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Effects of Testosterone on Cognition and Mood in Male Patients With Mild Alzheimer Disease and Healthy Elderly Men

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Background: There is a compelling need for therapies that prevent, defer the onset, slow the progression, or improve the symptoms of Alzheimer disease (AD).

Objective: To evaluate the effects of testosterone therapy on cognition, neuropsychiatric symptoms, and quality of life in male patients with mild AD and healthy elderly men.

Design: Twenty-four–week, randomized, double-blind, placebo-controlled, parallel-group study.

Setting: Memory disorders clinics as well as general neurology and medicine clinics from University of California medical centers at Los Angeles, San Francisco, and Irvine.

Patients or Other Participants: Sixteen male patients with AD and 22 healthy male control subjects. Healthy elderly control men were recruited from the community through advertisements as well as through the university-based clinics.

Intervention: Testosterone and placebo, in the form of hydroalcoholic gel (75 mg), were applied daily to the skin of the participants.

Main Outcome Measures: Instruments assessing cognitive functioning (Alzheimer's Disease Assessment Scale–Cognitive Subscale, California Verbal Learning Test, Block Design Subtest, Judgment of Line Orientation, Developmental Test of Visual-Motor Integration), neuropsychiatric symptoms (Neuropsychiatric Inventory), global functioning (Clinician's Interview-Based Impression of Change), and quality of life (Quality of Life–Alzheimer Disease Scale).

Results: For the patients with AD, the testosterone-treated group had significantly greater improvements in the scores on the caregiver version of the quality-of-life scale ($P=.01$). No significant treatment group differences were detected in the cognitive scores at end of study, although numerically greater improvement or less decline on measures of visuospatial functions was demonstrated with testosterone treatment compared with placebo. In the healthy control group, a nonsignificant trend toward greater improvement in self-rated quality of life was observed in the testosterone-treated group ($P=.09$) compared with placebo treatment. No difference between the treatment groups was detected in the remaining outcome measures. Testosterone treatment was well tolerated with few adverse effects relative to placebo.

Conclusions: Results suggest that testosterone replacement therapy improved overall quality of life in patients with AD. Testosterone had minimal effects on cognition.

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THERE IS A COMPELLING need for therapies that prevent, defer the onset, slow the progression, or improve the symptoms of Alzheimer disease (AD). Hormonal therapies for AD have been the focus of research attention in recent years. Estrogen-replacement therapy has been shown to have cognitive benefits in healthy elderly women.[1-3] Several epidemiological studies provide evidence that estrogen-replacement therapy, when given alone, decreases the risk and delays the onset of AD in postmenopausal women.[4-9] Despite the apparent cognitive benefits reported in several observational trials, the Women's Health Initiative Memory Study recently concluded that postmenopausal women receiving

estrogen-replacement therapy, either a combined estrogen/progesterone preparation or estrogen alone, showed evidence of deleterious cognitive effects and were more likely to develop dementia.[10-12] Furthermore, 3 controlled clinical trials of estrogen therapy in women with AD uniformly found a lack of benefit in delaying disease progression.[13-15]

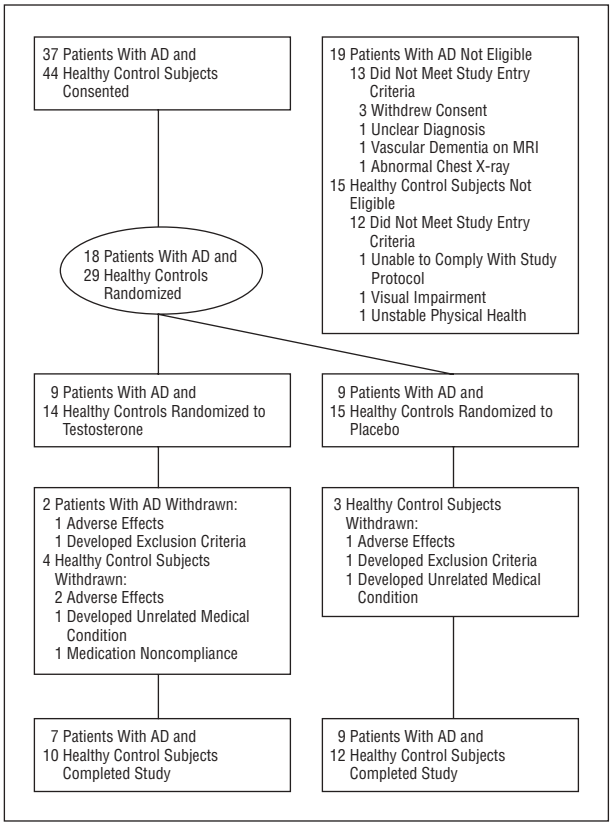

Figure 1. Study flow diagram showing number of patients and subject disposition through the course of study. AD indicates Alzheimer disease; MRI, magnetic resonance image.

