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Exogenous Testosterone Alone or With Finasteride Does Not Improve Measurements of Cognition in Healthy Older Men With Low Serum Testosterone

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Abstract

Testosterone (T) levels decline as men age, but it is unclear whether this has an effect on cognition. Some studies indicate that lower T levels are associated with memory loss; thus, maintaining a higher T level could have positive effects on aspects of cognitive function. Concerns exist, however, about the effect of T therapy on the prostate in older men. We hypothesized that T replacement in older men with low T levels would improve aspects of cognitive function and that the addition of finasteride would not affect the T-induced cognitive improvements. Healthy men, 65 to 83 years of age, with baseline total T below 350 ng/dL and no evidence of cognitive impairment were randomly assigned to 1 of 3 regimens: 200 mg of T every 2 weeks by intramuscular injection with placebo pill daily (T-only), 200 mg of T every 2 weeks by intramuscular injection with 5 mg of finasteride daily (T+F), or placebo injections and pills (placebo). Sixty-nine men completed baseline cognitive testing; 65 completed at least 4 months, and 46 completed all 36 months of the study. Participants were given a battery of cognitive evaluations at baseline, 4 months, and 36 months, along with measurement of serum hormone levels. Serum total T, bioavailable T, and estradiol levels in the T-only and T+F groups significantly increased throughout the treatment period, whereas these hormone levels did not change in the placebo group. Only minimally significant differences were seen among the 3 groups in any evaluation of cognitive performance, either in the short-term (4 months) or the long-term (36 months) analysis. These results indicate that T

replacement, whether given alone or in combination with finasteride, for 36 months in healthy older men without cognitive impairment at baseline has no clinically significant effect on tests of cognitive function. Further studies are warranted to determine whether hormone replacement in men with preexisting cognitive impairment is beneficial.

Key words: Aging, testosterone replacement, memory, visual spatial function

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The influence of sex hormones on cognitive ability in aging men and women is a topic that has yielded research results that are not entirely intuitive. In women, the Women's Health Initiative Memory Study did not find improvement in cognitive function after treatment with conjugated estrogen plus progestin and, to the surprise of many, the risk of dementia increased in those receiving hormone replacement therapy (Shumaker et al, 2003). Some cross-sectional epidemiologic studies have reported that older men with higher levels of total or bioavailable testosterone (T) performed better on specific cognitive tests (Barrett-Connor et al, 1999a; Yaffe et al, 2002), whereas other studies have noted no relationship between androgen levels and cognitive function test results (Fonda et al, 2005). A prospective study of healthy older men, with no cognitive impairment and who were followed for a mean of 10 years reported that men with higher baseline free T levels had higher baseline cognitive scores for visual and verbal memory and visuomotor function and that the men with higher free T levels also had a slower decline in some aspects of cognitive function, especially visual memory (Moffat et al, 2002). An evaluation of this same study group, when followed for almost 20 years, reported that men with baseline lower levels of testosterone were more likely to develop Alzheimer disease (Moffat et al, 2004). A prospective study of men undergoing intermittent androgen suppression while being treated for prostate cancer showed adverse effects on spatial ability but improvement in verbal memory (Cherrier et al, 2003b). A dose-response trial of testosterone in older men with hypogonadism induced by treatment with a gonadotropin-releasing hormone analog reported improvement in the speed of information processing on a test of visuospatial function, but only at the highest T dose used (Gray et al, 2005).

Randomized controlled trials of T replacement therapy in older men have enrolled small numbers, partly because of uncertainties about T-related morbidity, including prostate health (Liverman and Blazer, 2004). Some studies have examined T replacement in men with low endogenous levels and others have studied those with normal baseline T levels, and the duration of T treatment has been limited, ranging from 1 to 12 months (Janowsky et al, 1994; Sih et al, 1997; Janowsky et al, 2000; Cherrier et al, 2001; Kenny et al, 2002). Results have varied, from showing improvement in working memory (Janowsky et al, 2000), verbal memory (Cherrier et al, 2001), and spatial cognition (Janowsky et al, 1994) to no change in performance on cognitive tests (Sih et al, 1997; Kenny et al, 2002).

