

Effects of Transdermal Testosterone on Cognitive Function and Health Perception in Older Men With Low Bioavailable Testosterone Levels

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Background. Many men older than 50 years have bioavailable testosterone levels below the reference range for young adult men. The impact of the decreased androgen levels on cognition and health perception has received little attention.

Methods. Sixty-seven men (mean age 76 ± 4 years, range 65–87) with bioavailable testosterone levels below 128 ng/dl (lower limit for adult normal range) were randomized to receive transdermal testosterone (2–2.5 mg patches/d) or placebo patches for 1 year. All men received 500 mg supplemental calcium and 400 IU vitamin D. Outcome measures included sex hormones [testosterone, bioavailable testosterone, sex hormone binding globulin (SHBG), estradiol, and estrone], cognitive tests (Digit Symbol, Digit Span, Trailmaking A and B), health perception (Medical Outcome Survey Short-form 36 or SF-36), lower extremity muscle strength and power, and calcium intake.

Results. Twenty-three men (34%) withdrew from the study; 44 men completed the trial. Bioavailable testosterone levels increased from 93 ± 34 (SD) to 162 ± 100 ng/dl ($p < .002$) at 12 months in the testosterone group ($n = 24$) while no change occurred in the control group ($n = 20$). While there was no change in estradiol levels in either group, estrone levels increased in the testosterone group (28 ± 7 to 32 ± 9 pg/dl, $p = .017$). Scores on the Digit Symbol test improved in both the testosterone and placebo groups. Scores on Trailmaking B improved in men treated with testosterone ($p < .005$), although the changes were not statistically different from the changes seen in the placebo group. Twelve-month scores on Trailmaking B for the entire group were correlated with 12-month testosterone levels ($p = .016$). Scores for health perception measured by SF-36 did not change significantly, though scores of mental and general health declined in both groups during the 12-month intervention. Twelve-month bioavailable testosterone scores were directly correlated with scores for physical role ($p = .022$), vitality ($p = .036$), and the physical composite score ($p = .010$).

Conclusions. Transdermal testosterone treatment in men with low bioavailable testosterone levels does not impair and may improve cognitive function. Treatment did not improve health perception but this may have been due to the side effects of skin irritation suggested by similar reactions in both the testosterone and placebo groups.

MANY men older than the age of 50 have bioavailable testosterone levels below the normal young adult range. There is a progressive decrease in bioavailable testosterone levels with increasing age and further declines associated with medical comorbidity (1–3). The significance of the gradual decline in testosterone levels on cognition and health perception has received little attention. In animal studies, testosterone replacement reverses memory loss and decreases amyloid precursor protein production (4,5). Young hypogonadal men with low testosterone levels have impaired cognitive function, compared with eugonadal men, that improved following testosterone replacement (6). Similarly, in studies of younger men with severe testosterone deficiency, testosterone levels and spatial cognition are inversely associated (7–11). While few studies exist in older men, higher testosterone levels were predictive of performance in several domains of cognition (12,13), and testosterone supplementation improved performance on spatial cognition and verbal and working memory compared to placebo in three small studies (14–16).

Health perceptions related to testosterone replacement have not been extensively investigated in older men. Young hypogonadal men reported decreased irritability, tiredness, anxiety, and sadness and increased energy level, cheerfulness, and sense of well being on testosterone replacement (17,18). Similarly, untreated young men with hypogonadism reported higher scores for anger, fatigue, and confusion than eugonadal control subjects (19). However, no association has been found between health perception and baseline testosterone levels in other studies (18,20), including studies of older men (21). In studies of men receiving testosterone replacement, no changes in health perception have been detected in men with testosterone levels 1 SD below the young adult mean (22) or in men with normal testosterone levels (23).

This study is part of a larger study to assess the effects of testosterone on bone and muscle (24) and in addition, we sought to determine the effects of transdermal testosterone supplementation on cognition and health perception in men older than 65 years with low levels of bioavailable testosterone. We hypothesized that transdermal testosterone replace-

ment would improve cognitive function and health perception in older men compared with placebo.

METHODS

Study Population and Design

Men were recruited to take part in a study to determine the effects of testosterone on bone and muscle (24). As part of that study, we also measured cognition and health perception. Information on recruitment and eligibility are described elsewhere (24). A total of 67 men were enrolled in the study.