In the male brain, testosterone is converted to estrogen by aromatase enzymes; therefore, testosterone can exert its effects on cognition independently or indirectly via conversion to estrogen. Several studies have reported positive associations between testosterone level and spatial cognitive function and memory for verbal and visual stimuli in older men.[16-21] In small, placebo-controlled clinical trials of relatively short duration (1 to 12 months), testosterone supplementation was reported to improve spatial cognition[22-24] and working memory.[25,26]

Male aging is associated with a gradual, progressive decline in serum levels of total testosterone, bioavailable testosterone, and free testosterone.[27] The gradual decline in testosterone level is associated with decreased muscle mass and strength, osteoporosis, decreased libido, mood alterations, and changes in cognition,[28] conditions that may be reversed with testosterone replacement.[29,30] The age-related decline in testosterone is potentially relevant to AD. Moffat et al[31] reported significantly lower free testosterone concentrations in middle-aged and elderly men who developed AD; Hogervorst et al[32] suggested that low total serum testosterone may be a comorbid feature of AD in men. In laboratory models, testosterone reduces formation of β-amyloid from the amyloid precursor protein[33] and decreases hyperphosphorylation of tau protein.[34]

We report the results of a randomized, double-blind, placebo-controlled trial investigating the effects of testosterone treatment on cognition and mood in male patients with mild AD and age-matched healthy control men. We hypothesized that testosterone therapy would yield benefits in cognition, mood, and quality of life.

METHODS

STUDY DESIGN AND SUBJECTS

The study had a 24-week, double-blind, placebo-controlled, randomized, parallel-group design. Male participants with AD were recruited from memory disorders clinics and general neurology and medicine clinics from University of California campuses at Los Angeles, San Francisco, and Irvine. Healthy elderly control men were recruited through advertisements and university-based clinics. Hormone measurements for all sites were performed at Harbor-UCLA Medical Center, Torrance, Calif. Written informed consent, approved by the institutional review board at each participating institution, was obtained from each subject or legally authorized representative. Complete medical and psychiatric history was taken, and subjects underwent a physical examination (including prostate examination and urinary flow study), a complete neurological examination, laboratory evaluation (complete blood cell count, blood chemistry, lipid profile, and prostate-specific antigen and hormone levels), and cognitive screening for determination of eligibility.

All subjects with AD met the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) for probable AD[35] and had a caregiver informant who was available to monitor and administer medication and accompany the subject to clinical visits. In addition, subjects with AD scored 15 or above on the Mini-Mental State Examination,[36] indicating a mild to moderate stage of disease. The healthy control subjects did not meet criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[37] for dementia and scored 0 (normal) on the Clinical Dementia Rating Scale.[38] All subjects were aged 50 years or older, demonstrated sufficient English to be able to perform cognitive testing, and were stable on concomitant medications for 1 month prior to starting the study medication.

Subjects were excluded from the study if they had current or recent history of major psychiatric illness, non-AD neurological illness, or significant uncontrolled systemic illness; history of alcoholism or substance abuse within the past year; history of taking other drugs that might interfere with the results of the study (ie, antiandrogen, estrogens, p450 enzyme inducers, barbiturates); known history of prostate cancer; abnormal prostate evidenced by prostatic symptoms, prostatic masses or induration on rectal examination, elevated levels of prostate specific antigen (>4 mg/mL), a urine flow rate of less than 8 mL/s, or an International Prostate Symptom Score greater than 25; serum testosterone levels greater than 600 ng/dL; hematocrit greater than 50%; greater than 140% or less than 80% of their ideal body weight based on Metropolitan Life Insurance tables; generalized skin disease that could affect the absorption of T-gel (ie, psoriasis) or known skin intolerance to alcohol; or morning prolactin level greater than 40 mg/mL. The flow of subjects through the study and completion rate is shown in **Figure 1**.

PROCEDURES AND TREATMENT

Subjects who met the entry criteria were randomized to either the testosterone or placebo group. Testosterone was provided in the form of 1% hydroalcoholic dermal gel (T-gel; Laboratoires Besins-Iscovesco, Paris, France) for daily application to the skin. Subjects randomized to the testosterone treatment group were instructed to apply 75 mg of T-gel (3 packets of 25

mg) to 3 different sites each morning after showering or bathing (75 mg total dose). The placebo group performed an identical application of the placebo gel to the same 3 sites. The treatment trial was 24 weeks in duration; subjects returned on weeks 4 and 12 for monitoring of any treatment adverse effects or occurrence of any intercurrent illness, review of current medication list, and neuropsychological testing. A telephone interview was conducted at week 18 to monitor any adverse effects of treatment. The T-gel and placebo gel packets were returned at each visit; unused medication was tabulated to ensure compliance. Neuropsychiatric outcome measures were administered at baseline, prior to randomization, and repeated at weeks 4 and 12 and at end of study. Cognitive measures were administered at baseline and at end of study.

