Sex Hormones and Cognitive Function in Older Men

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OBJECTIVES: Recent studies have suggested that estrogen may improve cognitive function or prevent cognitive decline in older women. Little research has been conducted on exogenous or endogenous sex hormones and cognition in older men, yet it has been hypothesized that testosterone, either directly or by conversion to estrogens, may improve cognitive function. We investigated whether serum level of testosterone and estradiol is associated with cognition in older community-dwelling men.

DESIGN: A cross-sectional study.

SETTING: Population-based listings in the Monongahela Valley near Pittsburgh, Pennsylvania.

PARTICIPANTS: Three hundred ten men (mean age ± standard deviation = 73.0 ± 7.1) who were part of a cohort study.

MEASUREMENTS: We measured cognitive function using the Mini-Mental State Examination (MMSE), Trails B, and Digit Symbol. Sex hormone levels were determined by radioimmunoassay from serum obtained at the time of cognitive testing and analyzed by tertile.

RESULTS: No consistent association between total testosterone level and cognitive test scores was observed. However, men with high bioavailable (loosely protein-bound) testosterone had better cognitive test scores on all three tests ($P \leq .001$). Total estradiol levels were associated with worse cognitive scores on Digit Symbol ($P < .001$) and Trails B ($P = .002$), but bioavailable estradiol levels were not associated with cognitive function. Level of sex hormone binding globulin (SHBG) was negatively associated with cognitive scores on all three tests ($P \leq .001$). After adjusting for age and education, the statistical significance lessened for bioavailable testosterone (MMSE, $P = .086$; Digit Symbol, $P = .047$; Trails B, $P = .076$) and became nonsignificant for SHBG (all cognitive tests $P > .10$).

CONCLUSIONS: Our findings support the hypothesis that higher levels of bioavailable testosterone, but not of bioavailable estradiol, are associated with better cognitive function in older men. In addition, bioavailable measures of testosterone may better reflect hormone levels available to the brain and thus be more closely associated with central nervous system outcomes such as cognition. Future studies, especially randomized trials, should be undertaken to determine whether testosterone may protect against cognitive decline in older men. **J Am Geriatr Soc 50:707–712, 2002.**

Key words: testosterone; estradiol; cognition; aging; hormones

Several recent studies suggest that estrogen may improve cognitive function in older women and decrease the risk of developing cognitive disorders such as Alzheimer's disease.[1–3] Androgen receptors tend to co-localize with estrogen receptors in the rodent brain and are distributed in areas critical for learning and memory, such as the thalamus, the hippocampus, and the deep layers of the cerebral cortex.[4] Testosterone is converted to estrogens by aromatase, which are present throughout the body, including the central nervous system.[5] Thus, testosterone could exert an effect on cognition in men independently or indirectly via conversion to estrogens.

Although several studies in young men have examined the correlation of serum levels of testosterone and cognitive function, especially visuospatial abilities,[6–8] very few studies have been conducted on older men. Recently, Barret-Connor et al. found that, in 547 older men, high serum bioavailable testosterone levels were associated with better performance on two of 12 cognitive tests administered. However, cognitive testing was conducted approximately 5 years after the hormones were measured.[9] Another recent study found that testosterone supplementation improved working memory in 19 older men and that this improvement was positively associated with serum free testosterone level but negatively associated with serum total estradiol level.[10]

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We investigated whether serum testosterone level (measured at the time of cognitive testing) is associated with cognitive performance in a large cohort of community-dwelling older men. We also asked, if such an association was present, whether it was mediated by estradiol level. Finally, we determined whether the bioavailable (or loosely protein-bound) form of sex hormones is more closely associated with cognition than the total (mostly sex hormone binding globulin-bound (SHBG)) form.

METHODS

Subjects

All men were enrolled in the Study of Osteoporotic Risk in Men, a prospective study of risk factors for bone loss in 523 predominantly white, community-dwelling men aged 50 and older.[11] Participants were recruited from population-based listings in the Monongahela Valley near Pittsburgh, Pennsylvania. Black men were excluded because of their low incidence of fracture, as were men who were unable to walk without assistance or who had had bilateral hip replacements. The baseline visit was in 1991/92, and the follow-up visit took place an average of 6.5 years later in 1997–1999. Our analytic cohort consisted of the 310 men (71% of survivors) who had cognitive testing and serum hormones measured at the follow-up visit. Men who were taking hormone supplements (such as testosterone, androstenedione, or dehydroepiandrosterone) were excluded from the study. The institutional review board of the clinical center approved the study; all participants signed informed consent at each clinic visit.