Men were randomized to receive 12 months of treatment with either transdermal testosterone supplementation (5 mg/d) using the nonscrotal testosterone patch or a placebo patch; all men received 500 mg of calcium and 400 IU of cholecalciferol. We measured total and bioavailable testosterone, sex hormone binding globulin (SHBG), estrone, and estradiol, and we administered the Medical Outcome Survey Short-form 36 (SF-36) and standardized tests of cognitive function (Digit Symbol, Digit Span, Trailmaking A, Trailmaking B) at baseline and 12 months. We assessed skin effects of the transdermal patch and symptoms of itching using a 5-point scale (0 = no rash; 4 = erythema, induration, and bullae) and a 4-point scale (1 = none; 4 = persistent), respectively (25).

Biochemical Assays

Total and bioavailable testosterone and SHBG measurements were performed at Endocrine Sciences Inc., Calabasas Hills, California. Testosterone levels were measured by radioimmunoassay, SHBG by competitive binding assay, and bioavailable testosterone by competitive binding of the non-SHBG-bound portion of testosterone following ammonium sulfate precipitation of the SHBG-bound steroid as described by Nankin (26). Estradiol and estrone were performed using radioimmunoassay (Diagnostic Systems Lab, Inc., Webster, TX).

Statistical Analysis

Baseline and clinical characteristics were reported using means and standard deviations stratified by treatment group. One-way analysis of variance (ANOVA) or chi-square analysis was used to test the difference in baseline characteristics between the treatment groups. Wilcoxon signed ranks test was used to assess change within groups over time, and ANOVA was used to compare the percent change in health perception or cognitive scores between groups. Multiple linear regression analysis was performed using 12-month scores of the domains of the SF-36, controlling for baseline scores, as the dependent variable; these domains included physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health. The changes in cognitive test scores from baseline to 12 months were also entered as dependent variables, including change in Digit Scan, Digit Symbol, Trailmaking A, and Trailmaking B scores. Independent variables in the regression models were those variables found to correlate with the dependent variables; variables entered into the correlation matrix included sex hormone levels, physical activity,

strength, and skin effect (rash and itching) scores. All analyses were done using SPSS version 10.0 (SPSS, Inc., Chicago, IL).

RESULTS

Sixty-seven men were randomized to treatment. Twenty-three men (33%) discontinued due to rash ($n = 4$), elevation in prostate specific antigen level ($n = 5$), intercurrent illness ($n = 9$), and personal reasons ($n = 5$) with no significant differences between the groups. Forty-four men completed the study: 24 men in the testosterone group and 20 men in the placebo group. The baseline characteristics of the study sample are presented in Table 1; no significant differences existed in baseline information between the treatment and control groups.

Following treatment, bioavailable testosterone increased in the testosterone group from 93 ± 34 ng/dl to 162 ± 100 ng/dl ($p = .002$) and was unchanged in the placebo group (101 ± 26 ng/dl, $p = .86$). Estrone levels increased from 28 ± 7 pg/dl to 32 ± 9 pg/dl ($p = .017$) in the testosterone treatment group but did not change in the placebo group ($p = .12$). There were no significant changes in SHBG or estradiol in either group.

Results of cognitive testing are summarized in Table 2. Digit Symbol test scores improved in both groups. Trailmaking B scores improved in the testosterone group compared to baseline ($p < .01$). No changes were found in scores on Trailmaking B in the placebo group, and no significant difference could be detected between scores from the testosterone and placebo groups ($p = .19$). After controlling for baseline scores, the change in Trailmaking B score in the entire group was significantly associated with 12-month testosterone levels by linear regression analysis ($R^2 = .18$, $p = .016$).

Table 1. Baseline Characteristics of 44 Men Selected for Low Testosterone Levels Completing 1 Year of Testosterone or Placebo Supplementation

Variable	Testosterone $n = 24$	Placebo $n = 20$
Age (years)	76 ± 4	75 ± 5
Testosterone (nmol/l)	13.5 ± 6.1	13.5 ± 3.6
BioT (nmol/l)	3.23 ± 1.28	3.47 ± 0.80
Estradiol (pmol/l)	70 ± 26	58 ± 21
Estrone (pmol/l)	28 ± 8	27 ± 7
Calcium intake (mg/d)	805 ± 322	876 ± 333
Strength (Newtons)	735 ± 223	755 ± 220
Power (Watts)	368 ± 114	380 ± 140
Marital status (n married)	21 (87%)	17 (85%)
Education (% with college degree or higher)	12 (50%)	15 (75%)
History of depression	0	1
History of heart disease	12	15
History of hypertension	12	15
Antihypertensive treatment	8	4
Cholesterol-lowering agent	3	4
Antidepressant therapy	0	1

Notes: Values are mean and standard deviation. Comparison made either by analysis of variance for continuous variables or chi-square analysis for dichotomous variables. BioT = bioavailable testosterone.