OUTCOME MEASURES

Cognition

The Alzheimer's Disease Assessment Scale–Cognitive Subscale[39] was used to quantify global cognitive functioning across study visits. In addition, the California Verbal Learning Test[40] was administered to assess short-term retention of verbal information; the number of words recalled after a 20-minute delay was the variable of interest. Visuospatial functions were assessed using the Block Design Subtest of the Wechsler Adult Intelligence Scale-Revised,[41] which measures visual perception and spatial construction; Judgment of Line Orientation (JOLO),[42] which examines visual recognition and perception of angular relationships; and the Developmental Test of Visual-Motor Integration (VMI),[43] a constructional task that integrates perceptual activity with motor response.

Neuropsychiatric Symptoms

The Neuropsychiatric Inventory (NPI)[44] provides a multidimensional profile of the behavioral disturbances occurring in patients with dementia based on responses from an informed caregiver. The symptoms assessed by this scale include delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep, and appetite. The Beck Depression Inventory[45] is a 21-item self-administered measure of depressive symptoms that determines the presence and intensity of depression.

Global Assessment and Quality of Life

The Clinician's Interview-Based Impression of Change[46] systematically evaluates cognition and behavior to assess the severity of illness at baseline (scored on a 7-point scale with 1 being "not at all ill" and 7 being "among the most extremely ill patients") and global change from baseline (also scored on a 7-point scale, ranging from 1 ["markedly improved"] to 7 ["markedly worse"]). The Quality of Life–Alzheimer Disease (QOL-AD)[47] scale is a 13-item questionnaire covering the domains of physical health, energy, mood, living situation, memory, family, marriage, friends, chores, fun, money, self, and life as a whole. The items are scored on a 4-point Likert scale, ranging from 1 (poor) to 4 (excellent). The scale obtains separate ratings of the patient's quality of life from the patient and the caregiver.

Hormone Assays

The serum testosterone (T) concentration used for screening was measured at each center's clinical laboratory; all subsequent hormone assays were performed at the Endocrine Research Laboratory of the Harbor-UCLA Medical Center. The procedure has been previously described in detail[48] so will only be summarized here. Serum T, dihydrotestosterone (DHT), and estradiol (E_2) were measured by specific radioimmunoassays. Free T was measured by a radioimmunoassay of the dialysate after an overnight equilibrium dialysis using the same radioimmunoassay reagents as in the T assay. Serum follicle-stimulating hormone and luteinizing hormone were measured by highly sensitive and specific fluoroimmunometric assays with reagents provided by Delfia (Wallac, Inc, Gaithersburg, Md).[48]

ADVERSE EFFECTS

Adverse events were reported and recorded at each follow-up contact. In addition, we used the Overt Aggression Scale,[49] a modified version of the Change in Sexual Functioning Questionnaire,[50] and the agitation/aggression subscale from the NPI to monitor adverse effects.

DATA ANALYSES

Data analyses were performed using an analysis of covariance. Treatment groups were the independent variables, and the outcome measures were the dependent variables with baseline scores treated as covariates. Paired-sample *t* tests were conducted to evaluate the significance of within-group change between baseline and end of study. The analyses were performed on subjects who completed the trial. As a check for effects of excluding cases that did not complete the study, we performed intent-to-treat analyses with last observation carried forward, including all cases who were randomized and had at least 1 post-baseline assessment. These results did not differ meaningfully from the primary analyses with subjects who completed the study and are therefore not reported. Although the statistical results are based on covariance analyses adjusting for baseline, the adjusted means were very close to the raw means in all cases. Because raw means and standard deviations are easier to interpret, they are reported in result tables.