Measurement of Hormones

During the follow-up clinic visit, serum was collected from each participant. Blood samples were collected in the morning after an overnight fast and stored at −70°C until analysis. Stored samples were sent directly from storage to the analytical laboratory (Endocrine Sciences, Calabasas Hills, CA) without thawing. Total testosterone and total estradiol were measured by radioimmunoassay after extraction and purification by column chromatography.[12,13] Intra- and interassay coefficients of variation, respectively, are 4.9% and 6.6% for total testosterone and 5.2% and 7.5% for total estradiol. Bioavailable hormone levels were determined by separation of the SHBG-bound steroid from albumin-bound and free steroid with ammonium sulfate as described by Mayes et al.[14] SHBG was precipitated by the addition of ammonium sulfate and the samples centrifuged. Intra- and interassay variability for SHBG are 2.0% and 3.2%, respectively. Aliquots of the supernatant containing the non–SHBG-bound steroids were removed for scintillation counting. The bioavailable steroid concentration was then derived from the product of the total serum steroid and the percentage of non–SHBG-bound steroid determined from the separation procedure. Intra- and interassay coefficients of variation are, respectively, 3.3% and 12.4% for bioavailable testosterone and 4.9% and 6.0% for bioavailable estradiol. The lower limit of detection for the hormone measurements was 0.1 μg/dL for SHBG, 3 ng/dl for total testosterone, 0.3 ng/dL for bioavailable testosterone, 0.5 ng/dL for total estradiol, and 0.05 ng/dL for bioavailable estradiol.

Cognitive Function Assessment

Trained staff administered cognitive testing to the subjects. The Mini-Mental State Examination (MMSE) is a brief, global cognitive function test with concentration, language, and memory components designed to screen for cognitive impairment.[15] The MMSE scale ranges from 0 to 30, with higher numbers indicating better performance. Trails B is a test of speeded mental operations, attention, visual scanning, visual sequential abilities, and executive function.[16] Scores are measured in seconds, with higher scores indicating slower or poorer performance; an upper cut-off score of 181 seconds was used when time to complete the test exceeded 180 seconds. Digit Symbol is a measure of attention, psychomotor performance, and perceptual organization.[17] Scores on Digit Symbol reflect the number correct within the timed trial, thus lower scores indicate poorer performance. We defined cognitive impairment using standard cut-off criteria for the MMSE (score <24)[15] and Trails B (score >180 seconds)[16] and a score of less than 1 standard deviation from the mean for Digit Symbol (score <29).

Other Variables

At the time of cognitive testing, we ascertained age, highest level of education, alcohol use (drinks per week in the past 30 days), smoking history, and physical activity in the past week (the number of times performing physical activity rigorous enough to induce a full body sweat). Subjects were asked to rate their overall health compared with other men as excellent, good, fair, poor, or very poor. Medical histories were obtained, including a self-reported physician diagnosis of stroke, myocardial infarction, or diabetes mellitus. Participants were asked about current use of medications; these reports were checked by examining labels of drugs brought to the clinic. The 15-item Geriatric Depression Scale was administered. Scores range from 0 to 15, with higher scores indicating more symptoms of depression.[18] During the clinic examination, we measured weight and height; body mass index was defined as weight in kilograms divided by the square of height in meters.

Statistical Analysis

Correlations between the sex hormones were analyzed using Pearson correlation coefficients. Baseline subject characteristics were compared by analysis of variance (ANOVA) for continuous variables and chi-square for dichotomous variables across bioavailable testosterone tertile. To determine whether cognitive scores differed by hormone tertile, we performed ANOVA with hormone tertile as the independent variable and test score as the dependent variable. We then adjusted these analyses for age and education using ANOVA. For the total estradiol and testosterone analyses, we also adjusted for SHBG tertile. We determined what percentage of men had cognitive impairment on each of the three cognitive tests and whether the percentages differed by hormone tertile using chi-square analysis. All significance levels reported are two-sided and all analyses were performed using SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

