneous erections (C), intercourse frequency (D), masturbation frequency (E), and libido (F). Data are the mean ± SE. Changes in overall sexual function ($P = 0.003$) and waking erections ($P = 0.024$) differed by dose. *Post hoc* analysis of changes in sexual function indicated significant differences between men in the 300-mg group, on the one hand, and men in the 25- and 50-mg groups, on the other as indicated by an *asterisk* ($P < 0.05$). *Post hoc* analysis of changes in waking erections indicated significant differences between men in the 300- and 25-mg groups as indicated by an *asterisk* ($P < 0.05$). An interaction between changes in libido and being sexually active at the start of the study was observed ($P = 0.009$). No changes in spontaneous erections, masturbation rates, or intercourse frequency were observed by dose ($P > 0.05$).

not significant. As expected, serum DHT levels were highly correlated with serum testosterone levels. Therefore, we performed partial correlations between DHT levels and changes in sexual function scores after controlling for serum testosterone levels. The partial correlation analyses revealed that log-transformed, serum DHT levels during treatment were not significantly correlated with changes in overall sexual function or any of the subcomponents (all $P \geq 0.238$).

## Discussion

This study evaluated the relationship between testosterone dose and several domains of sexual and cognitive functions and mood over a wide range of testosterone concentrations in older men and uncovered important differences in the androgen responsiveness of young and older men. In contrast to the previously reported data for young men, changes in overall sexual function in older men differed depending upon the dose of testosterone the men received. Men's self-reports of waking erections also differed according to the testosterone dose group, although the number of spontaneous erections did not differ significantly across testosterone groups. Changes in libido showed an interaction with being sexually active, where libido changed among those men who reported being sexually active at the start of the study. All four of these variables were significantly and positively correlated with log testosterone levels during