RESULTS

BASELINE COMPARISONS OF TESTOSTERONE- AND PLACEBO-TREATED GROUPS

Table 1 and **Table 2** compare the treatment groups on baseline measures for AD and healthy control men, respectively. With the exception of a chance significant finding in education level, with the testosterone-AD group averaging more years of education, the 2 AD treatment groups did not differ on any of the cognitive, mood, behavioral, quality-of-life, and hormone measures at baseline. For the control group, no significant differences in demographic and outcome variables were observed between treatment groups. At baseline, 5 (28%) of 18 subjects with AD and 6 (21%) of 29 healthy control subjects were identified as hypogonadal (T levels below 298 ng/dL).[48]

OUTCOME COMPARISONS OF THE TESTOSTERONE- AND PLACEBO-TREATED GROUPS

Sixteen patients with AD and 22 healthy control men completed the study. Mean scores of the study vari-

Table 1. Comparison of Testosterone- and Placebo-Treated Groups on Demographic Characteristics, Outcome Measures, and Hormone Levels for Male Patients With Alzheimer Disease at Baseline

Characteristic or Measure	Testosterone (n = 9), Mean (SD)	Placebo (n = 9), Mean (SD)
Demographic		
Age, y	69.3 (8.4)	70.3 (9.0)
Education, y	18.0 (1.8)	15.2 (2.9)
Cognitive		
MMSE total score	22.0 (3.5)	22.0 (4.0)
ADAS-COG total score	29.1 (13.0)	26.7 (9.1)
CVLT long delay score	1.8 (2.5)	1.3 (1.4)
VMI score	19.1 (2.8)	17.0 (2.6)
JOLO score	18.3 (7.9)	18.1 (9.9)
WAIS-BD raw score	10.4 (6.1)	10.1 (8.7)
Neuropsychiatric symptoms		
NPI total score	8.3 (8.0)	7.8 (7.3)
CIBIC baseline severity score	3.7 (0.5)	3.5 (0.5)
BDI score	8.9 (4.9)	9.2 (5.5)
QOL-AD score		
From self	39.8 (3.2)	42.0 (4.8)
From caregiver	39.9 (4.4)	39.5 (5.4)
Hormone levels		
Serum T, ng/dL	362.0 (163.0)	352.2 (105.2)
DHT, ng/dL	53.7 (25.3)	60.6 (29.2)
Free T, ng/dL	5.2 (2.3)	4.8 (2.0)
E_2, pg/mL	42.0 (11.4)	46.4 (15.7)
FSH, μIU/mL	8.7 (7.8)	10.5 (9.9)
LH, μIU/mL	4.7 (3.8)	6.8 (5.9)

Abbreviations: ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive Subscale; BDI, Beck Depression Inventory; CIBIC, Clinician's Interview-Based Impression of Change; CVLT; California Verbal Learning Test; DHT, dihydrotestosterone; E_2, estradiol; free T, free testosterone; FSH, follicle-stimulating hormone; JOLO, Judgment of Line Orientation; LH, luteinizing hormone; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; QOL-AD, Quality of Life–Alzheimer Disease; serum T, serum testosterone; VMI, Developmental Test of Visual-Motor Integration; WAIS-BD, Block Design Subtest of the Wechsler Adult Intelligence Scale-Revised.

Table 2. Comparison of Testosterone- and Placebo-Treated Groups on Demographic Characteristics, Outcome Measures, and Hormone Levels for Male Healthy Control Subjects at Baseline*

Characteristic or Measure	Testosterone (n = 14), Mean (SD)	Placebo (n = 15), Mean (SD)
Demographic		
Age, y	63.6 (5.9)	61.2 (7.3)
Education, y	16.5 (3.2)	17.6 (2.5)
Cognitive		
MMSE total score	29.9 (0.4)	29.6 (0.6)
ADAS-COG total score	4.8 (2.4)	4.8 (1.7)
CVLT long delay score	10.5 (3.1)	10.4 (2.8)
VMI score	25.0 (1.9)	25.0 (2.5)
JOLO score	27.4 (2.1)	26.8 (2.7)
WAIS-BD raw score	29.6 (7.0)	32.9 (9.2)
Neuropsychiatric symptoms		
NPI total score	1.1 (3.0)	0.0 (0.0)
CIBIC baseline severity score	1.0 (0.0)	1.0 (0.0)
BDI score	1.7 (4.5)	2.0 (4.9)
QOL-AD score from self	44.5 (5.8)	45.0 (5.7)
Hormone levels		
Serum T, ng/dL	409.2 (77.0)	352.2 (115.3)
DHT, ng/dL	63.0 (21.6)	71.3 (36.6)
Free T, ng/dL	6.8 (2.5)	6.9 (3.0)
E_2, pg/mL	52.3 (13.2)	49.0 (9.0)
FSH, μIU/mL	6.3 (6.0)	6.6 (8.0)
LH, μIU/mL	4.2 (3.0)	3.7 (3.3)

*Abbreviations are explained in the first footnote to Table 1.

ables at baseline and at end of study for the AD treatment groups are presented in **Table 3**. The change in scores across the study interval is also provided (as within-group *t* tests) along with the results of the analysis-of-covariance models (between-group comparisons) for the outcome measures at end of study (adjusted for baseline). The results for the healthy control subjects are presented in **Table 4**.