We hypothesized that prolonged replacement of T for up to 3 years in healthy older men with low serum T levels would lead to improved performance on cognitive tests and that adding finasteride, a 5α-reductase inhibitor, to potentially protect the prostate from any adverse effects of the replacement T, would not affect the T-induced improvement in cognitive performance significantly. We also hypothesized that the effect of T treatment, compared with placebo, would be more pronounced after 3 years of treatment compared with a shorter treatment duration.

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Study Subjects

Men 65 years of age or older were recruited and screened as has been described previously (Amory et al, 2004). The primary inclusion requirement was 2 morning serum total T levels below 12.1 nmol/L (350 ng/dL). All participants were community-dwelling men with a Mini Mental Status Exam of 28 or higher. Exclusion criteria were severe illness, use of anabolic steroids, antiandrogens, glucocorticoids, bisphosphonates, diuretics, calcitonin, seizure medications, warfarin, antidepressants, cholinesterase inhibitors, or anxiolytics; Paget's disease; smoking or heavy alcohol use; sleep apnea; hematocrit above 48%; total cholesterol over 300 mg/dL; abnormal kidney, liver, thyroid, adrenal, or pituitary function; regular exercise more than 3 times a week; prostate issues (prostate cancer, prostate nodule on exam, prostate-specific antigen [PSA] above 4.0 ng/mL, or International Prostate Symptom Score above 8); urinary postvoid residual by ultrasound of more than 149 mL; or an abnormal transrectal ultrasound. The Institutional Review Board of Emory University—where all participant interactions occurred—approved the study, and men gave written informed consent before screening. Seventy men were included in the original study, but 1 man did not agree to undergo baseline cognitive testing.

Study Design

Participants were randomized by computer-generated assignment in permuted blocks of 6 to 1 of 3 treatment groups: 1) T-only group, T enanthate (TE; 200 mg intramuscularly every 2 weeks; Schein Pharmaceuticals, Florham Park, NJ) plus placebo pill orally daily; 2) T+F group, TE 200 mg intramuscularly every 2 weeks plus finasteride (5 mg/d orally; Merck & Co, Rahway, NJ); or 3) placebo group, sesame oil injections, 1 mL intramuscularly every 2 weeks, plus placebo pill daily. Testosterone therapy was by intramuscular injection because this study was initiated before the availability of reliable transdermal T. The sample size was estimated by assessing for a 1% change in bone mineral density, the primary endpoint of the study. Results of study treatment as regards bone, prostate, and other safety parameters have been reported previously (Amory et al, 2004).

Participants were treated for a total of 36 months. Only the research pharmacist and safety monitoring board knew the randomization assignment. A nurse administered the injections, and 98% occurred within 2 days of the scheduled time. Compliance was 95% on the basis of monthly pill counts of daily finasteride or placebo in the enrolled subjects. The study design included the potential for dose reductions of T or placebo injection for a hematocrit of more than 52% on safety monitoring tests.

Measurements

Blood was drawn in the morning at baseline and just before the injections every 2 week throughout the study, including after 4, 12, 24, and 36 months of treatment. Serum was stored frozen at −70 ° until the end of the study, when samples were concurrently assayed in duplicate for each participant. Testosterone, dihydrotestosterone (DHT), bioavailable T, and estradiol (E2) assays have been reported previously (Amory et al, 2004).

Cognitive tests were all done at baseline, 4 months, and 36 months. Testing was performed at the end of the 2-week T injection period, just before the next injection, and thus at the nadir T level for each participant. Tests were conducted on a separate day to avoid testing after fasting. All evaluations were made by the same psychometrist throughout the entire study. The psychometrist was blinded to the participants' group membership. The following cognitive domains were evaluated: attention (sequencing of numbers with a pencil [Trails A; US Army, 1944] and forward and backward sequencing of numbers presented orally [Digit Span test; Wechsler, 1981]), executive functioning (alternation between numbers and letters with a pencil [Trails B; US Army, 1944]), visuospatial skills (judgment of the angular orientation of lines [Judgment of Line Orientation test; Benton et

al, 1983]), visual memory (immediate and delayed recall of designs [Benton Visual Retention test; Benton, 1974]), and verbal memory (learning and recall of words [Selective Reminding test; Buschke, 1973]). Assessment of baseline depression and anxiety were also performed with the Beck Depression Inventory (Beck et al, 1961) and the Speilberger State-Trait Anxiety Questionnaire (Speilberger, 1983), respectively. Three alternative forms were available for assessing verbal and visual memory, and these forms were counterbalanced across study participants and time periods.