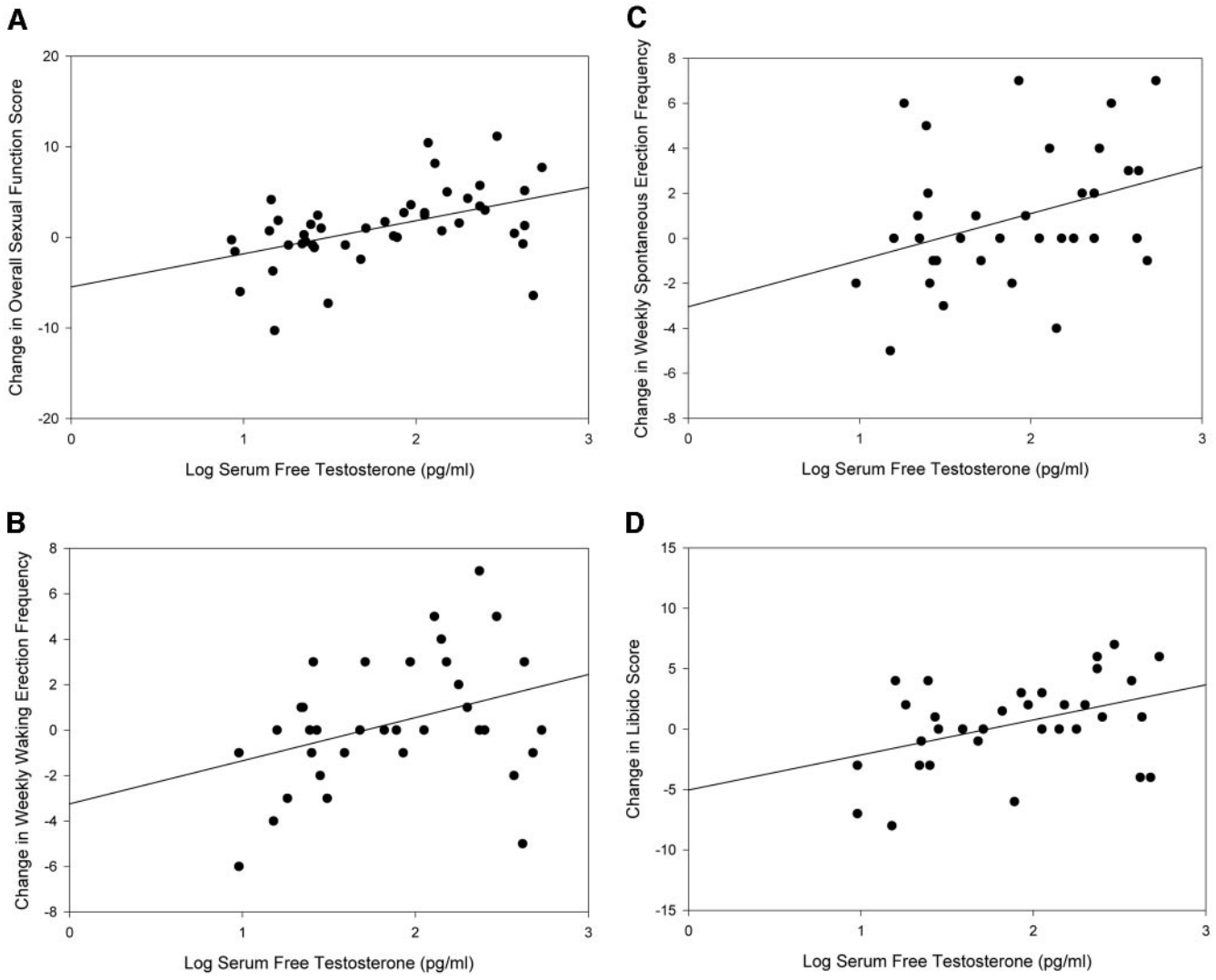


FIG. 3. Change in overall sexual function (A), waking erections (B), spontaneous erections (C), and libido (D) according to log (10) of men's serum free testosterone levels on d 113. Testosterone levels were significantly correlated with changes in overall sexual function ($P = 0.001$), waking erections ($P = 0.040$), spontaneous erections ($P = 0.047$), and libido ($P = 0.027$), but not with masturbation or intercourse frequency ($P > 0.05$).

treatment. Neither masturbation nor coital rates were changed by testosterone intervention. The number of trials completed on the visuospatial test differed according to testosterone group, with significant improvements among men receiving 600 mg testosterone compared with men receiving 25 mg testosterone. No differences in the number of squares correctly marked in this visuospatial task were noted across testosterone groups, nor were there significant dose effects on changes in depression or mania.

Studies in young men are in agreement that many aspects of sexual function are normalized at testosterone levels that are at or near the lower limit of the normal range for healthy, young men. Similarly, in sexually mature, young, male rats, many domains of mating behavior are impaired by lowering testosterone levels (31, 32); conversely, testosterone replacement of orchidectomized rats restores mating behavior at doses that are insufficient to restore prostate and seminal vesicle weights. These observations have led to speculation that a threshold of testosterone level exists near the lower limit of the normal male range; sexual function is impaired when testosterone levels fall below this threshold and is normalized at levels above this threshold. The available data from studies in young men and male rats do not exclude the possibility of a dose-response relationship between sexual function and circulating testosterone levels in a range that is below the lower limit of normal and whose asymptote approximates the lower limit of the normal male range.

A number of recent studies suggest that the dose-response relationship between testosterone and several domains of sexual function might be different in older men compared with young men. Thus, in contrast with the studies performed in healthy, young men and in young, hypogonadal men that generally show no relationship between testosterone dose and measures of sexual function, Steidle *et al.* (3) reported that sexual desire, sexual motivation, and spontaneous erections were related to testosterone dose in a population of largely middle-aged and older hypogonadal men. A meta-analysis of testosterone replacement in men with

**TABLE 3.** Mood and visuospatial cognition descriptive data

| Variable | 25 mg | 50 mg | 125 mg | 300 mg | 600 mg |
|---|---|---|---|---|---|
| Mood | | | | | |
| Depression | | | | | |
| Baseline | 1.7 (0.9) | 2.8 (1.2) | 1.6 (0.6) | 1.2 (0.6) | 1.9 (0.8) |
| Wk 20 | 1.1 (0.5) | 0.2 (0.2) | 0.3 (0.2) | 1.3 (1.2) | 3.0 (1.4) |
| Change | 1.3 (1.0) | −0.3 (1.2) | −1.6 (0.5) | −0.7 (1.2) | 1.1 (1.8) |
| Mania | | | | | |
| Baseline | 0.6 (0.4) | 1.1 (0.6) | 1.2 (0.6) | 0.0 (0.0) | 0.6 (0.4) |
| Wk 20 | 0.1 (0.1) | 1.6 (1.0) | 1.3 (0.8) | 0.6 (0.3) | 0.9 (0.5) |
| Change | −0.6 (0.4) | 0.5 (1.1) | 0.4 (0.9) | 0.6 (0.3) | 0.1 (0.8) |
| Visuospatial cognition | | | | | |
| No. of trials completed | | | | | |
| Baseline | 6.6 (0.2) | 6.3 (0.2) | 6.0 (0.2) | 6.2 (0.2) | 6.0 (0.4) |
| Wk 20 | 6.5 (0.2) | 6.1 (0.2) | 6.2 (0.2) | 6.4 (0.2) | 7.0 (0.3) |
| Change[a] | −0.2 (0.3) | −0.1 (0.3) | 0.1 (0.3) | 0.3 (0.2) | 1.2 (0.5)[b] |
| No. of correct squares | | | | | |
| Baseline | 26.5 (1.3) | 22.9 (1.9) | 20.9 (1.0) | 24.0 (2.7) | 22.9 (2.9) |
| Wk 20 | 25.1 (1.5) | 25.4 (1.7) | 23.4 (1.7) | 22.5 (2.4) | 26.3 (1.9) |
| Change | −1.4 (1.1) | 2.6 (2.0) | 1.6 (1.8) | −1.3 (1.5) | 4.5 (2.8) |

