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A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease

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ABSTRACT

The male aging process brings about declines in hormonal function including a gradual decline in bioavailable testosterone levels. Animal studies suggest that testosterone modulates cognitive function through enhancing acetylcholine release and up-modulation of nicotinic receptors. Tau protein deposition is also affected by androgen supplementation in animals. We hypothesize that testosterone replacement in elderly hypogonadal males may improve cognition, in particular the visual-spatial domain. Thirty-six male patients with a new diagnosis of Alzheimer's disease had their total and bioavailable testosterone levels measured. None of the patients had been on acetylcholinesterase inhibitors. Ten of the 36 patients (28%) were deemed biochemically hypogonadal (total testosterone < 240 ng/dl or 7 nmol/l). Five of the hypogonadal patients were randomized to testosterone and five to placebo. Initial Alzheimer's Disease Assessment Scale cognitive subscale (ADAScog) and Mini Mental Status Examination (MMSE) ranged from 31 to 19 and from 17 to 22, respectively. The clock drawing test (CDT) and the pentagon-tracing portion of the MMSE were used as measures of visual-spatial abilities. Normal prostate-specific antigen (PSA) levels were essential before treatment with intramuscular testosterone, 200 mg every 2 weeks. Measurement of testosterone, complete blood count, lipids, PSA and neuropsychological cognitive tests were repeated at 3, 6, 9 and 12 months of treatment. In the testosterone-treated group, levels of total testosterone increased from a mean of 126.4 ng/dl to 341 ng/dl or 3.6 nmol/l to 9.7 nmol/l (p = 0.11). Bioavailable testosterone also increased from a mean of 48.7 ng/dl to 142 ng/dl or 1.39 nmol/l to 4.05 nmol/l (p = 0.10). PSA levels were also elevated from a mean of 0.98 to 1.37 ng/ml (p = 0.07). ADAScog improved from a mean of 25 to 16.3 (p = 0.02); MMSE improved from a mean of 19.4 to 23.2 (p = 0.02), CDT also improved from 2.2 to 3.2 (p = 0.07). One patient stopped treatment because of hypersexual behavior. The placebo-treated group deteriorated gradually. This small pilot study performed in aging male patients suggests that testosterone could indeed improve cognition, including visual-spatial skills in mild to moderate Alzheimer's disease.

INTRODUCTION

It is known that hormones modulate cognition through interaction with neurotransmitters[1]. Testosterone may also prevent hyperphosphorylation of tau protein[2]. More is known about the

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effects of loss of estrogen than loss of testosterone on cognition. The levels of total, bioavailable and free testosterone decline in aging males. Total testosterone declines about 100 ng/dl or 2.9 nmol/l per decade after age 50, but bioavailable testosterone and free testosterone decline far more dramatically[3]. Testosterone may affect cognitive function in various ways. The hormone is synthesized from cholesterol and the pathway to testosterone includes dehydroepiandrosterone (DHEA), DHEA sulfate (S), androstenedione and progesterone. In turn, testosterone is broken down to estrogen by the enzyme aromatase. Estradiol affects cognitive function positively in females[4], but the role of estradiol in cognitive function in aging males is unclear.

Associations have been found between bioavailable testosterone and memory. Our previous study of men reporting memory loss in the andropause suggests that memory loss is perceived as an important symptom in the aging process in males[5]. A study of 547 community-dwelling men[6] found that those with higher levels of bioavailable estradiol had poorer scores on the Blessed Information Memory Concentration (BIMC) scale and Mini Mental Status Examination (MMSE)[7]. Men with higher levels of bioavailable testosterone levels had better scores on the BIMC test and the selective reminding test. In another recent observation, it appeared that amyloid β-peptide increased when testosterone was withdrawn in six men aged between 44 and 83 years who underwent hormonal suppressive therapy for adenocarcinoma of the prostate[8].

Despite the above observations, it is well known that an association does not prove causality. With informed consent from caregivers, we went ahead to give testosterone to hypogonadal patients with a diagnosis of Alzheimer's disease who had previously not been treated with acetylcholinesterase inhibitors. The primary purpose was to measure testosterone effects on cognitive ability. The other purpose of our study was to gain information on the safety and tolerability of testosterone in the treatment of early-moderate stage aging male patients with Alzheimer's disease.

