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Effects of testosterone administration on cognitive function in hysterectomized women with low testosterone levels: a dose–response randomized trial

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Abstract

Purpose—To determine the dose-dependent effects of testosterone administration on cognition in women with low testosterone levels.

Methods—71 hysterectomized women with or without oophorectomy with total testosterone <31 ng/dl and/or free testosterone <3.5 pg/ml received a standardized transdermal estradiol regimen during the 12-week run-in period and were then randomized to receive weekly intramuscular injections of placebo, 3, 6.25, 12.5, or 25 mg testosterone enanthate for 24 weeks. Total testosterone was measured in serum by LC–MS/MS, and free testosterone levels were measured by equilibrium dialysis. Cognitive function was evaluated using a comprehensive battery of standardized neuropsychological tests at baseline and 24 weeks.

Results—46 women who had baseline and end-of-treatment cognitive function data constituted the analytic sample. The five groups were similar at baseline. Mean on-treatment nadir total testosterone concentrations were 15, 89, 98, 134, and 234 ng/dl in the placebo, 3, 6.25, 12.5, and 25 mg groups, respectively. No significant changes in spatial ability, verbal fluency, verbal memory, or executive function were observed in any treatment arm compared to placebo even after adjustment for baseline cognitive function, age, and education. Multiple regression analysis did not show any significant relation between changes in testosterone concentrations and change in cognitive function scores.

Conclusion—Short-term testosterone administration over a wide range of doses for 24 weeks in women with low testosterone levels was neither associated with improvements nor worsening of cognitive function.

Keywords

Testosterone; Menopause; Cognition; Androgen deficiency

Introduction

There has been an increasing interest in the use of testosterone therapy to improve sexual function and body composition in postmenopausal women. Although testosterone administration has been reported to improve some domains of sexual function and body

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composition in menopausal women as well as women with antidepressant-induced sexual dysfunction [1–3], the effects of testosterone therapy on cognitive function remain unclear.

Brain is an important target for the action of gonadal hormones as it expresses receptors for both estrogen and testosterone, particularly in regions responsible for memory and higher cognitive function, such as hippocampus. Indeed, observations that men tend to perform better in visuospatial tasks and that women have better verbal memory suggest that sex hormones exert sexually dimorphic effects on different domains of cognition [4]. Several observational studies suggest that estrogen is associated with better cognitive performance in healthy postmenopausal women [5]. However, data from controlled trials of estrogen replacement have not shown benefit [6]; some trials have even reported detrimental effects of estrogen replacement on cognition [7, 8].

Recently, research has focused on evaluating the role of androgens on cognitive function in postmenopausal women. Testosterone is aromatized to estradiol, both in the periphery and in the brain. In addition to its direct effects via the androgen receptor, some effects of testosterone administration might be mediated via its aromatization to estradiol [9]. However, the data on the relation of circulating androgen concentrations and cognitive function are inconsistent across studies. In women with polycystic ovary syndrome (PCOS), higher endogenous serum testosterone levels are associated positively with visuospatial memory and negatively with verbal fluency and verbal memory [10, 11]. Similar findings have been noted in healthy pre- and postmenopausal women [12, 13]. However, these findings have not been confirmed by other studies [14, 15]. Furthermore, only a few studies have prospectively examined the effect of exogenous testosterone administration on cognitive performance in the setting of controlled randomized trials [16].

Recently, we demonstrated that short-term (24-weeks) testosterone administration over a wide range of doses (physiologic and supraphysiologic) to hysterectomized women with low testosterone levels improved several domains of sexual function, body composition, and muscle performance with few androgenic adverse effects [17]. Furthermore, there was no worsening of serum cardiovascular risk markers [18]. However, it remains unknown whether the administration of testosterone over a wide range of doses impacts cognitive function. Hence, we investigated the dose–response relation of testosterone administration, across multiple domains of cognitive function in hysterectomized women with low testosterone levels.