Statistical Analysis

One-way analyses of variance were performed for each neuropsychological measure, examining potential differences among the 3 participant groups at baseline, 4 months, and 36 months. Repeated measures analyses of variance were also performed for participants who received all 3 assessments.

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Sixty-nine men, with mean age of 70.8 ± 4.2 (range 65–83 years) and mean education of 15.8 ± 2.1 (range 12–20 years), participated in the study. Twenty-four were randomized to the T-only group, 22 to T+F, and 23 to placebo. At the 4-month evaluation, 65 men were available for testing, whereas 46 men completed the entire 36 months of the study. Of the 23 men who dropped out, 7 were in the T-only group and 8 each were in the T+F and placebo groups. Reasons for discontinuation included the following: personal reasons, concurrent illness, or a diagnosis of prostate cancer. At baseline, the groups did not significantly differ from each other with respect to age, education, and hormone levels (Table 1). The placebo group scored higher at baseline, 4 months, and 36 months than the T-only group on the Speilberger Anxiety Questionnaire, and the placebo group scored higher at 4 months than the T+F group on the Beck Depression Inventory. However, changes in level of anxiety and depression for the groups over time were not significant. Differences in the baseline characteristics between the men who discontinued and those who completed the study were not significant, although there was a trend toward fewer years of education among the dropouts (14.8 ± 2.5 years compared with 16.1 ± 1.8 years; $P = .06$).

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Table 1. *Hormone, prostate, anxiety, and depression measurements ($\bar{X}$ ± SD) at baseline, 4–6 months, and 36 months in 3 treatment groups of older men*

Mean nadir serum total T, bioavailable T, and total estradiol (E2) levels in the T-only and T+F groups significantly increased throughout the treatment period (Table 1), whereas these hormone levels did not change in the placebo group. Nadir serum total T and E2 levels tended to be higher in the T+F group compared with the T-only group, but this difference did not reach statistical significance for any time point for total T and was only significant at month 36 for E2. Serum DHT levels did not change throughout the treatment period in the placebo group but increased slightly in the T-only group by month 36 and, as expected, decreased significantly in the T+F group (Table 1). The maximum decline in serum DHT was to 47% of baseline, which was reached by month 4.

For the subset of men from whom blood was sampled at multiple times throughout the 2-week T dosing

period (6 men in the placebo group, 7 men in the T-only group, and 9 men in the T+F group), peak serum total T levels were at or above the normal serum T range for the 2 T treatment groups, with mean peak value for the T-only group being 35.9 ± 12.1 nmol/L and that for the T+F group being 43.5 ± 7.6 nmol/L. Average total T levels during the 2-week dosing interval were 25.8 ± 6.9 for the T-only group, 33.0 ± 6.4 for the T+F group, and 11.8 ± 2.3 nmol/L for the placebo group. Between the 2 treatment groups, peak T levels were not different (P = .13), but the average total T levels were somewhat higher in the T+F group (P = .04).

As reported previously (Amory et al, 2004), increase in serum PSA in the T-only group was small but significant (P < .001 by month 36) but did not change in the other 2 treatment groups (Table 1). Prostate volume increased significantly in all treatment groups over the 36-month period, but the increase in volume in the T+F treatment group was small and significantly less (P = .02) than the increase in prostate volume of the placebo and T-only groups, with the latter 2 groups having a similar increase in volume over the 36 months (Table 1).

Among the 6 cognitive measures administered during this study, 1 index of attention (ie, reversing a series of digits) was statistically significantly different (P < .05) at 36 months (Table 2). The T-only group correctly reversed more digits ($\bar{X}$ ± SE, 8.38 ± 0.49) than the T+F group (6.64 ± 0.44) and the placebo group (6.63 ± 0.47). One index of verbal memory also was statistically significantly different (Table 2). The T+F group recalled more words (46.07 ± 1.72) than the T-only group (40.25 ± 1.61) and the placebo group (38.38 ± 2.32). Otherwise, cognitive differences between the treatment and placebo groups were not observed in any other cognitive domain and its associated dependent variables.