COGNITIVE FUNCTION

For the subjects with AD, no significant group differences were detected on any of the cognitive measures at end of study. However, within-group analysis indicated that placebo subjects displayed a significant decline on VMI score at the end of study while the testosterone-treated group performed at near baseline levels. Similar trends were observed for the JOLO score, but the findings were not statistically significant. Introducing years of education into the model as a covariate did not meaningfully alter the results.

For the healthy control subjects, the testosterone-treated group demonstrated a statistically significant improvement on the VMI score at the end of study while the mean score for the placebo-treated group remained near baseline levels. Between-subject comparisons at the end of study did not reveal significant treatment group differences on this score. Significant improvements on the Alzheimer's Disease Assessment Scale–Cognitive Subscale and California Verbal Learning Test were observed within the placebo group; however, both measures are subject to practice effects, particularly in a cognitively intact population. Within-group and between-group analyses at the end of study did not reveal significant results on other cognitive measures.

NEUROPSYCHIATRIC SYMPTOMS

For the AD patients, testosterone treatment produced no change in NPI or Beck Depression Inventory scores ($P>.30$). Closer inspection of the NPI data revealed that 4 (44%) of 9 patients in the testosterone-treated group and 7 (78%) of 9 subjects in the placebo group displayed at least 1 neuropsychiatric symptom of mild severity at baseline. In contrast, the number of testosterone-treated patients with symptoms of mild severity declined to 2 at the study end point while the 7 placebo subjects continued to manifest behavioral disturbances of at least mild severity. This difference did not reach statistical significance ($\chi^2<2.0$, $P>.16$). The healthy control group did not endorse any neuropsychiatric symptoms.

Table 3. Within-Group and Between-Group Comparisons of Neuropsychiatric and Cognitive Outcome Measures at End of Study for Testosterone- and Placebo-Treated Men With Alzheimer Disease*

Outcome Measures	Group	No.	Baseline, Mean (SD)	End of Study, Mean (SD)	Change, Mean (SD)	Within-Group		Between-Group	
						t Test	*P* Value	F Test	*P* Value
ADAS-COG total score	Testosterone	5	25.0 (13.2)	27.4 (8.4)	+2.4 (5.0)	0.91	.39	0.05	.82
	Placebo	6	25.2 (8.9)	28.3 (10.3)	+3.2 (7.3)	1.33	.22		
CVLT long delay score	Testosterone	6	2.3 (2.7)	1.0 (2.4)	–1.3 (1.5)	1.84	.09	0.59	.46
	Placebo	8	1.3 (1.4)	0.9 (1.7)	–0.4 (1.6)	0.94	.37		
VMI score	Testosterone	6	20.0 (2.4)	19.8 (3.1)	–0.2 (1.0)	0.44	.67	1.88	.20
	Placebo	8	17.0 (2.6)	15.4 (2.9)	–1.6 (1.6)	2.81	.02		
JOLO score	Testosterone	6	19.0 (7.6)	20.3 (7.0)	+1.3 (3.3)	1.05	.32	3.02	.11
	Placebo	8	18.1 (9.9)	16.5 (8.7)	–1.6 (3.8)	1.44	.18		
WAIS-BD raw score	Testosterone	6	9.5 (6.1)	10.8 (8.0)	+1.3 (2.2)	0.71	.49	0.46	.51
	Placebo	8	10.1 (8.7)	9.8 (7.3)	–0.4 (5.5)	0.21	.84		
NPI total score	Testosterone	5	4.2 (3.5)	5.4 (7.6)	+1.2 (5.4)	0.12	.90	0.11	.74
	Placebo	8	7.8 (7.3)	11.1 (17.1)	+3.4 (16.4)	0.71	.49		
BDI score	Testosterone	4	6.8 (4.3)	6.5 (2.5)	–0.3 (3.6)	0.70	.51	1.11	.32
	Placebo	7	8.6 (4.9)	9.1 (3.8)	+0.6 (6.0)	0.84	.42		
QOL-AD score from self	Testosterone	6	39.8 (3.2)	42.0 (2.1)	+2.2 (2.3)	0.85	.41	0.90	.36
	Placebo	9	42.0 (4.8)	44.3 (4.1)	+2.3 (5.5)	2.58	.02		
QOL-AD score from caregiver	Testosterone	5	39.6 (5.3)	42.4 (2.9)	+2.8 (4.0)	1.97	.08	9.83	.01
	Placebo	8	39.5 (5.4)	36.6 (6.2)	–2.9 (2.7)	2.56	.03		

*Abbreviations are explained in the first footnote to Table 1.