Methods

Study design

The Testosterone Dose response in Surgically Menopausal Women (TDSM) trial was a two-center, parallel group, placebo-controlled, double-blind, randomized trial designed to determine the dose–response effects of testosterone on a range of androgen-dependent outcomes [17]. The trial consisted of a 12-week run-in period of transdermal estradiol administration, a 24-week treatment period, and a 16-week recovery period. The study was approved by the institutional review boards of Boston University Medical Center (BUMC)

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and Charles Drew University of Medicine and Science (Los Angeles, CA, USA), and all participants provided written informed consent.

Subjects

Healthy women aged 41–62 years without cognitive impairment who had undergone hysterectomy with or without partial or total oophorectomy were recruited. The participants had serum total testosterone concentrations <31 ng/dl or free testosterone concentrations <3.5 pg/ml (less than the median for healthy young women [17]). We included women who had hysterectomy alone or partial oophorectomy if their FSH levels were ≥30 U/l or if they were already receiving estrogen therapy. We excluded women diagnosed with major psychoses or bipolar disorders in the past year and depression in the previous 3 months, and dementia as assessed by the mini-mental status examination. Women with a history of breast, ovarian, endometrial, or cervical cancer, hyperandrogenic disorders, cardiac disease or thromboembolic disorders, and those taking glucocorticoids, androgens, spironolactone, and GnRH agonists were also excluded. Women were required to have a normal Pap smear and mammogram within the last 12 months.

Study interventions and randomization

All eligible women were administered a transdermal estradiol (E2) patch applied twice a week and designed to achieve nominal delivery of 50-μg estradiol daily (Alora, Watson Pharmaceuticals) for a 12-week run-in phase. After run-in, the subjects were randomized in a double-blinded fashion to one of five groups to receive weekly IM injections of placebo, 3, 6.25, 12.5, or 25 mg testosterone enanthate for 24 weeks.

Hormone assays

Serum total testosterone levels were measured by liquid chromatography-tandem mass spectrometry (LC–MS/MS) with a sensitivity of 2 ng/dl, free testosterone was measured using equilibrium dialysis with a sensitivity of 0.3 pg/ml, and sex hormone-binding globulin levels were measured using an immunofluorometric assay with a sensitivity of 0.5 nmol/l [17].

Assessment of cognition

The University of Wisconsin (UW) oversaw staff training, data collection, and quality control. All participants were tested by the same psychometrician. Cognitive function was evaluated using a comprehensive battery of standardized neuropsychological tests which included measures of visuospatial ability (Puget Sound Route Learning and Complex Figure tests), verbal memory (Paragraph Recall and Buschke Selective Reminding Test), verbal fluency (Phonemic and Category Fluency) attention, and executive function (Visual Spatial Learning Test, Letter–Number Sequencing, Stroop Color-Word Interference Test, and Trail Making Test B and Mazes). Cognitive test procedures are discussed in detail in the supplementary appendix.

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Statistical considerations

The analytic sample consisted of subjects who had baseline and follow-up data on efficacy outcomes. Mean change in outcomes was compared across treatment doses by linear regression incorporating adjustment for baseline cognitive test scores, age, and education. Differences in the responses at each dose category were estimated using treatment contrasts and 95 % confidence intervals. Evidence in favor of an overall dose effect was assessed using a Wald-type (F) significance test of the hypothesis that all groups had equal mean response adjusting for baseline age, level of education, and baseline level of the relevant cognitive function measure. Multiple linear regression analyses were performed to test the association between mean changes in cognitive function scores and changes in serum testosterone concentrations, likewise adjusted for these covariates. Analyses were conducted using R version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria). While cognitive function was not the primary endpoint of the TDSM trial, analyses described here were sufficiently powered to detect overall effect sizes [19], quantifying overall between-group differences, of 0.52 with 80 % probability.