$p < .05$.

Table 2. Comparison of Cognitive Test Scores Prior to and Following 12 Months of Testosterone or Placebo Treatment

Test	Testosterone		Placebo	
	Baseline	12 mo	Baseline	12 mo
Digit Span	11.4 ± 2.6	11.5 ± 2.5	11.8 ± 1.8	12.4 ± 1.9
Digit Symbol	42 ± 8	46 ± 9*	43 ± 8	47 ± 7**
Trailmaking A (sec)	42 ± 14	38 ± 8	39 ± 16	38 ± 17
Trailmaking B (sec)	104 ± 39	87 ± 29*	95 ± 30	90 ± 38

Notes: Values are mean and *SD*. No differences between groups by analysis of variance.

* $p \leq .01$ compared to baseline; ** $p \leq .05$ compared to baseline.

SF-36 scores are shown in Table 3. Overall, there were few changes in health perception. Significant declines in the general and mental health domains are seen in both groups, and the changes were similar. Twelve-month bioavailable testosterone levels predicted 12-month scores for role-physical ($R^2 = .39$, $p = .022$), vitality ($R^2 = .17$, $p = .036$), and physical component composite ($R^2 = .17$, $p = .010$) by linear regression analysis, after controlling for baseline scores. In similar analysis, the 12-month score for bodily pain, after correcting for baseline score, was negatively associated with itching score ($R^2 = .08$, $p = .05$).

There were no significant differences in rash irritation between the testosterone groups (1.9 ± 0.3 vs 0.8 ± 0.2 ; $p = .09$), but 77% of the men in the testosterone group compared with 40% of men in the placebo group reported a score of 2 or greater, signifying a rash with induration. Itching was more frequent in the men in the testosterone group compared with the placebo group (3.2 ± 0.2 vs 2.6 ± 0.2 , $p = .001$).

DISCUSSION

Treatment with testosterone did not result in overall changes in cognition compared with placebo, though significant improvements from baseline scores were detected on

Table 3. Comparison of Scores on Individual Domains of Health Perception Measured by Medical Outcome Survey Short-Form 36 Prior to and Following 12 Months of Testosterone or Placebo Treatment

Variable	Testosterone		Placebo	
	Baseline	12 mo	Baseline	12 mo
Physical function	79 ± 25	78 ± 23	81 ± 21	77 ± 16
Role-physical	73 ± 42	71 ± 39	64 ± 41	59 ± 37
Bodily pain	76 ± 26	72 ± 31	74 ± 23	74 ± 20
General health	79 ± 15	71 ± 24*	72 ± 18	67 ± 17**
Vitality	69 ± 18	68 ± 21	67 ± 17	61 ± 15
Social function	96 ± 10	91 ± 19	96 ± 11	85 ± 21
Role-emotional	93 ± 22	85 ± 30	96 ± 11	82 ± 31
Mental health	89 ± 9	85 ± 12**	88 ± 9	82 ± 14*
Physical composite score	47 ± 10	47 ± 10	45 ± 11	44 ± 10
Mental composite score	58 ± 5	56 ± 8	58 ± 6	54 ± 10*

Notes: Values are mean and *SD*. No differences between groups by analysis of variance.

* $p \leq .05$ compared to baseline; ** $p \leq .01$ compared to baseline.

the Trailmaking B test. The inability to detect differences in Trailmaking B scores between the testosterone and placebo groups may have been due to the small sample size. However, an association between the 12-month testosterone levels and the changes in scores of the Trailmaking B test suggests that our results are not spurious. Others who used Trailmaking B in their evaluations have not found differences or changes associated with testosterone levels or supplementation, but the study populations were not selected for low testosterone levels and are not directly comparable with our study (12,14). Trailmaking B is a test that requires both right and left cerebral hemisphere and overall general brain functions for integration (27,28). Testosterone deficiency may impair performance on this test, although this theory has not been directly tested. Testosterone may also exhibit its effect indirectly via estrogen after aromatization. Estrone increased following testosterone supplementation in our study while Janowsky and colleagues report a decrease in estrogen levels following testosterone replacement (14). An inverse relationship between estrogen levels and spatial cognition has been found in several studies of women (29).

