Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment

M.M. Cherrier, PhD; A.M. Matsumoto, MD; J.K. Amory, MD; S. Asthana; W. Bremner, MD; E.R. Peskind, MD; M.A. Raskind, MD; and S. Craft, PhD

Abstract—*Objective:* To determine the efficacy of testosterone (T) supplementation on cognition in a sample of men with Alzheimer disease (AD) or mild cognitive impairment (MCI). *Methods:* Fifteen patients with AD and 17 patients with MCI aged 63 to 85 years completed a randomized, double-blind, placebo-controlled study. Nineteen participants received weekly intramuscular (IM) injections of 100 mg T enanthate and 13 participants received weekly injections of placebo (saline) for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, week 3, and week 6 of treatment and again after 6 weeks of washout. *Results:* Peak serum total T levels were raised from baseline an average of 295% in the active treatment group. Improvements in spatial memory ($p < 0.05$) and constructional abilities ($p < 0.05$) and verbal memory were evident in the T group. No changes were noted for selective and divided attention or language. Prostate specific antigen did not significantly change during this brief treatment. *Conclusion:* Testosterone supplementation may benefit selective cognitive functions in men with Alzheimer disease and mild cognitive impairment.

NEUROLOGY 2005;64:2063–2068

Environmental disorientation (i.e., episode of getting lost) is an early hallmark of Alzheimer disease (AD) that places increased burden on the caregivers for continued monitoring. Spatial memory, spatial ability, and navigation are all involved in successful learning and navigation of complex environments,[1-4] and episodes of environmental disorientation are related to poor spatial memory,[3,4] as well as other cognitive processes.[2,5-7] Studies in both animals and humans have suggested that poor spatial memory and navigational/spatial skills are correlated with low levels of testosterone (T).[8-12]

Several recent epidemiologic studies involving large samples of healthy older men have found bioavailable or free T to be significantly and positively correlated with performance on tests of global cognitive functioning, such that lower levels of free T are associated with poor cognitive functioning and higher levels are associated with better cognitive functioning.[13-16] In addition, low testosterone levels over time are associated with increased risk for developing AD, independent of health status, age, or education.[17] T levels appear to remain low with the onset of AD in comparison to controls[16,18,19] and patients with Parkinson disease[20] and are associated with high plasma amyloid beta peptide 1–40 levels.[19] These studies suggest that age-related declines in T levels may be related to cognitive function and risk for dementia.

Two studies have examined T supplementation in patients with AD or mild cognitive impairment (MCI). MCI is widely believed to represent a prodromal stage of AD with some studies indicating up to 80% of patients with MCI progressing to diagnosable AD within 6 years.[21,22] A study of T supplementation in hypogonadal men with MCI found no beneficial effect on tests of attention.[23] However, a study of T supplementation in male nursing home residents with AD found beneficial results as measured by a global cognitive functioning measure.[24] These mixed findings suggest that further studies of hormone supplementation in memory impaired individuals are needed.

In the present study, we examined androgen supplementation in men with AD or MCI. We utilized a battery of neuropsychological tests shown to be sensitive to androgen manipulation in our previous studies of healthy eugonadal and hypogonadal older

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the June 28 issue to find the title link for this article.

From the Department of Psychiatry and Behavioral Sciences (Drs. Cherrier, Peskind, Raskind, and Craft), Department of Medicine (Drs. Matsumoto, Amory, and Bremner), Division of Gerontology and Geriatric Medicine (Dr. Matsumoto), University of Washington School of Medicine, Seattle; Geriatric Research, Education and Clinical Center (S. Asthana), Veterans Hospital, Madison, WI; and Geriatric Research, Education and Clinical Center (Drs. Matsumoto, Peskind, Raskind, and Craft), Mental Illness Research, Education and Clinical Center (Drs. Cherrier, Peskind, and Raskind), Department of Veterans Affairs, Puget Sound Health Care System, Seattle, WA.

Supported in part by NIA award #K01AG00858, Department of Veterans Affairs Puget Sound Health Care System and Clinical Research Center Facility at the University of Washington #M01-RR-00037.

Received September 28, 2004. Accepted in final form March 14, 2005.