METHODS

This was a randomized controlled study of testosterone versus placebo, performed in a Veterans Administration nursing home in Texas. The Institutional Review Board at Texas Tech University Health Sciences Center approved the protocol. Consecutive admissions to the nursing home were screened for Alzheimer's disease using the Folstein MMSE. If the patients had suggestion of Alzheimer's disease on screening, they were subjected to further neurological evaluation including blood analysis and computed tomography (CT) of the brain. As this was a specific study on the impact of testosterone on Alzheimer's disease, CT of the brain was used to exclude other causes of dementing illnesses including stroke, brain tumors, etc. If the patient met the National Institute of Neurological Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[9] criteria for probable Alzheimer's disease, they had their testosterone status determined, along with their prostate-specific antigen (PSA) levels. None of the patients had other neurological disorders including strokes, nor had they been treated with acetylcholinesterase inhibitor drugs. They also had to have normal rectal examinations and PSA results. If entry criteria were met, informed consent was discussed with the caregiver, usually the spouse. There were no refusals. Five patients were randomized to receive intramuscular testosterone enanthate 200 mg every 2 weeks. Five patients were randomized to receive a placebo. Physical, cognitive and behavioral assessments were performed every 3 months; along with blood analysis including testosterone, PSA, lipids and hemoglobin. The clock drawing test (CDT)[10] and the pentagon-tracing portion of the MMSE were used as measures of visual-spatial abilities. Alzheimer's Disease Assessment Scale cognitive subscale (ADAScog) and the Folstein MMSE were used to assess changes in cognitive and global function. The cognitive tests were performed by a single certified geriatric nurse practitioner, and verified by a board certified, fellowship-trained geriatrician. Physical examinations included examination for side-effects of testosterone including leg and breast swelling, and a rectal examination. Hemoglobin and lipids were assayed to follow any potential side-effects from testosterone. Testosterone was measured using tracer analog methods. Data were entered into Excel. Descriptive and comparative analyses were performed using the SPSS package.

RESULTS

Thirty-six male patients were diagnosed to have Alzheimer's disease by NINCDS-ADRDA criteria. However, only ten of the 36 (27%) proved to be hypogonadal as defined by a total testosterone level < 250 ng/dl (< 10 nmol/l). Five of these patients were treated with testosterone and five served as the control group. The mean age of the patients was 72.4 years (range 68–80). In the testosterone-treated group, mean baseline ADAScog was 25 (range 31–19), MMSE was 19.4 (range 17–22). The CDT could be quantified and the mean baseline CDT was 2.2 (range 2–3). In the placebo-treated group, the mean age was 68.9 years (range 67–82), mean ADAScog was 26, mean MMSE was 20.5 and mean CDT was 2.5. However, as the pentagon-tracing portion of the MMSE could not be quantified, it was compared qualitatively at monthly intervals.

The improvement in ADAScog was noted as early as 3 months (Figure 1). The mean gain from baseline was 7.2. At 6 months, the mean gain from baseline was maximal at 12.0. The effect of testosterone then seems to wane, and at 9 months, the mean gain dropped to 9.6 ($p = 0.02$). Of those who completed the trial, the mean gain in ADAScog at 12 months was 4.8. At 9 months, mean MMSE of the five patients improved from a mean of 19.4 to 23.2 ($p = 0.02$). CDT served as a simple measure of visual-spatial abilities. There was improvement of the mean CDT of the five patients from a mean of 2.2 to 3.2 ($p = 0.07$) at 9 months. The pentagon-tracing portion of the five patients was compared and subjectively, three of the five patients could copy better pentagons, some having omitted a side of the pentagon at baseline. The untreated-group improved on average four ADAScog points at 3 months, and went on to worsen seven points below baseline over 9 months.

The safety aspect of testosterone was considered in this trial. At 9 months of treatment, total testosterone levels increased in the testosterone-treated group from a mean of 126.4 ng/dl or 3.6 nmol/l to 341 ng/dl or 9.7 nmol/l ($p = 0.11$). Bioavailable testosterone also increased from a mean of 48.7 ng/dl to 142 ng/dl or 1.39 nmol/l to 4.05 nmol/l ($p = 0.10$). PSA levels were also elevated from a mean of 0.98 to 1.37 ng/ml ($p = 0.07$), all within the safety limits and not demonstrating significant PSA velocity[11]. None of the five treated patients developed polycythemia or hyperlipidemia. Physical examination also did not reveal changes in prostate size, leg swelling or breast enlargement. At the 9th month, one patient was dropped from the trial because he was exhibiting aggressive and hypersexual behavior, possibly secondary to the testosterone administration. After discontinuing the testosterone injections, his behavior settled. No antipsychotics were needed to control his behavior.