Results

Flow of participants

Of the 850 women who underwent telephone screening, 218 met eligibility criteria, 85 entered the estrogen run-in-period, 71 were randomized, and 46 who had baseline and end-of-treatment cognitive function data constituted the analytic sample [placebo (n = 8), 3 mg (n = 9), 6.25 mg (n = 10), 12.5 mg (n = 10), or 25 mg (n = 9)].

Baseline characteristics

Baseline characteristics across the five treatment groups are displayed in Table 1. Mean age of women in the analytic sample was 53 years and average BMI 29.7 kg/m^2. Participants across the dose groups were comparable in terms of age, race, depression history, mini-mental status exam scores, and BMI. The majority of women had received higher education (defined as having at least a university- or college-level degree). 74 % of the women had undergone bilateral oophorectomy.

Hormone levels

Baseline mean total and free testosterone concentrations were 13.1 ng/dl and 1.1 pg/ml, respectively, well below the range for healthy, menstruating women [17]. Serum nadir total and free testosterone levels, measured during week 24, increased from baseline in a dose-dependent fashion. Mean on-treatment nadir total testosterone concentrations were 15, 89, 98, 134, and 234 ng/dl, and mean free testosterone concentrations were 2.7, 14, 15, 24, and 44 pg/ml at the 0, 3, 6.25, 12.5, and 25 mg doses, respectively.

Cognitive function

The participants in different groups were similar at baseline in their performance on various tests of cognition (Table 1). There were no significant dose-dependent changes in the measures of spatial ability, verbal memory, verbal fluency or attention, and executive

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function from baseline to end of treatment after adjusting for baseline scores, age, and education (dose effect, all *p* values >0.05; Table 2). We also compared individual active doses to placebo using ANCOVA adjusting for these same covariates and found no significant differences (*p* value >0.05 for all comparisons; Supplementary Table 1). The changes in cognitive test scores from baseline in any of the domains tested were not significantly related to changes in total or free testosterone concentrations after adjusting for baseline scores, age, and education (all *p* values >0.05; Supplementary Table 2).

Discussion

In this trial of hysterectomized women with low testosterone levels, short-term testosterone administration over a wide range of doses was not associated with significant changes in cognitive function. Data from epidemiologic studies in specific patient populations have suggested that serum testosterone levels in women influence specific aspects of cognition. For example, women with PCOS perform better on spatial tasks and worse on verbal tasks compared to controls [10, 11]. Similarly, endogenous testosterone levels during the menstrual cycle are positively correlated with visuospatial ability and negatively with verbal fluency in healthy women [12, 20]. In female-to-male transsexuals, administration of supraphysiologic doses of testosterone worsens verbal fluency and improves spatial skills [20]. Contrary to these studies, our 24-week dose–response study did not show improvement or worsening of cognitive performance in a number of domains of cognitive function (spatial reasoning, verbal memory, verbal fluency, and executive function) over a wide range of testosterone doses and concentrations, including doses that achieved supraphysiologic serum testosterone concentrations.

The effects of testosterone administration on cognitive performance in postmenopausal women have not been extensively studied in the setting of clinical trials. In a study of surgically menopausal women, the addition of testosterone to estrogen replacement had a negative effect on immediate verbal memory compared with estrogen replacement alone [22]. These findings stand in contrast to those observed in women with hypopituitarism where no changes in cognitive function were observed during administration of transdermal testosterone for 12 months [23]. Although androgen effects on cognitive function are domain specific, previous trials of androgen replacement have evaluated only a limited number of cognitive domains. Furthermore, most trials have only used a single dose of testosterone, and therefore the dose-dependent effects of testosterone on cognition have not been previously demonstrated.