Table 4. Within-Group and Between-Group Comparisons of Neuropsychiatric and Cognitive Outcome Measures at End of Study for Testosterone- and Placebo-Treated Healthy Control Men*

Outcome Measures	Group	No.	Baseline Mean (SD)	End of Study, Mean (SD)	Change, Mean (SD)	Within-Group		Between-Group	
						t Test	*P* Value	F Test	*P* Value
ADAS-COG total score	Testosterone	10	4.3 (1.6)	3.7 (1.6)	–0.6 (1.6)	1.32	.20	0.37	.55
	Placebo	12	4.4 (1.7)	3.4 (2.2)	–1.0 (1.3)	2.35	.03		
CVLT long delay score	Testosterone	10	9.6 (2.7)	10.6 (2.2)	+1.0 (2.2)	1.43	.17	3.00	.10
	Placebo	12	10.3 (2.8)	12.4 (2.6)	+2.1 (2.1)	4.15	<.001		
VMI score	Testosterone	9	25.3 (1.3)	26.2 (1.0)	+0.9 (1.3)	2.26	.04	2.21	.15
	Placebo	12	25.6 (1.7)	25.7 (2.0)	+0.1 (1.1)	0.33	.74		
JOLO score	Testosterone	10	27.4 (2.2)	27.9 (2.2)	+0.5 (2.1)	0.92	.37	0.00	.96
	Placebo	12	27.5 (2.0)	27.9 (1.7)	+0.4 (1.6)	0.92	.37		
WAIS-BD raw score	Testosterone	10	29.5 (6.7)	28.6 (8.2)	–0.9 (2.7)	0.86	.40	0.02	.90
	Placebo	12	34.8 (9.0)	33.8 (8.6)	–1.1 (4.7)	0.75	.46		
QOL-AD score from self	Testosterone	10	44.7 (6.1)	45.3 (6.0)	+0.6 (2.0)	0.71	.48	3.29	.09
	Placebo	11	45.3 (6.1)	43.7 (8.1)	–1.5 (3.3)	1.88	.08		

*Abbreviations are explained in the first footnote to Table 1.

GLOBAL ASSESSMENT AND QUALITY OF LIFE

No significant differences between testosterone and placebo treatment for the AD patients were evidenced on the Clinician's Interview-Based Impression of Change (mean ± SD score: testosterone, 4.7 ± 0.49; placebo, 5.0 ± 0.49; $t = 1.1$, $P = .30$). The 2 AD treatment groups differed significantly in response to treatment on the QOL-AD scale, based on the caregivers' ratings of the patients' quality of life. Higher mean scores were obtained by the testosterone-treated group compared with the placebo-treated group. Within-group analysis revealed that the quality-of-life score for the placebo subjects declined significantly from baseline while a nonsignificant trend toward improved scores was observed for the testosterone-treated group. The divergent trajectory of the quality-of-life outcome between week 12 and the end of study accounted for the significant between-group differences (**Figure 2**). Within the healthy control sample, the self-rated QOL-AD score remained at baseline levels for the testosterone group but declined for the placebo-treated group, although the mean reduction in score was not statistically significant ($P = .08$).

HORMONE MEASURES

As expected, subjects with AD in the testosterone-treated group, compared with those in the placebo group, showed large increases in serum T and its metabolites and significant decreases in follicle-stimulating hor-

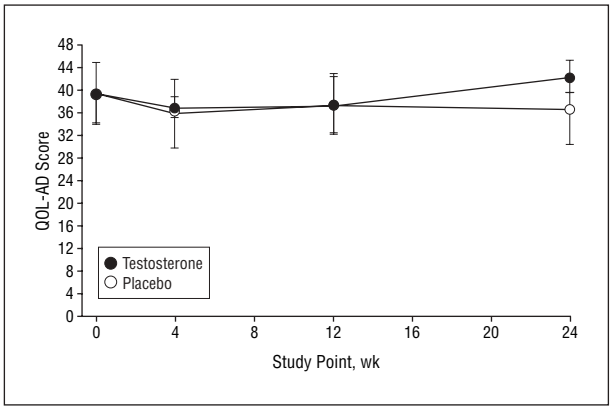

Figure 2. Change in Quality of Life–Alzheimer Disease (QOL-AD) scores (caregiver) across study points in male patients with AD receiving testosterone and placebo.

mone and luteinizing hormone at the end of the study (**Table 5**). The healthy controls showed similar changes in hormone levels following testosterone treatment, but the difference did not reach statistical significance in serum T and E_2 levels ($P=.10$).

In the AD sample, Pearson correlation analyses revealed significant positive associations between changes (from baseline to end of study) in hormone level (serum T, free T, DHT, E_2) and JOLO score ($r>0.59$, $P<.03$). A significant positive correlation was also found between changes in DHT level and QOL-AD (caregiver) score ($r=0.60$, $P=.04$). In the healthy elderly sample, none of the associations between hormone and outcome changes reached statistical significance ($P>.10$).