DISCUSSION

This pilot study represents the first attempt to treat hypogonadal aging male Alzheimer's disease patients with testosterone. Animal studies suggest that androgens can modulate cognitive function through enhancing acetylcholine release and up-modulation of nicotinic receptors[12,13]. Previous studies proving the link of testosterone with cognition have been largely epidemiological studies demonstrating associations but not causality[2]. In

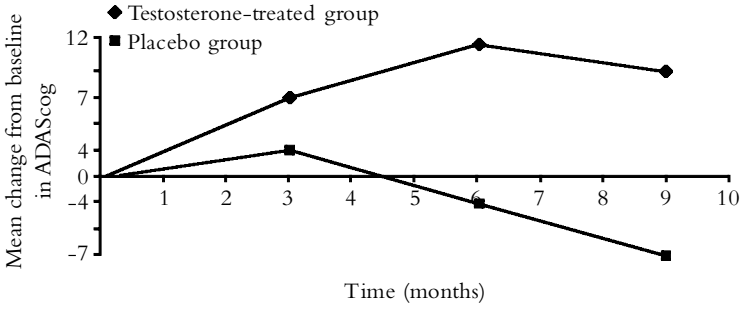

Figure 1 Graph showing mean change from baseline in Alzheimer's Disease Assessment Scale cognitive subscale (ADAScog) with time

Barrett Connor's study there is a suggestion that in older men, low estradiol and high testosterone levels predicted better performance on several tests of cognitive function including memory. Chemical andropause with hormonal suppressive therapy for prostate cancer led to an increased amount of amyloid β-peptide in the brain of six patients[8].This also suggests an association of the role of testosterone in protecting the brain from Alzheimer's disease.

Previous studies on cognition focused on the effect of testosterone in healthy eugonadal patients without Alzheimer's disease. In these studies it was demonstrated that testosterone could modulate visual-spatial cognitive function[14,15]. Another study on the effects of testosterone in hypogonadal non-demented men found that testosterone did not improve memory[16]. We demonstrated improvements in visual-spatial domains of the testosterone-treated patients with Alzheimer's disease who were at the same time hypogonadal. It was quite remarkable that the patients in this trial obtained as much benefit, if not more in terms of gain of ADAScog, as compared to acetylcholinesterase inhibitors[17]. Unfortunately, it seems that like acetylcholinesterase inhibitors, the effect on cognition is short lived and testosterone does not offer a cure but may alter deterioration by as much as one year. Alzheimer's disease is a devastating disease, and it is our belief that any attempt to improve the quality of life of these patients, if the drug is safe, will be a step forward. The pilot study was terminated at 9 months, as an acetylcholinesterase inhibitor, donezepil (Aricept®), was instituted at this point. Donezepil is one of the FDA-approved drugs for Alzheimer's disease.

In our trial, we assessed whether testosterone was safe for aging male patients with Alzheimer's disease. Elevation of PSA was not significant in our pilot study, partly because of the small sample size. Fear of prostate cancer limits many physicians in the prescription of testosterone especially in the elderly[18]. While trials of testosterone replacement in elderly patients have not demonstrated remarkable changes in PSA levels[19], it must be appreciated that the prevalence of prostate cancer is significantly higher with aging. We also note that testosterone may worsen dementia symptoms as demonstrated by the patient who exhibited aggressive and hypersexual behavior. This side-effect should be studied in more detail in later trials.

There may be several possible mechanisms as to how testosterone changed cognition in our study cohort. The hippocampus is endowed with several thousand testosterone receptors, and it is believed that exogenous testosterone given to these patients led to increased locking of the hormone with the receptors. Acetylcholine release occurs and there may even be up-regulation of nicotinic receptors.

The results of our pilot study are preliminary but encouraging. It is in no way conclusive, but does open a Pandora's box. The world is aging[20] and many aging men will also be having failing cognition as a result of the aging process. The study is limited by sample size, and better measures of visual-spatial functioning. The effect of testosterone in Alzheimer's disease may extend beyond cognitive benefits, but may also improve functionality of Alzheimer's disease patients, as muscle wasting is often associated with later stages of Alzheimer's disease[21]. Further studies should be performed to confirm our pilot study results, and also to determine if testosterone might work in conjunction with existing acetylcholinesterase therapy in delaying deterioration of Alzheimer's disease.

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