The sex hormone measurements (mean and intratertile range) are presented in Table 1. The serum hormones were

moderately but statistically significantly correlated with one another (for total testosterone and total estradiol, $r = 0.52$, $P < .001$; for bioavailable testosterone and bioavailable estradiol, $r = 0.45$, $P < .001$; for SHBG and total testosterone, $r = 0.56$, $P < .001$; for SHBG and total estradiol, $r = 0.27$, $P < .001$; for SHBG and bioavailable testosterone, $r = -0.25$, $P < .001$; and for SHBG and bioavailable estradiol, $r = -0.17$, $P = .003$). Based on age-adjusted cutoffs (provided by Endocrine Sciences, Calabasas Hills, CA), 17.7% of the men were below the normal range for total testosterone and 7.7% were under the normal range for bioavailable testosterone. The mean age ± standard deviation of the subjects was 73.0 ± 7.1 (range 58 to 91). Men in the low bioavailable testosterone tertile were older than men in the mid and high tertiles (75.6 vs 72.9 and 70.6, $P < .001$) but were similar on other characteristics such as education, alcohol intake, depression score, body mass index, comorbidities, health status, sedative-hypnotic medication use, and physical activity (Table 2).

Cognitive scores on all three tests were similar across the total testosterone tertile with the exception of a trend for worse performance in the higher tertile compared with the lowest tertiles for Trails B (P for trend = .07). (Table 3) However, scores on all three cognitive tests were better in the higher bioavailable tertiles (P for trend <.001 for all tests) and worse in the higher SHBG tertiles (P for trend <.001 for all tests). After adjusting for age and education, the statistical significance lessened for bioavailable testosterone (mean cognitive scores ± standard error for lowest to highest tertile: MMSE 26.8 ± 0.2, 27.1 ± 0.2, 27.4 ± 0.2, $P = .086$; Digit Symbol 40.4 ± 0.9, 39.2 ± 0.9, 43.1 ± 0.9, $P = .047$; Trails B 131 ± 4, 129 ± 3, 122 ± 3, $P = .076$) and became nonsignificant for SHBG tertile (all cognitive tests $P > .10$). For total estradiol, men in the high tertile had worse performance on Digit Symbol and on Trails B (Table 3) but not on MMSE. These results were similar after adjusting for age and education. There were no differences on cognitive test score across bioavailable estradiol tertile. When SHBG level was added to the age- and education-adjusted models for total testosterone, hormone level was positively associated with cognitive score on Digit Symbol ($P = .036$), and there was a trend for a positive association for Trails B ($P = .083$). There was no statistically significant association between SHBG-adjusted total estradiol level and any of the three cognitive tests.

Of the 310 subjects, 33 (11%) had cognitive impairment according to the MMSE, 42 (13%) had impairment according to Digit Symbol, and 61 (20%) had impairment according to Trails B. Men with cognitive impairment were older and less educated and had higher depression scores than those without cognitive impairment ($P < .05$ for all comparisons). For total testosterone, more men in the higher tertile had cognitive impairment on Digit Symbol and on Trails B than those in the mid and low tertiles (Table 4). However, there was a trend for the opposite direction for bioavailable testosterone in which men in the higher tertile had lower prevalence of cognitive impairment on all three tests than men in the mid or low tertiles. Men in the high SHBG tertile were more likely to have cognitive impairment than men in the lowest tertile (23% vs 5% on MMSE, 25% vs 6% on Digit Symbol, and 31% vs 11% on Trails B). Consistent with this finding was an association for greater impairment on Digit Symbol and Trails B for men in the high total estradiol tertile but no association between bioavailable estradiol and cognitive impairment on any of the cognitive tests.

DISCUSSION

In this cross-sectional study, we found that bioavailable but not total testosterone level was positively associated with cognitive scores in older men. We also observed that SHBG level and total but not bioavailable estradiol level were negatively associated with cognitive function. Our findings support the hypothesis that testosterone may improve cognitive function in older men and that this association appears to be a direct effect of testosterone and not an indirect effect via aromatization to estradiol.