Address correspondence and reprint requests to Dr. Monique M. Cherrier, S-116 MIRECC VAPSHCS, 1660 S. Columbian Way, Seattle, WA 98108; e-mail: cherrier@u.washington.edu

men. We hypothesized that both the AD and MCI groups would experience beneficial effects on memory with little or no change on measures of attention or language.

Methods. This study was approved by the Human Subjects Review Committee of the University of Washington. Written informed consent was obtained from all subjects and from the legal representatives of the patients with AD. Patients included subjects diagnosed with probable AD (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association)[25] or amnestic MCI.[22] Amnestic MCI patients were included because MCI is believed to represent a prodromal stage of AD with up to 80% of patients receiving an AD diagnosis within 6 years.[21,22] Participants underwent a screening visit to determine eligibility including a physical examination and psychiatric and laboratory evaluation to exclude any significant physical or medical illness. This included tests of hypertension, liver function, and prostate disease (prostate specific antigen [PSA] level and digital rectal examination [DRE]). Participants with abnormal findings, including uncontrolled hypertension, were excluded from the study. Participants also underwent a cognitive screening examination consisting of the Mattis Dementia Rating Scale (DRS) to establish a baseline measure of general cognitive functioning.[26] Participants with a history of significant alcohol abuse, psychiatric illness, head injury with loss of consciousness greater than 1 hour, or who were taking Lupron, finasteride, spironolactone, or cimetidine were excluded. Participants with previous or current prostate cancer, elevated PSA levels, history of myocardial infarction, abnormal renal or hepatic disease, sleep apnea, previous testosterone or other androgen treatment, or other gonadal endocrine disorders were also excluded.

Study design. Eligible participants were randomly assigned to one of two treatment groups. Assignment for each consecutively enrolled participant was made by pharmacists, using a predetermined assignment sheet that was created using a random number generator. Study personnel, participants, and investigators were blind to treatment condition.

Participants reported to the Veterans Affairs Puget Sound Health Care System (VAPSHCS) Clinical Research Unit or the University of Washington General Clinical Research Center Clinical Research Unit and were randomized to receive either weekly IM injections of 100 mg T enanthate (Delatestryl, manufactured for BTG Pharmaceuticals Corporation by Bristol-Myers Squibb, Princeton, NJ) or placebo (saline) for 6 weeks followed by 6 weeks of no medication (washout). At these weekly visits, blood samples were taken to measure serum T and estradiol levels by IFMA and RIA (see below). Cognitive testing was conducted at baseline and repeated at weeks 3 and 6 of treatment and again after 6 weeks of washout. Blood sampling and testing sessions occurred within 24 to 48 hours following T or placebo injection to capture peak T levels for the treated group. Therefore, cognitive performance results reflect the effects of peak T levels. Endogenous T levels measured at baseline prior to the start of the study were in the low to normal range (15 to 20 nmol/L) and did not differ significantly between groups. PSA and hematocrit levels were measured at screening, week 4 of treatment, and again at washout. Mean PSA level of 1.69 ng/mL for all participants at the start of the study was within normal limits (0 to 4 ng/mL). DRE was also conducted at screening and at the washout visit with no abnormal findings.

Neuropsychological test measures. The cognitive tests included measures of spatial and verbal memory, working memory, language, and selective attention. Previous studies have suggested that these cognitive domains are most likely to change in response to androgen manipulation. Comparable, alternate versions of each test were administered at each time point. Test versions were randomized and counterbalanced. A complete administration of the testing session was conducted at the screening visit to reduce practice effects. Psychometrists, participants, and investigators were blind to the treatment condition.

Spatial memory measure. Route test. This test measured the ability to navigate a short route within a room.[27] The task used a 6 × 24 foot piece of black flooring on which a diamond pattern was placed using bright yellow tape. A particular route was indicated using a bright red ribbon and the subject walked the route as shown. The ribbon was removed, and the subject was asked to immediately retrace the route. Three trials were administered followed by three trials of a new route using pictures placed on the floor as landmarks. A delayed recall is administered after 20 minutes. Performance was assessed by calculating the number of correct sequential units summed across all trials.