For the participants who completed the study, 4 (25%) of 16 subjects with AD and 5 (23%) of 22 healthy controls were identified to have baseline testosterone levels below the normal range.[48] For the patients with AD, significant inverse relationships were observed between change in JOLO score and baseline free T ($r=-0.57$, $P=.03$) and E_2 ($r=-0.64$, $P=.01$). Baseline DHT was negatively correlated with the change in VMI score ($r=-0.61$, $P=.02$). These associations suggest that in AD, a lower hormone level at baseline is associated with a greater positive change in spatial cognition, findings that were not replicated in the healthy elderly sample ($P>.09$).

ADVERSE EFFECTS

Figure 1 indicates that 2 (22%) of 9 patients with AD dropped out of the testosterone-treated group; 1 subject complained of rash at the site of application and the other patient was discontinued from the study because he scored an 11 on the Mini-Mental State Examination during a follow-up visit, thus failing the inclusion/exclusion criteria. No patients with AD withdrew from the study in the placebo group. In the healthy control sample, of the 4 subjects (29%) who discontinued from the testosterone group, 2 reported adverse events (decreased sexual functioning; testicular failure/shrinkage). A similar dropout rate was observed in the placebo group (3/15 or 20%), but only 1 of the subjects reported adverse effects involving nausea and sexual dysfunction. Analysis of the differential rate of study withdrawal did not reveal significant differences in frequency of dropout for the treatment groups ($\chi^2<2.3$, $P>.13$).

Medication adverse effects were further assessed using the Overt Aggression Scale and the agitation/aggression subscale of the NPI. The AD-testosterone patients did not exhibit more aggression or agitation than placebo subjects ($P>.11$). Sexual functioning, as measured by the modified Change in Sexual Functioning Questionnaire, did not reveal significant treatment group differences for AD or healthy control subjects on the total or any of the subscale scores. Caregivers did not observe any marked changes in sexual behavior of study patients on this scale.

COMMENT

The results from this 6-month randomized, placebo-controlled trial demonstrate that testosterone-treated patients with AD, as a group, displayed significantly better quality of life (as assessed by their caregivers on the QOL-AD scale) than their placebo-treated counterparts. Specifically, testosterone treatment in patients with mild AD produced a nonsignificant trend toward improved quality of life over a 6-month period while the placebo-treated group exhibited a significant decline. A similar pattern was observed in healthy control men although the results were not statistically significant.

Controlled clinical trials of supplemental testosterone treatment in healthy elderly men have yielded equivocal results in relation to quality of life. Some studies found increased sense of well-being[30,51,52] while others detected no effect of testosterone supplementation on quality of life.[53] Overall quality of life has been demonstrated to be significantly associated with dementia severity, functional impairment, and neuropsychiatric symptoms in patients with AD.[47,54] In the absence of direct observational methods, assessment of quality of life provides a window into the effects of intervention on the patients' and the caregivers' perceived well-being and helps inform the consumers and clinicians on the potential functional benefits and risks of therapy. To our knowledge, this is the first study to report on the positive effects of testosterone treatment on the quality of life of patients with AD.

With regards to cognition, the treatment groups did not differ significantly on any of the cognitive variables within the AD and healthy control populations. However, the testosterone-treated AD group exhibited either numerically greater improvement or less decline in scores on all 3 measures of visual-spatial functioning when compared with the placebo group. The present results generally support the existing literature reporting improved spatial cognition with testosterone treatment in men with AD[55] and healthy elderly[21-23,56] men, although other studies have failed to detect discernible changes in cognitive functioning with treatment with dehydroepiandrosterone[57] and intramuscular testosterone administration.[58] The absence of any treatment effect on visual-spatial skills in the healthy control group may reflect the observation that the subjects are performing at near maximal levels on these measures. The results on the effects of testosterone treatment on mood and psychiatric symp-

Table 5. Between-Group Comparisons of Hormone Levels at End of Study for Testosterone- and Placebo-Treated Healthy Control Men*