Our study has notable strengths and some limitations. The trial had many features of a good trial design: concealed randomization, placebo control, blinding, and oversight by an independent DSMB. Total and free testosterone levels were measured using LC–MS/MS and equilibrium dialysis, respectively; both widely considered the reference methods with the highest sensitivity and specificity. Unlike other studies, we characterized a comprehensive range of cognitive functions using well-validated neuropsychological tests with emphasis on domains reported to be affected by testosterone. However, measurement of cognitive function was not the primary outcome of the trial, and the trial was not designed to detect a difference in changes in cognitive measures. Our analysis was therefore limited

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by small sample size that may have had insufficient power to detect small effects. The 6-month duration of intervention may not have been long enough to demonstrate a significant change in cognitive function. Based on previous trials of hormone replacement and cognition [6], we would expect that the trial duration would be adequate to detect an effect of testosterone on cognition. As some trials have reported adverse effects of estrogen replacement on cognition, it is possible that positive effects of testosterone administration on cognition may have been attenuated with concurrent estrogen therapy. Finally, the women in our study were not recruited for impairments in cognition; hence, it is conceivable that testosterone replacement might be beneficial in women with baseline cognitive deficits. Although we excluded women with psychiatric disorders by self-report and review of their medical history, future trials should incorporate standardized assessments for mental health to ensure exclusion based on this potential confounding factor.

In conclusion, testosterone administration over a wide range of doses for 24 weeks in hysterectomized women with low testosterone levels was not associated with either beneficial or harmful effects on cognitive function. Long-term, adequately powered trials are needed to evaluate the cognitive effects of testosterone therapy in women. Based on the findings of our trial, short-term use of testosterone could be considered in select populations of women with low testosterone levels to improve sexual function and body composition without the concern of worsening cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic and cognitive characteristics by treatment group (n = 46)

Dose of testosterone enanthate (mg/week)	**Placebo (n = 8)**	**3 (n = 9)**	**6.25 (n = 10)**	**12.5 (n = 10)**	**25 (n = 9)**
Demographics					
Age (year)	54 ± 5	55 ± 4	52 ± 5	52 ± 6	54 ± 3
Race *n* (%)					
Black	5 (63)	6 (67)	5 (50)	3 (30)	3 (33)
White	3 (38)	3 (33)	3 (30)	4 (40)	5 (56)
Other	0 (0)	0 (0)	2 (20)	3 (30)	1 (11)
Higher education (proportion having at least college level)	0.75	0.43	0.67	0.71	0.86
Mini-mental examination (score out of 30)	27	29	29.2	28.3	29.6
History of depression (self-report) *n*	4	2	2	3	3
BMI (kg/m^2)	33 ± 4	31 ± 6	28 ± 6	30 ± 5	33 ± 4
Hysterectomy alone *n* (%)	3	2	0	1	4
Partial oophorectomy *n* (%)	1	1	0	0	0
Bilateral oophorectomy *n* (%)	4	6	10	9	9
Baseline blood levels					
Total testosterone (ng/dl)					
Screening	9.3 ± 4	13 ± 9	20 ± 17	11 ± 7	15 ± 8
Post-estrogen run-in	16 ± 10	13 ± 5	14 ± 14	10 ± 6	17 ± 9
Free testosterone (pg/ml)					
Screening	1.0 ± 0.5	1.0 ± 0.9	1.1 ± 1.3	1.0 ± 0.6	1.0 ± 0.7
Post-estrogen run-in	2.8 ± 2.0	2.1 ± 0.7	2.2 ± 2.8	1.8 ± 0.9	2.3 ± 1.1
SHBG (nmol/l)	68 ± 27	71 ± 33	58 ± 23	56 ± 26	93 ± 41
Baseline cognitive function scores					
Spatial ability tests					
Route learning test (immediate)	0.38 ± 0.17 (7)	0.42 ± 0.07 (7)	0.56 ± 0.08 (8)	0.40 ± 0.13 (7)	0.33 ± 0.16 (9)
Route learning test (delayed)	0.39 ± 0.15 (7)	0.50 ± 0.10 (7)	0.53 ± 0.18 (8)	0.52 ± 0.18 (7)	0.39 ± 0.21 (9)
Complex figure (immediate)	0.73 ± 0.11 (8)	0.62 ± 0.12 (8)	0.61 ± 0.16 (9)	0.60 ± 0.10 (10)	0.58 ± 0.23 (8)
Complex figure (delayed)	0.63 ± 0.10 (8)	0.58 ± 0.16 (8)	0.56 ± 0.13 (9)	0.56 ± 0.12 (10)	0.45 ± 0.30 (8)
Verbal memory tests					

