Associations between Serum Testosterone Fall and Cognitive Function in Prostate Cancer Patients

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ABSTRACT

Data on the association between cognition and testosterone levels in elderly men are inconclusive. Androgen deprivation therapy is commonly used in the treatment of prostate cancer with the aim of achieving castration levels of serum testosterone. The study group comprised 26 elderly men (mean age 65 years) with newly diagnosed prostate cancer. Cognitive testing was done at baseline and at 6 and 12 months on androgen deprivation therapy. Cognitive performances were evaluated using verbal, visuomotor, and memory tests as well as tests of processing speed and attention. Castration levels of testosterone were achieved in all patients by 6 months. Significant associations between cognitive performances and testosterone decline were documented: visuomotor slowing, slowed reaction times in some attentional domains including working memory and impaired hit rate in a vigilance test, impaired delayed recall and recognition speed of letters, but improvement in object recall. The results suggest selective associations between testosterone decline and cognition. Documentation of cognitive performance with changes in serum testosterone levels has substantial implications for informed patient support in prostate cancer.

INTRODUCTION

Studies on associations between serum testosterone and cognition in elderly men are few, and the theories presented are contradictory. There are findings from a linear association to U-shape to no association at all (1). Circulating testosterone levels have behavioral and neurological effects in humans, and both testosterone concentrations and cognitive function decrease with ageing in men (2). Higher free testosterone has been found to be associated with better scores on visual and verbal memory, visuospatial function, and visuomotor scanning, with a decrease with ageing and declining testosterone levels in healthy subjects during a period of 10 years (2). In another study involving elderly men, significant associations were shown between testosterone and some cognitive test performances but not with acquired skills nor with verbal long-term memory (3). It has been suggested that age-dependent decreases in visuospatial ability and memory may relate to a decline in testosterone levels (4).

During recent years it has become common practice to combine androgen deprivation causing castration levels of testosterone with radical radiotherapy in a neo-adjuvant setting in the treatment of prostate cancer (PC). This approach has been shown to improve the survival of patients with poor prognosis (5). Androgen deprivation therapy (ADT) is also widely used as a means of preventing progression if, for reasons of patient preference or poor general condition, local therapies cannot be used (6). At least 22,000 PC men in the United States each year have been estimated to receive hormonal therapy (6). The number of patients treated is increasing, likewise the duration of ADT even over a number of years.

The effects of ADT on the quality of life have been studied (7, 8), but less is known as to the relation between hormonal changes and specific domains of cognitive functioning.

No significant effect of radiotherapy alone on cognitive function in PC patients has been observed (9). The effects of androgen deprivation therapy are substantially different: i.e., decline in testosterone to castration level impacts strongly on the quality of life, causing fatigue, loss of sexual function, and osteoporosis (7, 10). A few studies have suggested that a lowered testosterone level is also associated with changes in some cognitive functions, both when measured by objective tests (11, 12) and in subjective evaluation by PC patients (13).

The aim of this prospective study was to investigate the associations between serum testosterone decline and specific cognitive functions using a systematic set of methods in newly diagnosed PC patients treated with ADT to castration testosterone level. We hypothesized that the testosterone level may have an impact on cognitive performances and therefore conducted a prospective study with simultaneous collection of serum samples for hormone analysis. The aim was to establish whether cognitive functions are selectively sensitive to changes in serum testosterone levels.

PATIENTS AND METHODS

Patients. During the period 1999 to 2002 extensive cognitive testing was undertaken in a group of 26 men from South-Western Finland at baseline, at 6 months and at 12 months on androgen deprivation. Only patients with PC diagnosed recently and without previous ADT were accepted. Twenty-three of the patients had hormone measurements taken at the time of testing.

To be eligible for neuropsychological testing, patients had
to meet the following inclusion criteria: (a) no evidence of progressive or metastatic disease; (b) no history of neurologic/psychiatric signs or symptoms that might lead to deviant neuropsychological test results; (c) no abuse of alcohol or drugs; and (d) a mother tongue of Finnish and normal hearing and sight. Signed informed consent was obtained from all patients. The study was approved by the joint ethical committee of Turku University Hospital and the University of Turku.