		Testosterone		Placebo			
Hormone	Time	No.	Mean (SD)	No.	Mean (SD)	F Test	*P* Value
Patients With Alzheimer Disease							
Serum T, ng/dL	Baseline	7	385.8 (170.1)	9	341.2 (108.7)	13.8	.003
	End of study	7	737.5 (241.9)	8	387.3 (110.1)		
Free T, ng/dL	Baseline	7	5.1 (2.5)	9	4.9 (2.1)	12.1	.005
	End of study	7	9.4 (3.6)	8	4.3 (1.6)		
DHT, ng/dL	Baseline	7	60.1 (25.1)	9	64.5 (28.6)	18.7	.001
	End of study	7	343.0 (178.7)	8	65.6 (24.5)		
E_2, pg/mL	Baseline	7	39.7 (10.2)	9	46.3 (16.8)	7.6	.02
	End of study	7	58.6 (7.9)	8	48.9 (11.4)		
FSH, μIU/mL	Baseline	7	10.2 (8.4)	9	10.9 (10.5)	11.7	.005
	End of study	7	1.4 (2.0)	8	11.9 (11.9)		
LH, μIU/mL	Baseline	7	5.1 (4.0)	9	6.8 (6.3)	10.9	.006
	End of study	7	0.5 (1.0)	8	5.8 (5.5)		
Healthy Controls							
Serum T, ng/dL	Baseline	10	387.7 (76.6)	12	346.8 (111.9)	1.94	.18
	End of study	10	597.1 (554.3)	11	310.7 (94.4)		
Free T, ng/dL	Baseline	10	6.2 (1.8)	12	6.5 (2.9)	2.57	.13
	End of study	10	11.2 (13.0)	11	5.1 (1.9)		
DHT, ng/dL	Baseline	10	62.3 (17.7)	12	73.1 (40.8)	5.70	.03
	End of study	10	180.7 (132.6)	11	78.6 (28.8)		
E_2, pg/mL	Baseline	10	50.5 (11.5)	12	50.3 (9.6)	1.20	.29
	End of study	10	58.9 (13.9)	11	52.0 (15.8)		
FSH, μIU/mL	Baseline	10	7.3 (6.8)	12	7.1 (9.3)	1.26	.28
	End of study	10	3.0 (2.4)	11	4.2 (2.3)		
LH, μIU/mL	Baseline	10	4.9 (3.1)	12	4.1 (3.7)	0.02	.89
	End of study	10	2.2 (2.0)	11	2.4 (1.3)		

*Abbreviations are explained in the first footnote to Table 1.

toms of patients with AD paralleled that of cognitive functioning but were not statistically significant.

In the AD sample, significant positive relationships were observed between changes in hormone level and a measure of visual-spatial recognition. Additionally, inverse relationships were observed between baseline levels of free T, DHT, and E_2 and improved performance on measures of visuospatial functions (JOLO and VMI). These findings are consistent with previous reports indicating that benefits of testosterone administration may be greater in more severely androgen-deficient men rather than men with less marked testosterone deficiency.[59] Therefore, selection of only hypogonadal men or individuals with low normal testosterone levels may result in greater response to treatment.

Hormone levels of 8 (47%) of 17 subjects assigned to the testosterone group did not display a discernible increase in serum T level at the end of study. Neither patients nor their caregivers reported poor adherence to protocol or improper application of the gel during the follow-up visits, but suboptimal compliance to treatment remains a possibility. Poor absorption of the testosterone gel is another potential cause for the minimal increase in testosterone level. It is also possible that the blood sampling occurred more than 24 hours since the last application, when testosterone level was at its nadir. Future studies should establish a dose that achieves a desired hormone level for each patient prior to follow-up assessment.

The major limitation of this study is the small sample sizes. Subject recruitment was more difficult than anticipated due to the strict inclusion and exclusion criteria and the caregivers' fear of adverse events associated with testosterone. However, testosterone treatment was actually well tolerated with few adverse effects reported or documented on objective measures. It should also be noted that the *P* values reported were not adjusted for multiple comparisons. The small sample sizes and large number of outcome variables limit conclusive interpretation of the study findings and require replication in larger-scale studies with more focused primary outcome variables.

Additional study limitations must be acknowledged. Testosterone treatment in hypogonadal men has shown improvement in mood, muscle mass, strength, bone density, libido, and certain focused cognitive functions[28]; many of these changes are related to the degree of improvement in testosterone levels and inversely related to baseline testosterone concentration. The present study also found baseline free T and E_2 levels to be inversely correlated with visuospatial functions; thus, it is possible that the cognitive findings would be more robust if low T level were an inclusion criterion. In addition, the ethnicity of the sample was predominantly white, limiting the generalizability of the results to other ethnic groups; the chosen instruments may lack sensitivity to detect small changes or are vulnerable to ceiling effects in cognitively intact subjects; longer duration of study may have

yielded greater effects; and proxy reports of quality of life should be interpreted with caution.

In conclusion, the present results should be considered preliminary and do not warrant routine treatment of AD and healthy control men with testosterone. Future studies with larger sample sizes are needed before clinical decisions regarding testosterone therapy can be rationally based. For men with compromised quality of life, as reflected on the type of measure employed in this study, and who suffer from low serum T levels, testosterone therapy may be a reasonable consideration.

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