Verbal memory measures. Story recall. The story recall task was modeled on the Wechsler Memory Scale Revised (WMS-R) and measures memory for aurally presented contextual material. Participants listened to two brief narratives, each containing 25 informational bits, and were asked to recall as much as possible immediately after hearing each story and following a 20-minute delay. Reliability and validity of WMS-R and WMS-III Logical Memory and this modified version are very good.[28,29]

Proactive interference (PI). Participants listened to a list of 10 words from the same semantic category (e.g., articles of clothing), and then recalled as many of these words as possible. The task was adapted from a previous task.[30] The procedure was repeated for a total of four trials, each containing different words drawn from the same semantic category. For the fifth trial 10 words from a new semantic category (e.g., types of furniture) were read and participants were asked to recall these words. The total number of words recalled correctly on each trial was recorded. Normal adults recall progressively fewer words across trials two through four due to the build-up of interference from the semantically similar preceding items. Reliability of the test is generally good, including validity studies conducted with brain injured patients and controls.[31]

Selective attention measure. Stroop Color Word Interference Task. This task was based on the original version and utilized three trials for which total reading time and errors were recorded.[32] The first condition (word reading) required participants to read 100 color words (red, green, blue), presented in rows on a sheet of paper as quickly as possible. The second condition (color naming) required participants to name the color of 100 colored blocks presented in rows on a sheet of paper. In the third condition (color word interference), stimuli consist of color names that are printed in discordant colors (e.g., the word "blue" printed in green letters). Participants were asked to name the ink color of the printed words, and are thus required to inhibit reading the words.

Verbal ability measure. Verbal fluency. The verbal fluency measure is based on the Controlled Oral Word Association Test (COWAT) and is sensitive to verbal dysfunction and frontal lobe functioning. Participants were asked to verbally generate as many words beginning with a particular letter (e.g., P) as possible within a 60-second period.[33] Two trials were administered with two different letters. The total number of words generated was recorded for each letter and summed.

Spatial ability measure. Block design. This test is a modified version of the Wechsler Adult Intelligence Scale–Revised, Block Design subtest.[34] The test measures participants' ability to analyze and construct abstract figures from their component parts. The subject is shown individual, red and white designs on paper and asked to construct the design using nine three-dimensional blocks with red and white sides. Time to completion is recorded for each design, with an upper limit of 3 minutes per design. There are nine total designs, with three designs per difficulty level (easy, moderate, and hard). Average time per design was used for analysis.

Hormone assays. Blood samples were drawn at the time of cognitive testing and within 48 hours of injection to capture a peak blood level. Samples were kept frozen in a −70 °C freezer until the completion of the study when all samples were included in the assays. Serum estradiol and total testosterone levels were analyzed with radioimmunoassay (RIA) and ImmunoFluorimetric assay (IFMA), according to standard procedures for each commercial kit. Although studies examining the relationship between endogenous T levels and cognition have frequently used measures of free testosterone, we chose to measure total testosterone as this has been shown previously to be a sensitive and valid measure for hormone manipulation studies. Serum total T was measured using the DELFIA IFMA kit (Wallac OY, Turku, Finland) with sensitivity of 0.5 nmol/L and 4.5% intra-assay coefficient of variation for a mid-range pool of samples. Serum estradiol was measured by Estradiol RIA Kit (DSL-39100), from Diagnostic Systems Labora-

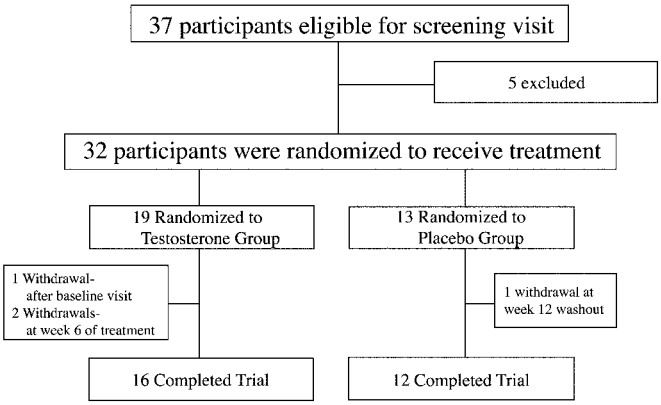

Figure 1. Schematic view of participant flow.

tory, Webster, TX. The sensitivity of this assay was 5.5-pmol/L and inter- and intra-assay coefficients of variation were 5.6%, and 7.0% for mid and 5.3% for high-range values. The normal range for the assay in men was 76 to 353 pmol/L. Samples from each participant were run in duplicate in the same assay to avoid inter-assay variability. Hormone levels reported were the average of the duplicate samples.