Data are means (SE). Baseline values refer to baseline scores, wk 20 values refer to scores at wk 20, and change scores refer to baseline scores subtracted from wk 20 scores. By ANOVA, no differences in baseline depression scores ($P = 0.729$), mania scores ($P = 0.444$), number of trials completed on the visuospatial test ($P = 0.250$), or number of correct squares on the visuospatial test ($P = 0.354$) were observed among testosterone treatment groups.

[a] $P = 0.042$ *vs.* 25- and 50-mg groups (by ANOVA).

[b] $P < 0.05$ *vs.* 25- and 50-mg groups (by ANOVA).

erectile dysfunction and low or low-normal testosterone levels reported significant improvements in overall sexual function compared with placebo (9). Our study is the first to evaluate the effects of a wide range of testosterone doses in healthy, older men; our data suggest that testosterone dose-response relationships for several domains of sexual function differ among young and older men. The significant dose-dependent effects of testosterone on sexual function and

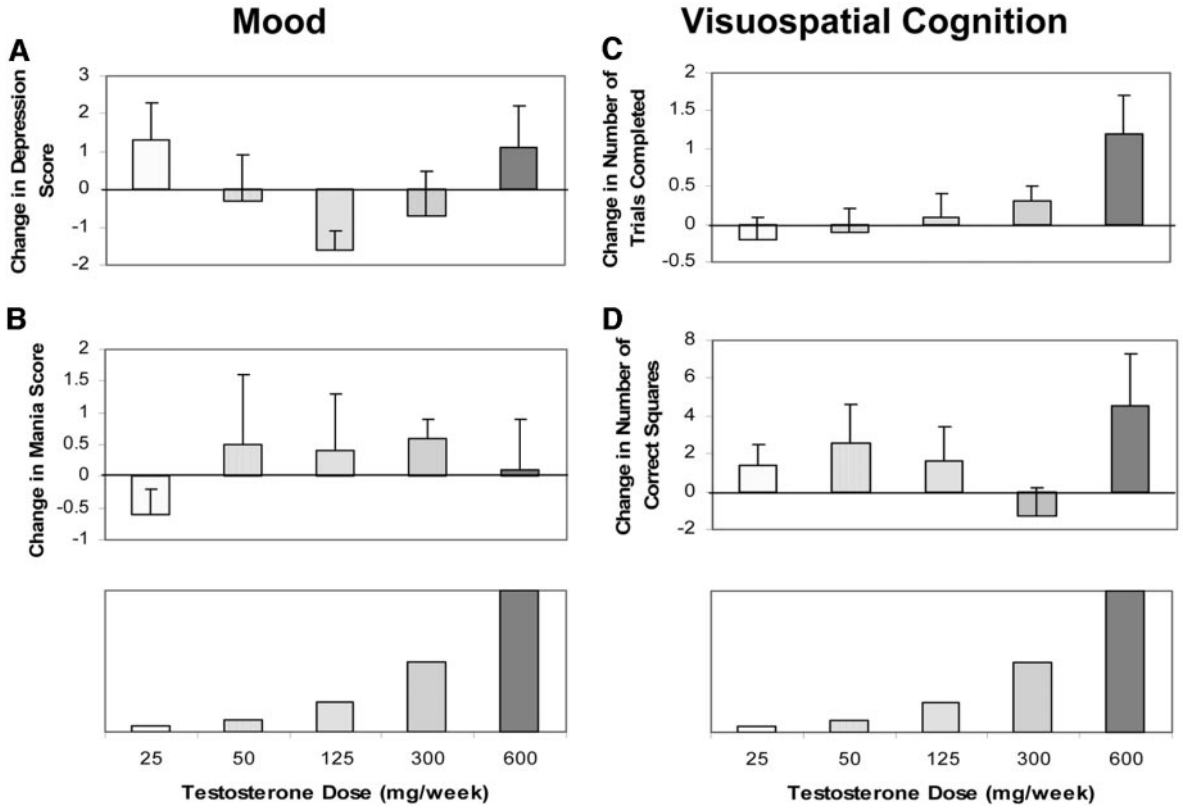


FIG. 4. Changes in depression (A), mania (B), number of visuospatial trials completed (C), and number of squares correctly marked (D). Data are the mean ± SE. Changes in the number of visuospatial trials completed differed significantly by testosterone dose ($P = 0.042$). *Post hoc* analysis of changes in the number of trials completed indicated significant differences between men in the 600- and 25-mg groups ($P < 0.05$). Changes in depression, mania, and number of squares correctly marked did not differ significantly by dose ($P > 0.05$).

visuospatial cognition in this sample of older men contrast with the null findings from an earlier study we conducted in younger men that used the same research design (20). Comparison of the same sexual function subcomponents (our unpublished observations) from that dataset showed no effects of dose on libido, masturbation, intercourse, or erectile function in young men (Bhasin, S., personal observations). This comparison suggests that it may be inappropriate to extrapolate the effects of testosterone in younger men to its effects in older men, or the converse.