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Dose of testosterone enanthate (mg/week)	Placebo (*n* = 8)	3 (*n* = 9)	6.25 (*n* = 10)	12.5 (*n* = 10)	25 (*n* = 9)
Paragraph (immediate)	0.52 ± 0.20 (8)	0.39 ± 0.12 (8)	0.36 ± 0.19 (9)	0.31 ± 0.12 (10)	0.40 ± 0.18 (9)
Paragraph (delayed)	0.42 ± 0.19 (8)	0.26 ± 0.11 (8)	0.28 ± 0.19 (9)	0.27 ± 0.16 (10)	0.31 ± 0.18 (9)
Buschke (immediate: total correct)	0.79 ± 0.06 (8)	0.64 ± 0.11 (9)	0.66 ± 0.19 (9)	0.66 ± 0.14 (10)	0.74 ± 0.16 (9)
Buschke (delayed: total correct-free)	0.89 ± 0.09 (7)	0.66 ± 0.30 (9)	0.73 ± 0.25 (9)	0.71 ± 0.18 (10)	0.76 ± 0.23 (9)
Verbal fluency tests					
Verbal fluency (I)	8.6 ± 3.5 (8)	6.6 ± 4.0 (8)	7.8 ± 3.1 (9)	5.6 ± 3.8 (10)	10.9 ± 5.1 (9)
Verbal fluency (K)	5.9 ± 2.0 (8)	4.9 ± 3.1 (8)	5.8 ± 3.1 (9)	5.3 ± 2.7 (10)	6.8 ± 3.2 (9)
Verbal fluency (P)	13 ± 2.7 (8)	13 ± 6.2 (8)	13 ± 6.4 (9)	11.5 ± 5.1 (10)	16 ± 4.6 (9)
Categorical fluency	21 ± 5.5 (8)	18 ± 6.7 (8)	15 ± 5.7 (9)	18 ± 4.9 (10)	21 ± 6.4 (9)
Attention and executive function tests					
VSLT I (immediate)	4.0 ± 1.6 (8)	2.6 ± 1.1 (9)	3.8 ± 1.8 (9)	3.2 ± 1.7 (10)	3.8 ± 2.6 (9)
VSLT II (delayed)	4.5 ± 2.5 (8)	4.3 ± 2.1 (9)	5.2 ± 2.2 (9)	4.3 ± 2.1 (10)	4.3 ± 2.8 (9)
Letter–number sequencing	0.45 ± 0.14 (8)	0.39 ± 0.15 (8)	0.47 ± 0.09 (9)	0.44 ± 0.08 (10)	0.43 ± 0.20 (9)
Stroop interference test	59 ± 20 (8)	64 ± 18 (9)	55 ± 9.1 (10)	53 ± 5.0 (10)	57 ± 22 (9)
Trails B	108 ± 63 (7)	141 ± 86 (8)	118 ± 42 (7)	102 ± 48 (10)	108 ± 87 (8)
Mazes	102 ± 23 (6)	184 ± 134 (8)	177 ± 88 (9)	131 ± 98 (10)	144 ± 75 (9)

Data represent mean ± SD or *n* (%)

Route learning score reflects baseline score out of 16 possible correct items

Complex figure score reflects baseline score out of 9 possible correct items

Paragraph recall score reflects baseline score out of 44 possible correct items

Buschke immediate and delay scores reflect baseline score out of 60 and 12 possible correct items, respectively

Letter–number sequencing score reflects baseline score out of 21 possible correct items

BMI body mass index, *SHBG* sex hormone-binding globulin, *VSLT* visual spatial learning test