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Table 2. *Analysis of performance differences at baseline, 4 months, and 36 months on cognitive tests between treatment and placebo groups*[*]

Repeated measures analyses of variance were performed for a subset of those patients (n = 46) who completed all 3 assessments. Group and Time for the number of intrusions on the Selective Reminding test interacted significantly (P < .05). The T-only and T+F groups exhibited a decline in the number of intrusions ($\bar{X}$ ± SE for baseline, 4 months, and 36 months, respectively): T-only: 1.94 ± 0.32, 0.94 ± 0.32, 0.75 ± 0.21 and T+F: 1.79 ± 0.57, 1.29 ± 0.57, 1.07 ± 0.32 in contrast to the placebo group: 0.57 ± 0.22, 2.13 ± 0.63, 1.56 ± 0.40. No other interactions were significant, indicating that the 3 groups performed differently across time periods. Consistent with the previous findings for the separate analyses of each time period alone (Table 2), the T-only group (P < .05) correctly reversed more digits (7.92 ± 0.46) than the T+F group (6.50 ± 0.48) and placebo group (6.56 ± 0.48). In addition, performance in judging the angular orientation of lines was overall significantly better (P < .01) for the T-only group (12.92 ± 0.45) and T+F group (13.21 ± 0.43) compared to the placebo group (11.63 ± 0.47). Finally, the effect of time was significant (P < .05) for 1 index of verbal memory performance. Delayed recall of words at baseline was higher (4.57 ± 0.56) compared with 4 months (3.98 ± 0.48) and 36 months (3.75 ± 0.51).

Analyses were also performed combining the T-only and T+F groups and comparing them with the placebo group. Separate between-group analyses of variance at each time period revealed only 1 significant difference (P < .05) at 4 months between the T-treated group compared with the placebo group, with

the placebo group recalling fewer total words (38.55 + 1.51) than the T group (42.16 + 0.99). The repeated measures analyses for those participants who completed all 3 assessments again indicated a significant interaction ($P < .01$) of Group and Time for the number of intrusions, with the T-treated group making fewer errors compared with the placebo group. The performance of the combined T-treated groups on the line-orientation task was better than in the placebo group ($P < .01$). Finally, a practice effect was found for digits forward ($P < .01$), with better performance from baseline to 4 months to 36 months.

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In this study of healthy older men with low serum T and no evidence of cognitive impairment, supplementation with exogenous T for a period of up to 3 years did not consistently affect performance on tests of attention, executive function, visuospatial skills, or visual and verbal memory skills. Participants receiving T alone showed small improvement in only 1 test of attention, whereas participants receiving testosterone and finasteride, a 5α-reductase inhibitor, showed improved performance in only 1 component of a test of verbal memory.

Interest in the effects of T on cognition in humans extends from animal studies of its effect on the brain on both the development and maintenance of cognitive function (Rosario et al, 2004; Yaffe, 2004). In a recent study in rats, the administration of T and its nonaromatized metabolites, DHT and 3α-androstanediol, all improved cognitive ability and decreased anxiety (Edinger and Frye, 2004), suggesting that T acts in the rodent brain to affect cognitive performance through aromatization to estrogen or conversion to 5α-reduced nonaromatizable metabolites.

In humans, studies of the effects of T on cognitive function tests in older men with normal, low-normal, or low baseline T levels, have provided mixed results. Similar to our study, Sih et al (1997) enrolled older men with low serum T at baseline and used injectable T for hormone replacement. Although cognitive function was not the primary outcome of the study, tests of memory, recall, and verbal fluency were given to subjects over a period of 12 months of T therapy. The group receiving T had higher baseline function on the cognitive tests, but throughout the study, no improvement or decline occurred, and the difference between the T and placebo groups remained unchanged from baseline. Other randomized placebo-controlled studies of T therapy and cognition in elderly men have included either men with low and low-normal T or men with normal baseline total T levels. In the study by Janowsky et al (2000), some improvement in working memory was seen after 4 weeks of T supplementation in men with baseline low to low-normal T levels. Another study (Cherrier et al, 2001) found that after 6 weeks of T supplementation in men with normal baseline total T levels, verbal memory improved. Both of these studies used injectable T. Two other studies that used scrotal patches to administer T also tested men with normal baseline total T levels. In one study (Kenny et al, 2002), the group receiving hormone replacement had improved performance on Trailmaking B, 1 of 4 cognitive tests administered, but did not differ at any time from the placebo treatment group. In another study (Janowsky et al, 1994), elderly men given supplemental T were found to have improved spatial cognition. The variability among the results of these randomized placebo-controlled trials hints at the complexity of hormonal interactions within the brain. Improvement in cognitive function test scores with T therapy in these studies was seen in elderly men who did not have frankly low levels of T before treatment.