Statistical analyses. Data were log transformed and a repeated measures analysis of variance (ANOVA) was used for each cognitive test and hormone measure with baseline assessment covaried, group as the independent factor (T vs placebo), and weeks (weeks 3 and 6 and washout) as the repeated factor. Post hoc comparisons were subjected to Bonferroni correction. ANOVAs to examine changes in PSA included measures at baseline, week 4, and week 12 and hematocrit at all weeks with post hoc comparisons subjected to Bonferroni correction. Bonferroni correction was calculated for each post hoc comparison p value by the following formula: n = the number of weeks {number of comparisons = n [n-1]/number of groups}; outcome of this formula is multiplied by post hoc LSD p value. Participants were analyzed according to their randomized assignment to treatment group without replacement of missing variables. Therefore, the analysis represents a modified intention-to-treat (ITT) analysis.

Results. Thirty-seven men gave informed consent and were screened for the study. Three participants decided to discontinue after the screening due to scheduling or other personal reasons. Two participants evidenced an elevated PSA and were ineligible. Thirty-two participants with a mean age of 76 ± 5 years (range 63 to 85) met screening criteria and were randomized. Nineteen subjects were randomized to testosterone (T) and 13 to placebo (figure 1). Analysis for all dependent measures included all 32 subjects except where noted otherwise. Mean education level was 15 ± 2 years (range 8 to 20) and mean DRS score was 105 ± 10 points (range 91 to 128) for patients with AD and 128 points ± 8 points (range 113 to 140) for patients with MCI. There were no significant differences between the T or placebo groups for age, education, or DRS score (table).

Peak T levels were increased significantly an average of 34 ± 24 nmol/L in the T group. The T group demonstrated an increase in both serum total testosterone and estradiol concentrations at weeks 3 and 6 compared to baseline ($p < 0.01$) and compared to placebo ($p < 0.01$) (figure 2, A and B). Testosterone and estradiol levels did not significantly change over time in the placebo group. Omnibus ANOVA results revealed a week by group interaction for total testosterone [$F(3,66) = 22.1$, $p < 0.01$] and estradiol [$F(3,66) = 22.3$, $p < 0.01$] and increase over weeks for the T group [$F(3,19) = 12.3$, $p < 0.01$] for total testosterone [$F(3,20) = 12.9$, $p < 0.01$] and estradiol. Testosterone and estradiol analysis included 29 subjects due to missing data for one time point for two control subjects. No significant differences between groups were evident for baseline measures.

The T group showed improved performance on both the route test [$F(2,24) = 3.29$, $p < 0.05$] and block design [$F(2,36) = 3.45$, $p < 0.05$] during treatment with no significant change over time in the placebo group resulting in a week by condition interaction [$F(2,50) = 3.46$, $p < 0.05$] for the route test (figure 3A) and for block design [$F(2,17) = 4.0$, $p < 0.05$] (figure 3B). Block design analysis included 28 subjects due to missing data at one time point for one control and two AD/MCI subjects. Verbal memory as measured by the PI test was better in the T group compared to the placebo group at week 6 [$F(1,24) = 5.48$, $p < 0.05$] and due to a decline in the placebo group from week 3 to 6, there was an interaction effect [$F(2,48) = 4.78$, $p < 0.05$]. Verbal memory as measured by the paragraph recall test was better in the T group compared to the placebo group at week 3 of treatment [$F(1,26) = 4.84$, $p < 0.05$] and due to a decline in the placebo group from week 3 to 6, there was an interaction effect [$F(2,52) = 7.1$, $p < 0.01$]. Although the T group was better than the placebo group on two verbal measures during treatment, a significant change over time

Table *Demographic information*

	T 100 mg/wk		Placebo	
	AD	MCI	AD	MCI
n	9	10	6	7
Age, y	77 (4)	76 (5)	75 (7)	74 (5)
Education, y	15 (3)	15 (2)	15 (3)	15 (2)
Dementia Rating Scale total score*	102 (10)	126 (9)	108 (14)	130 (8)
Baseline total testosterone, nmol/L	14.4 (7)	13.5 (5)	9.3 (3)	10.6 (2)
Prostate specific antigen, ng/mL†	1.7 (1.2)	2.9 (1.8)	0.7 (0.3)	1.0 (0.6)

Values are means (SD).