There is evidence of cognitive improvement associated with higher testosterone levels in the literature. Barrett-Connor and Goodman-Gruen, in a population-based study of 547 older men, found that older men with higher bioavailable testosterone levels had better scores on tests of verbal memory and mental control (12). Morley and colleagues similarly found bioavailable testosterone levels correlate with cognitive ability including tests of visual and verbal learning, memory, and naming ability (13). Janowsky and colleagues found that testosterone supplementation improved spatial cognition, but the improvement was more closely associated with the decrease in estradiol levels possibly due to central inhibition of gonadotropins; no differences were found between groups in verbal memory, speeded cognitive flexibility, or fine motor dexterity (14). In another study by Janowsky and Chavez (15), working memory improved after 1 month of testosterone supplementation to scores of young men. Cherrier and colleagues also reported significant improvement in spatial and verbal memory in testing during intramuscular testosterone replacement (16). In contrast, Sih and colleagues (30) found no change in memory in a small group of older hypogonadal men receiving testosterone. Our work does not answer the question of whether or by what mechanism testosterone affects neurocognitive function but suggests, along with the work of Janowsky and colleagues and Cherrier and colleagues, that further study of the role of testosterone on cognition in older men is warranted.

The men in this study reported baseline health perception by SF-36 scores comparable to those of age- and gender-matched subjects (31). These results are similar to other reports of self-perceived health in older men with both normal and low testosterone levels (21) and older men with low bioavailable testosterone levels (22,23).

We expected testosterone supplementation to improve health perception due to reports of improved mood and energy following testosterone supplementation in young, hypogonadal men (17,18). However, two aspects of health

perception, general health and mental health, declined over 12 months in both the placebo and treatment groups. Others, similarly, have found no improvement in health perception following testosterone or dihydrotestosterone replacement in older men (22,23,32). The decline in health perception scores may be due to the decline in health perception reported with increasing age (31), though this is unlikely given the relatively short duration of our study. More likely, testosterone replacement may be associated with improved health perception only in states of severe deficits as seen in studies of younger, hypogonadal men. Further studies are required to understand whether testosterone replacement is associated with better health perception in this population.

Another explanation for the lack of effect of testosterone therapy on self-perceived health may be due to the delivery system. Both the testosterone and placebo patches were associated with skin irritation (40% in placebo group and 77% in testosterone group) and itching. Itching predicted self-perceived bodily pain at the 12-month survey, suggesting that the rash and itching induced by the placebo and testosterone patches may be responsible for the overall lack of improvement in health perception and for the deterioration in self-perceived general and mental health in our study sample. There has been another report of decline in quality-of-life scores in a study involving allergic symptom induction (33). Other studies of transdermal testosterone or dihydrotestosterone delivery have also failed to demonstrate change in health perception (22,32), but one study of 13 older, hypogonadal men receiving intramuscular testosterone reported a general increase in sense of well-being (34) while another study of eugonadal men did not (23). Again, further studies of testosterone supplementation using various delivery systems are needed to determine whether there are associated changes in health perception and whether they are dependent on the mode of delivery.

Bioavailable testosterone levels at 12 months predicted some aspects of health perception, including self-perceived role limitations due to physical problems and self-perceived vitality, as well as the physical component composite score. This suggests that testosterone levels in older men may positively influence health perception associated with perceived physical function. Snyder and colleagues also reported improved self-perceived physical functioning in men receiving testosterone compared with placebo (22). Testosterone has been implicated in the process of sarcopenia and in the associated loss of muscle mass and strength (35), although we did not find that strength predicted self-perceived physical function scores. Further studies to understand the mechanism by which testosterone predicts physical function, other than by strength, are required.

The study has several limitations. The sample size is small with a large number of men discontinuing prior to study completion. This may have biased the results to only the most robust individuals answering questions. While baseline measures of changes in cognitive function were only compared in the men who completed the study, we may have missed an effect in less cognitively robust men. Similar effects may have been missed in relation to health perception.

Transdermal testosterone treatment in men with low bio-

available testosterone levels does not impair and may improve cognitive function. Treatment did not improve health perception, but this may have been due to the side effects of skin irritation suggested by similar reactions in both the testosterone and placebo groups. Further studies of testosterone supplementation will be required to fully address the role of testosterone in cognition and health perception in older men with testosterone decline.

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