It also is not clear which sex steroids contribute to various domains of cognitive function in men. A prospective study of mildly hypogonadal men receiving either T gel or DHT gel assessed both verbal

and spatial cognitive function (Cherrier et al, 2003a). Men receiving T gel showed improvement in verbal memory compared with those receiving DHT gel. This suggests that E2, or other aromatized products of T metabolism, could have an important influence on human verbal cognition. Those receiving only DHT performed better on tests of spatial memory, suggesting the nonaromatized products of T metabolism could have a greater effect on spatial cognition. Several studies have shown that higher levels of E2 negatively affect performance on tests of spatial function (Barrett-Connor et al, 1999b; Janowsky et al, 2000; Cherrier et al, 2003a). Bioavailable T levels might be more closely correlated with cognitive function than total T. Although total T levels might decrease only slightly with increasing age, bioavailable T might decrease by 50% (Barrett-Connor et al, 1999a; Yaffe et al, 2002). In our study, serum DHT levels were significantly lower in the T+F group, whereas serum E2 levels and bioavailable T levels both were higher in the 2 T therapy groups. Although the T-only group showed improved performance on 1 test of attention and the T+F group on 1 test of verbal memory, the treatment groups did not consistently demonstrate improved performance in any specific cognitive domain.

The 50% DHT reduction obtained with the use of finasteride in this study, however, was less than the 70%–80% reduction expected on the basis of studies of finasteride without T replacement (McConnell et al, 1998) and might have occurred because finasteride incompletely blocks the conversion of T to DHT (Rittmaster, 1997), especially in the presence of high serum T levels produced by the T injection regimen. This is mirrored by the prostate-related results, which demonstrated an attenuation of increase, rather than the expected decrease, in both serum PSA and prostate volume with the addition of finasteride (McConnell et al, 1998).

Although cognitive measures were not the primary outcome of our study, the duration of treatment and follow-up of the participants is the first to provide long-term data of the effects of T replacement on cognitive function in men with no obvious cognitive dysfunction at baseline. The dropout rate over the 36 months of the study was high, but analysis of the dropouts' baseline characteristics revealed only a nonsignificant difference in years of education. The educational status of the study participants was very high, with most participants having a college degree, many with a postgraduate degree. It is possible this affected our ability to find differences in cognitive function among groups. Population-based studies of elderly men suggest the relationship between T and certain cognitive functions are U-shaped, such that there is an optimal level of T for some cognitive functions (Muller et al, 2005). With the use of the injectable mode of administration of T in this study, serum levels of T varied greatly over the dosing interval, unlike those that might be found with replacement via patch or gel. Uniformly, however, all of the cognitive testing was done when the serum levels of supplemental T were at their lowest just before the next injection, and previous randomized, placebo-controlled trials of testosterone replacement therapy did not seem to demonstrate any differences in T effect on cognition, whether T was dosed by injection or by patch or gel. Although the men in this study had baseline serum T levels below the range of normal for young adult men, T therapy achieved the same levels of T that have shown effects on cognition in other studies. All of the cognitive assessments were performed by the same individual and at the same time of day and at the same point in the dosing schedule for T, just before the next injection, lessening the risk of variability in performance.

This study, in which we found minimal effects on cognitive test scores with up to 3 years of T therapy in healthy older men with low serum T levels and no significant baseline cognitive dysfunction, adds to the literature reporting inconsistent and doubtful clinically meaningful effects on cognition of T replacement therapy in men who have no evidence of cognitive impairment. Future research on the cognitive effects of T could address whether men who have cognitive impairment from a disorder such as Alzheimer disease might gain functional ability or slowed

progression of disease through T replacement. To date, several small studies of T therapy have been made in men with mild to moderate dementia, and these also have provided mixed results. Two such studies reported some improvement in cognitive testing with T therapy (Tan and Pu, 2003; Cherrier et al, 2005), and 2 reported no effect on cognitive function (Kenny et al, 2004; Lu et al, 2006).

Footnotes

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