**Treatment of Prostate Cancer.** The patients had to fulfill at least two of the following criteria to be eligible for ADT: tumor grade $\geq 2$, Gleason $\geq 5$, and/or prostate-specific antigen $\geq 20$ $\mu$g/L. ADT was started with 250 $\text{mg}$ of flutamide three times a day given for 4 weeks, and luteinizing hormone-releasing analog (11.25 $\text{mg}$ leuprolide subcutaneously every 3 months for 12 months) was added after 2 weeks and continued for 12 months. Radiotherapy was given after 2 months of ADT by the conformal technique by 15 MV photons/Varian Clinac 2100C/D linear accelerator (Varian Inc. Palo Alto, CA) to a mean tumor dose of 69 Gy (3.15 SD, range 61–77 Gy). During the test period of 12 months on ADT, one patient progressed and was therefore omitted from further testing. Median prostate-specific antigen was 28 $\text{ug}$/L at baseline; all patients tested at 12 months had prostate-specific antigen $< 1$ at 6 months and at 12 months.

**Hormone Determinations.** Serum samples for hormone analysis were collected before treatment and at 6 and 12 months, and stored at $-70^\circ$C. The samples were taken before early afternoon to avoid diurnal variation. We did the analyses using the DELFIA (dissociation-enhanced lanthamide fluorescence immunoassay) system for measurement of hormones, and the samples were batched for single analysis with the same kits to exclude interanalysis variability; commercially available kits were used (Perkin-Elmer, Turku, Finland). The mean values for each measured variable were not significantly different for two separate laboratory batch runs in which the measurements were made.

Testosterone was determined by Auto DELFIA assay, which is a solid phase fluoroimmunoassay based on competition between europium-labeled testosterone and sample testosterone for polyclonal antitestosterone antibodies derived from the rabbit (normal range for men 10–33 $\text{nmol}$/L).

Sexual hormone-binding globulin (SHBG) was determined by Auto DELFIA solid-phase fluoroimmunoassay.

We calculated free testosterone using the free androgen index or testosterone free index, calculated as testosterone concentration ($\text{nmol}$/L) $\times 100$, divided by SHBG concentration ($\text{nmol}$/L). This ratio is directly equivalent to the circulating concentration of free biologically available testosterone.

We conducted neuropsychological testing using the cognitive test battery presented in Fig. 1. The methods with corresponding references are explained in full detail in Appendix 1 and in a previous publication (14). Hormonal effects are likely to be reflected in a broad range of cognitive functions, especially attention and memory. Anterior brain regions have also been shown to be target areas of steroid receptors. Our aim was to determine the overall level of cognitive performance, and we evaluated the overall success of a subject in verbal, visuomotor, and memory performances using the SDs of an independent norm group (15, 16).

The test battery was the same on all sessions from baseline through 6 and 12 months testing times. The cognitive testing was done in about 3-hour sessions, and breaks were always allowed when needed. The testing was completed in standardized order, alternating simple and more complex tasks. Careful instructions preceded all of the tests, and the reaction time tests were likewise preceded by practice rounds to minimize random variation.

To rule out incipient dementia the Mini-Mental State Examination (MMSE; 17) was used; MMSE scores range from 0 to 30, and subjects with dementia generally score below 24. Depression was scored by the Beck depression inventory (18), which has a range of scores from 0 to 39, a score over 8 indicative of depressive mood.

We studied cognitive processing and attention using CogniSpeed software (19), planned to measure both automatic (well-learned) and controlled attention-demanding processing. Automatic tasks comprise recognition of familiar items (numbers and letters), whereas tasks of controlled processing demand working memory or sustained attention. Attention and memory performances may also reflect cognitive processing efficiency in everyday situations.