* Dementia Rating Scale total score: 144 possible points with 138–144 in the normal range.
† Prostate specific antigen normal range 0–4 ng/mL.

T = Testosterone-treated group; AD = Alzheimer disease; MCI = mild cognitive impairment.

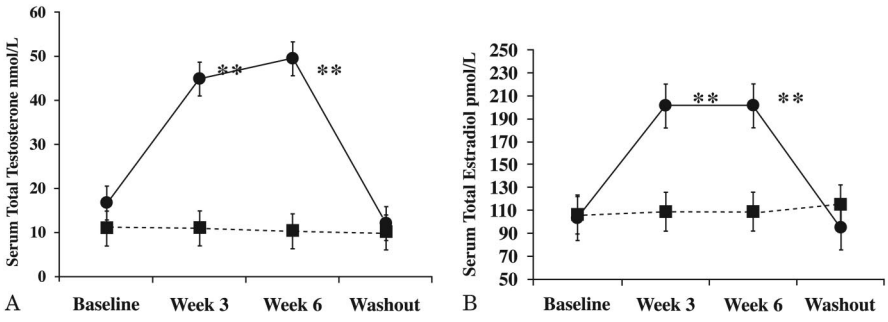

*Figure 2. (A) (Left) Mean serum total testosterone (nmol/L) and (B) (right) estradiol (pmol/L) levels in the testosterone treated group (T) indicated with solid circles and a solid line and the placebo groups indicated with a dashed line and solid squares. Error bars represent standard error of measurement. Estradiol levels increased at weeks 3 and 6 of treatment in the T group compared to baseline (**$p < 0.01$). An interaction effect was also evident ($p < 0.01$). Total T increased at weeks 3 and 6 in the T group compared to baseline (**$p < 0.01$) and compared to placebo ($p < 0.01$). An interaction effect was also evident ($p < 0.01$).*

during treatment in the T group alone was not observed. No significant changes were found on measures of language (verbal fluency), selective attention (Stroop test), or divided attention (Trail Making Test, part B).

PSA and hematocrit levels increased slightly in the T group although this increase was not significant compared to baseline (table E-1 on the *Neurology* Web site at www.neurology.org). Caregivers of patients with AD were asked at baseline and again at week 6 of treatment about the presence of agitated or other aggressive or unwanted behaviors. Caregivers did not report any change in behavior compared to baseline.

Discussion. Weekly administration of 100 mg T enanthate for 6 weeks significantly increased circulating total testosterone levels in the T group with peak levels in the normal to high normal range for healthy young men (see figure 2A). Peak serum estradiol concentrations also increased (to above the normal range) in the T group (see figure 2B). Consistent with our previous study in healthy older men, we found that T supplementation improved spatial memory and spatial or constructional ability and verbal memory.[35] These changes are equivalent to a SD change on widely used clinical measure of constructional ability.[36] A change of one-half to one SD may mean the difference between an impaired vs normal range performance. Findings of improved spatial memory and spatial ability are particularly important, as difficulties with environmental disorientation (e.g., getting lost) are one of the earliest symptoms in AD. In addition, once this symptom is present, it frequently results in increased burden on caregivers due to the heightened need for monitoring and the need to provide transportation.

Verbal memory as measured by a list learning task (PI) and story recall was better in the T group compared to the placebo group during treatment. However, we did not observe a significant change over time in the T group alone. Thus, it is not clear if these differences were due to improvement from treatment or a decline in the placebo group. However, it has been suggested that a lack of decline in the treatment group may be considered a positive treatment outcome for patients with AD or MCI. Our previous findings in a sample of healthy older men resulted in beneficial effects on verbal memory. Beneficial changes in verbal memory may be attributable to the rise in estradiol levels from aromatization of T into estradiol. Significant improvements in verbal recall have been found in healthy older women and patients with AD receiving estrogen replacement treatment.[37,38] However, other studies have failed to find beneficial cognitive changes from estrogen.[39,40] In men, exogenous increases in estrogen have been shown to improve verbal memory for a paired associate learning task, a task that generally favors women.[41] Other studies of testosterone supplementation in older men or patients with AD have