Our results are supported by several other studies, mostly in younger men, in which serum testosterone was associated with cognitive performance.[6–8,10] Unlike some of these studies, we did not observe a curvilinear relationship between serum testosterone and cognitive function. Our findings are also supported by several small trials of testosterone in healthy older men that have reported improvements in working memory and in visuospatial performance.[10,19] In mice, testosterone supplementation improves age-related cognitive impairment,[20] and, in rodent models, androgen receptors are distributed in areas critical for learning and memory, such as the thalamus, hippocampus, and the deep layers of the cerebral cortex.[4] Thus, testosterone may act directly on the brain to improve cognitive performance. The hormone levels we observed our similar to those from other cohorts of community-dwelling older men.[9]

We found a more consistent association with bioavailable testosterone and cognition compared with total testosterone and cognition. This finding suggests that it is the unbound or loosely bound form of testosterone that is correlated with central nervous system function. A possible explanation for this finding is that bioavailable testosterone crosses the blood-brain barrier more readily than total

Table 1. Mean ± Standard Deviation and Tertile Range for the Hormones

Hormone	Mean ± Standard Deviation	Low Tertile	Mid Tertile	High Tertile
Total testosterone (ng/dL)	425.8 ± 151.8	45–353	355–485	486–975
Bioavailable testosterone (ng/dL)	127.0 ± 45.1	10–107	108–139	140–305
Sex hormone binding globulin (μg/dL)	1.2 ± 0.5	0.2–0.9	1.0–1.3	1.4–3.8
Total estradiol (ng/dL)	2.3 ± 0.8	0.5–1.9	2.0–2.5	2.6–6.7
Bioavailable estradiol (ng/dL)	1.4 ± 0.5	0.2–1.1	1.2–1.5	1.6–3.9

Table 2. Characteristics of the 310 Men Enrolled in the Study of Osteoporotic Risk in Men Study by Bioavailable Testosterone

Characteristic	Bioavailable Testosterone Measurement			
	Low (n = 104)	Mid (n = 102)	High (n = 104)	*P*-value*
Age, years, mean ± SD	75.6 ± 7.3	72.9 ± 6.4	70.6 ± 6.8	<.001
Education, years, mean ± SD	12.6 ± 2.4	12.4 ± 2.7	12.9 ± 2.4	.411
Body mass index, kg/cm², mean ± SD	28.1 ± 4.6	28.6 ± 4.1	27.4 ± 3.5	.142
Geriatric Depression Scale, mean ± SD	1.6 ± 2.0	1.3 ± 1.5	1.2 ± 1.7	.138
Current cigarette smoking, %	1.9	4.9	6.7	.242
Alcohol use, drinks/week, mean ± SD	3.8 ± 8.2	6.0 ± 12.2	5.5 ± 9.5	.248
Excellent/good health status, %	69.2	74.5	81.7	.112
Current sedative/hypnotic drug use, %	2.9	3.9	1.9	.694
Prostate cancer medications, %	9.6	2.9	5.8	.134
Rigorous physical activity >1/week, %	26.5	32.3	36.9	.276
Diabetes mellitus, %	14.4	6.9	8.7	.166
Heart attack, %	16.4	17.7	20.2	.764
Stroke, %	9.6	6.9	4.8	.399

*P for analysis of variance for continuous variables, and chi-square for dichotomous variables.

testosterone, which is largely bound by SHBG. In humans with intact blood-brain barriers, cerebrospinal fluid concentrations of a variety of sex hormones are similar to the non–SHBG-bound levels,[21] and there is an inverse relationship between serum SHBG concentrations and transport of estradiol and testosterone into the rodent brain.[22] Another explanation for our finding is that non–SHBG-bound forms of hormones are more biologically active in a variety of tissues than SHBG-bound hormones. In men, total testosterone levels decrease slightly with age,[23] but bioavailable testosterone and estrogen levels may decline by up to 50%.[24] Compared with total estradiol, free and bioavailable estradiol have been shown in women to be more closely correlated with risk of breast cancer,[25,26] protection against osteoporotic fractures,[27] and bone mineral density.[24]

The negative unadjusted association between SHBG level and cognitive scores is a novel finding. It is important in that it may explain why we, and others,[9,10] have ob-