The mechanisms of these age-related differences in androgen responsiveness of sexual function in older men are unknown and should be investigated. The right shift in the testosterone dose-response curve in older men might be due to the age-related changes in the sensitivity of central as well as peripheral mechanisms that regulate sexual function. Sexual function in men is a complex, multicomponent system that includes central mechanisms for regulation of sexual desire, spontaneous sexual thoughts, and attentiveness to erotic stimuli. The peripheral processes involved in mediating penile erections include cavernosal smooth muscle relaxation, increased blood flow to the penis, engorgement of corpora cavernosa, and trapping of blood in the corpora cavernosa. Testosterone is well known to regulate central mechanisms involved in sexual desire, fantasies, and attentiveness to erotic stimuli. However, there is growing evidence that testosterone may also induce nitric oxide synthase activity in the cavernosal smooth muscle. Although androgen receptor expression is lower in the penis of older animals compared with young animals, most of this decrease occurs immediately after puberty. We do not know whether the androgen sensitivity of these central or peripheral mechanisms is altered in older men.

These data are consistent with previous findings of the effects of testosterone interventions on sexual function in older men. Earlier studies had shown that older men with low testosterone levels demonstrated increased libido after testosterone replacement. Also consistent with earlier findings, effects were shown more readily on libido than on sexual activity. Thus, our data also show that testosterone supplementation of older men can have positive effects on sexual function.

The finding that one aspect of visuospatial cognition was responsive to testosterone intervention is consistent with previously reported relationships between improved spatial cognition and testosterone supplementation (19), although negative findings have also been found (33, 34). The fact that only the number of trials completed, not the total number of squares correctly marked, varied with testosterone dose suggests that visuospatial cognition may represent a composite of more than one cognitive processes. Our data suggest that testosterone is more closely related to the speed of information processing or responsiveness than with spatial accuracy and is thus consistent with some recent work on the relationships between testosterone and spatial cognition in men (35).

We recognize that sex steroid interventions may have effects on other domains of cognition that were not examined in this study. Although we did not investigate verbal memory in this study, improvement in verbal memory during testosterone supplementation has been found (36). Androgens stimulate neuronal cell growth and survival (37). There is also evidence that androgens may act as neuromodulators. For instance, testosterone stimulates 5-hydroxytryptamine receptors and serotonin transport protein metabolism in various central nervous system regions (38). Testosterone decreases the $\gamma$-aminobutyric acid concentration in the hypothalamus (39) and also regulates neurotransmission. Recent studies using single-photon emission-computed tomography scanning have reported that testosterone administration is associated with increased cerebral perfusion in specific brain regions that are important for memory and cognitive function (40). Thus, testosterone may affect cognitive function through multiple mechanisms. Existing research also suggests that if only hypogonadal men (rather than men with normal serum testosterone levels) were recruited, elevations in positive mood and decreases in depression would have been more likely to emerge (41). It has also been suggested that many of the cognitive and behavioral effects of testosterone may be mediated through aromatization of testosterone to estrogen. In our data, partial correlations that controlled for log free testosterone levels during treatment did not show significant relationships between log estradiol levels and any of the sexual function and cognitive outcomes investigated in this study.

This study is subject to several limitations. The small sample size results in relatively low statistical power. Also, the questionnaire-based measurement of sexual function relied on the subjects' compliance in completing the questionnaires (resulting in some subjects, who did not turn in tests, being lost in analyses) as well as subjective assessment of their own sexual function. Inaccurate responses cannot be entirely avoided, and psychologists have identified the problems of assuming that self-reported measures of motivation (*e.g.* libido) are accurate. Nonetheless, the reduction in intercourse, masturbation, and other components of sexual function among the older men in this study (compared with the younger men in our other study) is consistent with age-related declines in male sexuality and suggests that the questionnaire has face validity. Furthermore, this was a physiological experiment designed to test specific hypotheses; the high testosterone doses used in this study are unlikely to be used in clinical practice because of the potential for adverse effects. However, the development of selective androgen receptor modulators that are free of the dose-limiting adverse effects of testosterone may allow clinical translation of these experimental findings.

In summary, the data reported here show that testosterone supplementation in older men can dose-dependently improve some components of sexual function, namely, libido and erectile function, as well as one aspect of visuospatial cognition. These behavioral outcomes respond differently to graded doses of testosterone in older men compared with younger men.

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