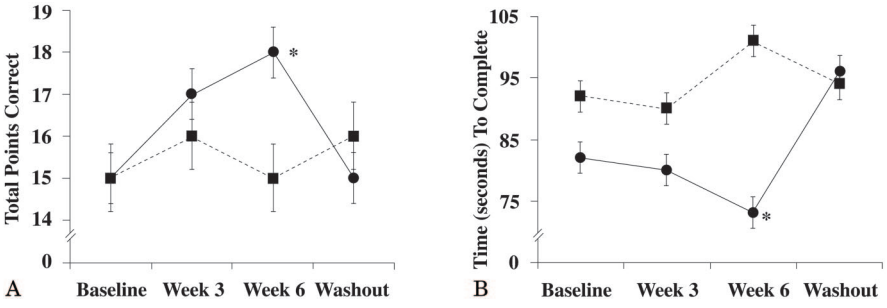

Figure 3. (A) (Left) Mean total points correct on the route test, a measure of spatial and navigational memory. Testosterone treated group (T) indicated with solid circles and a solid line and the placebo group indicated with a dashed line and solid squares. Error bars represent standard error of measurement. The T group demonstrated an improvement at week 6 compared to baseline ($p < 0.05$). An interaction effect was also evident ($p < 0.05$). (B) (Right) Average time (seconds) to complete a block design, a measure of visuoconstructional or spatial ability. Lower score represents a better performance. Testosterone treated group (T) indicated with solid circles and a solid line and the placebo group indicated with a dashed line and solid squares. Error bars represent standard error of measurement. The T group demonstrated an improvement ($p < 0.05$) at week 6 compared to baseline and an interaction effect was also evident ($p < 0.05$).*

either not included verbal memory measures or have not examined verbal memory tasks separate from other cognitive domains.[23,24,42] Thus, changes in verbal memory from T supplementation remain an area for further inquiry.

Our results are consistent with findings of improved cognition in hypogonadal, nursing home dwelling patients with AD treated with testosterone.[24] In that study, patients with AD were administered testosterone enanthate every 2 weeks for 1 year. Patients showed significant improvement on a clock drawing test and on the total score for the AD Assessment Scale–cognitive subscale (ADAS-Cog), a global measure of cognition, after 3 and 6 months of treatment compared to the placebo group. Information on individual subscales of the ADAS were not included in the report, thus, we cannot determine which specific cognitive domains on the ADAS were affected by testosterone supplementation. However, improvement on the Clock Drawing Test is consistent with our findings of improved spatial ability on the Block Design test.

A more recent study failed to find beneficial cognitive effects of testosterone replacement in community dwelling hypogonadal men with MCI.[23] Participants were given 200 mg q 3 weeks testosterone for 12 weeks and measures of simple and divided attention, language, and visuoconstruction (Clock Drawing) were administered at baseline and again at 4 and 10 weeks of treatment. The cognitive tests in this battery emphasized attention, language, and motor coordination, which are cognitive domains for which we have also failed to observe significant changes from testosterone supplementation. However, lack of improvement on Clock Drawing is not consistent with other findings of improved performance on Clock Drawing in patients with AD and our findings of improved performance on Block Design.

Although findings of cognitive effects of androgens in humans have been mixed, animal studies support mechanisms by which androgens may affect cognitive abilities. Androgen receptors are found widely throughout the brain, but in particular the hypothalamus and hippocampus are high density areas.[43] Animal studies have generally supported a link between androgen modulation and performance on maze tasks.[8,11,44-46] Human studies have found some relationship between endogenous T levels and cognitive performance in older men as well as an association of chronic low testosterone levels with increased risk for developing AD.[13-15,17]

Pathologic changes in AD are characterized by senile plaques and neurofibrillary tangles formed by abnormal accumulation of beta-amyloid and hyperphosphorylated tau. Testosterone has been shown to reduce neuronal secretion of beta-amyloid as well as to prevent the hyperphosphorylation of tau.[47-49] Thus, testosterone may exert effects on cognition in a rapid manner via androgen receptors in the brain as well as exerting more chronic effects of reducing AD pathology.