Table 3. Scores on the Cognitive Testing by Hormone Group

Cognitive Test	Low Tertile	Mid Tertile	High Tertile	*P*-Value*
	mean ± standard deviation			
Total testosterone				
MMSE	27.3 ± 2.3	27.2 ± 2.2	26.8 ± 2.6	.160
Digit Symbol	41.8 ± 11.0	41.4 ± 11.3	39.6 ± 12.6	.178
Trails B	124 ± 37	124 ± 41	134 ± 40	.070
Bioavailable testosterone				
MMSE	26.6 ± 2.6	27.0 ± 2.5	27.6 ± 1.9	.001
Digit Symbol	38.5 ± 11.3	39.0 ± 11.4	45.3 ± 11.2	<.001
Trails B	136 ± 39	130 ± 38	116 ± 41	<.001
Sex hormone binding globulin				
MMSE	27.6 ± 2.1	27.1 ± 2.2	26.5 ± 2.7	.001
Digit Symbol	44.7 ± 11.1	41.7 ± 10.8	36.4 ± 11.7	<.001
Trails B	115 ± 40	124 ± 37	142 ± 37	<.001
Total estradiol				
MMSE	27.0 ± 2.4	27.3 ± 2.2	26.9 ± 2.5	.683
Digit Symbol	43.3 ± 12.0	41.3 ± 11.7	37.8 ± 10.7	<.001
Trails B	121 ± 42	124 ± 38	138 ± 38	.002
Bioavailable estradiol				
MMSE	26.7 ± 2.4	27.4 ± 2.2	27.1 ± 2.4	.218
Digit Symbol	41.2 ± 11.5	40.6 ± 12.2	41.0 ± 11.4	.884
Trails B	129 ± 42	128 ± 39	125 ± 39	.464

*P for trend.
MMSE = Mini-Mental State Examination.

Table 4. Cognitive Impairment by Hormone Tertiles

	Low Tertile	Mid Tertile	High Tertile	
Cognitive Test		n (%)		*P* value*
Total testosterone				
MMSE	9 (8.7)	16 (15.4)	18 (17.5)	.166
Digit Symbol	7 (6.9)	13 (12.6)	22 (21.6)	.009
Trails B	13 (12.9)	20 (20.0)	28 (27.7)	.032
Bioavailable testosterone				
MMSE	19 (18.3)	16 (15.7)	8 (7.7)	.071
Digit Symbol	19 (18.5)	15 (14.9)	8 (7.8)	.076
Trails B	25 (25.0)	22 (22.2)	14 (13.6)	.107
Sex hormone binding globulin				
MMSE	5 (4.7)	14 (14.0)	24 (23.1)	<.001
Digit Symbol	6 (5.7)	10 (10.1)	26 (25.2)	<.001
Trails B	11 (10.6)	18 (18.8)	32 (31.4)	<.001
Total estradiol				
MMSE	13 (11.8)	13 (12.8)	17 (17.4)	.475
Digit Symbol	8 (7.3)	13 (12.8)	21 (21.9)	.010
Trails B	18 (16.7)	17 (16.8)	26 (28.0)	.081
Bioavailable estradiol				
MMSE	15 (14.7)	11 (11.0)	17 (15.7)	.587
Digit Symbol	13 (12.9)	13 (13.0)	16 (15.1)	.872
Trails B	25 (25.0)	17 (17.2)	19 (18.5)	.335

*P value for chi-square analysis.
MMSE = Mini-Mental State Examination.

served a negative association between total estradiol levels and cognitive performance in men. Yaffe et al. previously reported that, in older women, the free and bioavailable forms, and not the total estradiol form, are more closely associated with cognitive function.[28,29] However, it is important to note that, after adjustment for age and education, the association between SHBG and cognitive scores became nonsignificant. This underscores the importance of adjusting analyses of hormones and cognitive function in older adults for these variables that are the greatest predictors of cognitive function.[30]

Several limitations of our study deserve mention. Although we used standard and validated tests of cognitive function and for a definition of cognitive impairment, the men did not undergo a clinical assessment for dementia, and we cannot determine the etiology of the cognitive impairment. We also did not have sensitive measures of all cognitive domains, such as verbal memory and visuospatial abilities. Previous studies of testosterone have often found specific results for visuospatial tasks, and, although two of our tests (Trails B and Digit Symbol) use visuospatial skills, they are not isolated tests of visuospatial abilities. However, given that our cognitive tests were associated with hormone levels, it is possible that more-sensitive measures might detect even larger differences on cognitive testing. Finally, most of the study subjects were white, and we cannot conclude whether our findings would apply to other racial groups.

Men with high levels of bioavailable testosterone, but not estradiol, had higher scores on cognitive testing and were less likely to have cognitive impairment. This finding supports the hypothesis that higher levels of endogenous testosterone prevent cognitive decline and suggests that the bioavailable forms of testosterone may be more closely correlated with cognitive function. Future studies, especially randomized trials, should be directed toward the investigation of testosterone and cognition in older men.

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