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Table 2

Change in cognitive function test scores by treatment group

	Dose of testosterone enanthate (mg/week)					
Cognitive test	**Placebo**	**3 mg**	**6.25 mg**	**12.5 mg**	**25 mg**	**Dose effect *p* value**
Visual spatial tests						
Route learning test (immediate)	0.03 ± 0.23	0.07 ± 0.19	0.06 ± 0.22	−0.006 ± 0.16	0.10 ± 0.25	0.66
Route learning test (delayed)	0.08 ± 0.28	−0.07 ± 0.25	0.15 ± 0.26	−0.05 ± 0.21	0.03 ± 0.26	0.51
Complex figure (immediate)	−0.04 ± 0.12	0.07 ± 0.16	0.11 ± 0.11	0.06 ± 0.10	0.06 ± 0.10	0.34
Complex figure (delayed)	0.04 ± 0.18	0.08 ± 0.14	0.11 ± 0.10	0.11 ± 0.12	0.19 ± 0.21	0.72
Verbal memory tests						
Paragraph (immediate)	0.001 ± 0.100	0.03 ± 0.08	0.04 ± 0.06	0.07 ± 0.09	0.04 ± 0.17	0.99
Paragraph (delayed)	0.07 ± 0.10	0.08 ± 0.10	0.13 ± 0.08	0.03 ± 0.19	0.09 ± 0.13	0.30
Buschke (immediate: total correct)	0.08 ± 0.10	0.17 ± 0.10	0.02 ± 0.07	0.18 ± 0.15	0.06 ± 0.04	0.21
Buschke (delayed: total correct)	0.06 ± 0.09	0.20 ± 0.28	0.08 ± 0.12	0.17 ± 0.22	0.01 ± 0.11	0.87
Verbal ability/language tests						
Verbal fluency (I)	1.4 ± 6.1	0.33 ± 2.25	1.2 ± 4.4	0.14 ± 3.0	0.00 ± 2.2	0.96
Verbal fluency (K)	2.1 ± 5.1	−0.83 ± 2.32	0.20 ± 4.7	0.86 ± 3.5	−1.4 ± 3.3	0.43
Verbal fluency (P)	2.1 ± 2.7	−0.67 ± 1.37	0.80 ± 6.4	−0.14 ± 4.3	−1.3 ± 4.5	0.68
Category fluency	1.00 ± 8.4	2.5 ± 2.8	2.6 ± 1.9	1.3 ± 4.0	−2.7 ± 4.9	0.78
Attention and executive function tests						
VSLT (immediate)	1.2 ± 1.3	2.3 ± 1.4	0.24 ± 1.4	1.8 ± 1.9	0.63 ± 1.1	0.24
VSLT (delayed)	1.5 ± 2.4	−0.14 ± 1.8	0.00 ± 0.71	1.3 ± 2.1	0.43 ± 0.79	0.40
Letter–number sequencing	0.06 ± 0.10	−0.02 ± 0.09	0.01 ± 0.08	−0.03 ± 0.09	0.007 ± 0.06	0.18
Stroop interference test	−9.4 ± 11.1	−7.9 ± 13.5	−3.3 ± 8.9	−6.9 ± 7.0	−3.9 ± 9.3	0.92
Trails B (s)	−4.0 ± 53.4	−17 ± 41	−28 ± 12	−22 ± 19	14 ± 30	0.44
Mazes (s)	23 ± 63	−41 ± 127	29 ± 60	2.0 ± 14.2	−13 ± 85	0.27

Data represent mean ± SD of the change in cognitive test scores from baseline by dose group

The *p* value displayed represents the significance level of the overall dose effect after adjustment for baseline scores, age, and education

Route learning score reflects change from baseline score out of 16 possible correct items

Complex figure score reflects change from baseline score out of 9 possible correct items

Paragraph recall score reflects change from baseline score out of 44 possible correct items

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Buschke immediate and delay scores reflect change from baseline score out of 60 and 12 possible correct items, respectively

Letter–number sequencing score reflects change from baseline score out of 21 possible correct items

VSLT visual spatial learning test