Androgen supplementation safety concerns are an area of interest and controversy. T supplementation can result in erythrocytosis which is more common with higher doses and in the elderly.[50] Hematocrit did not increase beyond the normal range in the T group nor did PSA. Thus, similar to other studies of patients with AD and MCI, we did not observe any short-term adverse effects at this dose level for the 6-week period of treatment.[23,24] We also did not observe any change in agitated behavior as reported by caregivers, consistent with other T supplementation studies in patients with AD and MCI.

Our findings indicate that T supplementation resulted in some beneficial effects on spatial memory and constructional abilities in older men with memory deficits. These results were evident after a relatively short treatment period (6 weeks) and during the peak hormone period (24 to 48 hours post injection). These results indicate that additional studies are needed to assess the safety and efficacy of a longer treatment period and with a larger sample size. Performing more studies in this area is consistent with the findings of the recent Institute of Medicine study that recommended conducting additional short- and long-term studies to assess the overall physiologic consequences of T supplementation on safety and biologic outcome variables as well as cognitive function and quality of life.[51]

Acknowledgment

The authors thank Andreana Haley, Shawn Latendress, Maria Gonzales, Patti Boorkman, and Marisa Johnson for their technical assistance.

References

1. Shelton AL, Gabrieli JD. Neural correlates of encoding space from route and survey perspectives. J Neurosci 2002;22:2711–2717.
2. Maguire EA. The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. Scand J Psychol 2001;42:225–238.
3. Skelton RW, Bukach CM, Laurance HE, Thomas KG, Jacobs JW. Humans with traumatic brain injuries show place-learning deficits in computer-generated virtual space. J Clin Exp Neuropsychol 2000;22:157–175.
4. Turriziani P, Carlesimo GA, Perri R, Tomaiuolo F, Caltagirone C. Loss of spatial learning in a patient with topographical disorientation in new environments. J Neurol Neurosurg Psychiatry 2003;74:61–69.
5. Luzzi S, Pucci E, Di Bella P, Piccirilli M. Topographical disorientation consequent to amnesia of spatial location in a patient with right parahippocampal damage. Cortex 2000;36:427–434.
6. Monacelli AM, Cushman LA, Kavcic V, Duffy CJ. Spatial disorientation in Alzheimer's disease: the remembrance of things passed. Neurology 2003;61:1491–1497.
7. Mapstone M, Steffenella TM, Duffy CJ. A visuospatial variant of mild cognitive impairment: getting lost between aging and AD. Neurology 2003;60:802–808.
8. Roof RL, Havens MD. Testosterone improves maze performance and induces development of a male hippocampus in females. Brain Res 1992;572:310–313.
9. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. Behav Neurosci 1994;108:325–332.
10. Silverman I, Kastuk D, Choi J, Phillips K. Testosterone levels and spatial ability in men. Psychoneuroendocrinology 1999;24:813–822.
11. Naghdi N, Oryan S, Etemadi R. The study of spatial memory in adult male rats with injection of testosterone enanthate and flutamide into the basolateral nucleus of the amygdala in Morris water maze. Brain Res 2003;972:1–8.
12. Aleman A, Bronk E, Kessels RP, Koppeschaar HP, van Honk J. A single administration of testosterone improves visuospatial ability in young women. Psychoneuroendocrinology 2004;29:612–617.

13. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriatr Soc 2002;50:707–712.
14. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999;84:3681–3685.
15. Moffat SD, Zonderman AB, Metter EJ, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;87: 5001–5007.
16. Hogervorst E, De Jager C, Budge M, Smith AD. Serum levels of estradiol and testosterone and performance in different cognitive domains in healthy elderly men and women. Psychoneuroendocrinology 2004;29: 405–421.
17. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62:188–193.
18. Hogervorst E, Williams J, Budge M, et al. Serum total testosterone is lower in men with Alzheimer's disease. Neuroendocrinol Lett 2001;22: 163–168.
19. Gillett MJ, Martins RN, Clarnette RM, et al. Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. J Alzheimer Dis 2003;5:267–269.
20. Okun MS, DeLong MR, Hanfelt J, Gearing M, Levey A. Plasma testosterone levels in Alzheimer and Parkinson diseases. Neurology 2004;62: 411–413.
21. Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66.
22. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
23. Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. J Gerontol A Biol Sci Med Sci 2004;59:75–78.
24. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. Aging Male 2003; 6:13–17.
25. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:39–44.
26. Mattis S. Dementia Rating Scale. Odessa, FL: Psychological Assessment Resources, 1988.
27. Tiernan K, Schenk K, Shimonova M, et al. An examination of the validity and reliability of a novel route test in healthy older adults and AD patients. Clin Neuropsychol 2004;8:39–42.
28. Wechsler D. Wechsler Memory Scale III. San Antonio, TX: The Psychological Corporation, 1997.
29. Craft S, Murphy C, Wemstrom J. Glucose effects on memory and complex non-memory measures: the influence of age, sex, and glucoregulatory response. Psychobiology 1994;22:95–105.
30. Moscovitch M. Cognitive resources and dual-task interference effects on retrieval in normal people: the role of the frontal lobes and medial temporal cortex. Neuropsychology 1994;8:524–534.
31. Lezak MD. Neuropsychologcial assessment. Third ed. New York, NY: Oxford University Press, 1995.
32. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–662.
33. Spreen O, Strauss E. A compendium of neuropsychological tests. New York: Oxford University Press, 1991.
34. Wechsler D. Wechsler Adult Intelligence Scale–Revised. San Antonio, TX: The Psychological Corporation, 1981.
35. Cherrier MM, Asthana S, Baker LD, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57:80–88.
36. Wechsler D. WAIS-III administration and scoring manual. San Antonio, TX: The Psychological Corporation, 1997.
37. Asthana S, Craft S, Baker LD, et al. Cognitive and neuroendocrine response to transdermal estrogen in postmenopausal women with Alzheimer's disease: results of a placebo-controlled, double-blind, pilot study. Psychoneuroendocrinology 1999;24:657–677.
38. Hogervorst E, Boshuisen M, Riedel W, Willeken C, Jolles J. 1998 Curt P. Richter Award. The effect of hormone replacement therapy on cognitive function in elderly women. Psychoneuroendocrinology 1999;24:43–68.
39. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. JAMA 1993;269:2637–2641.
40. Buckwalter J-G, Crooks VC, Robins SB. Hormone use and cognitive performance in women of advanced age. J Am Geriatr Soc 2004;52:182–186.
41. Miles C, Green R, Sanders G, Hines M. Estrogen and memory in a transsexual population. Horm Behav 1998;34:199–208.
42. Janowsky JS, Chavez B, Orowoll E. Sex steroids modify working memory. J Cogn Neurosci 2000;12:407–414.
43. Kerr JE, Allore RJ, Beck SG, Handa RJ. Distribution and hormonal regulation of androgen receptor (AR) and AR messenger ribonucleic acid in the rat hippocampus. Endocrinology 1995;136:3213–3221.
44. Galea LAM, Kavaliers M, Ossenkopp KP, Hampson E. Gonadal hormone levels and spatial learning performance in the Morris water maze in male and female meadow voles, *Microtus pennsylvanicus*. Horm Behav 1995;29:106–125.
45. Flood JF, Farr SA, Kaiser FE, La Regina M, Morley JE. Age-related decrease of plasma testosterone in SAMP8 mice: replacement improves age-related impairment of learning and memory. Physiol Behav 1995; 57:669–673.
46. Naghdi N, Nafisy N, Majlessi N. The effects of intrahippocampal testosterone and flutamide on spatial localization in the Morris water maze. Brain Res 2001;897:44–51.
47. Papasozomenos S, Shanavas A. Testosterone prevents the heat shock-induced overactivation of glycogen synthase kinase-3 beta but not of cyclin-dependent kinase 5 and c-Jun NH2-terminal kinase and concomitantly abolishes hyperphosphorylation of tau: implications for Alzheimer's disease. Proc Natl Acad Sci USA 2002;99:1140–1145.
48. Papasozomenos SC, Papasozomenos T. Androgens prevent the heat shock-induced hyperphosphorylation but not dephosphorylation of t in female rats. Implications for Alzheimer's disease. J Alzheimer Dis 1999; 1:147–153.
49. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. Proc Natl Acad Sci USA 2000;97:1202–1205.
50. Basaria S, Dobs AS. Risks versus benefits of testosterone therapy in elderly men. Drugs Aging 1999;15:131–142.
51. Liverman CT, Blazer DG. Testosterone and aging: clinical research directions. Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy. Washington, DC: National Academies Press, 2004.