**Statistical Analyses.** The data were summarized showing mean values and SDs. Changes in hormone levels and in cognitive performances from baseline to study sessions at 6 months and at 12 months were calculated. ANOVA for repeated measures was used to study changes in hormone levels and cognitive performances during the follow-up periods, and the Bonferroni correction for post hoc comparisons was used. We carried out this analysis using a SAS/mixed procedure, which allows for missing observations in repeated measurements. Regression analysis and correlations were used to study the associations between changes in hormone levels and cognitive performances. The SAS System for Windows, release 8.02/2001, was used to do the analyses. $P$ values $< 0.05$ were considered statistically significant.

**RESULTS**

Twenty-three patients had both cognitive tests and laboratory results available for correlation analysis. Patient characteristics, cognitive and hormone data at baseline, at 6 and at 12 months are presented in Table 1. The mean (SD) age of the patients was 65 years (6.7) and their mean education 8.5 (3.1) years. The level of overall cognitive performances at baseline as determined by MMSE and deterioration score were well preserved and did not change significantly during the 12-month study period. Beck depression scores did not change significantly from baseline to 6 months and to 12 months ($P = 0.99$).

In cognitive variables, significant changes were observed in the visuosmotor speed test between 6 and 12 months, in the object recall test, delayed between baseline to 6 months and baseline to 12 months, and in the test of recognition speed of letters from baseline to 12 months. The mean (SD) values per
test session are shown in Table 1. The difference in cognitive performance between testing sessions in other cognitive performances was not statistically significant.

During the study period, serum levels of testosterone declined and remained at castration level, as shown in Table 1 and Fig. 2. Figure 2A shows the mean (SE) curve of testosterone values and individual serum testosterone values as a function of time. There was marked interindividual variation in testosterone levels between the study subjects at baseline. However, castration levels were achieved in all patients by 6 months. Figure 2B presents the respective changes in free testosterone during 12-month ADT, showing a steep decrease by 6 months in all patients.

Associations of hormonal changes with cognitive performances tests were studied (Table 2). The decline in testosterone was associated with visuomotor slowing in the digit symbol test, errors in the basic speed test of 10-choice reaction time (CRT), slowed CRT in tasks demanding working memory (subtraction time), impaired hit rate in the vigilance task of sustained attention, and slowed recognition speed of letters. However, there was a different association between the decline in testosterone and performances in the delayed recall of objects, which improved (Table 2).

Associated with the decline in testosterone, visuomotor slowing was observed at 6 months ($P = 0.07$), becoming significant by 12 months ($P = 0.006$; Fig. 3A). It seemed that visuomotor slowing or weakening of learning effect during the follow-up study was related to the magnitude of the decline in testosterone. More particularly, a 15 to 20 nmol/L decline in testosterone seemed to be a threshold for visuomotor slowing.

In one test of episodic memory function, a substantial association was observed between change in object recall and the decline in testosterone: *i.e.*, the greater the decline, the more there was improvement in the delayed recall of object memory (Fig. 3B; $P = 0.03$).

Errors, but not speed, in the basic speed test (10-CRT, errors) were associated with the decline in testosterone at 12 months ($P = 0.02$, Fig. 3C).

Slowed performance in the subtraction time, a measure demanding concentration and working memory (the difference between the subtraction test and the 10-CRT test, which imposes similar motor demands), was associated with the decline in testosterone at 6 months ($P = 0.04$, Fig. 3D) but not at 12 months.

In the sustained attention test, reaction speed and errors were not associated with testosterone, but a lower rate of correct
target hits (vigilance, correct %) was associated with lower testosterone values \( P = 0.005 \) and with lower free testosterone values \( P = 0.03 \) at 12 months (Fig. 3E). Performance in this test approximated its ceiling level.

In the recognition speed of letters, slowed recognition time was associated with the testosterone decline at 12 months \( P = 0.01 \); Fig. 3F).

Other cognitive domains such as verbal performances, visual episodic memory (Benton), digit span or visual span, visuoconstructive performances (block design), and some aspects of cognitive processing speed/accuracy remained unassociated with the decline in testosterone or free testosterone.

Some associations were observed between the SHBG change and impaired cognitive performances at 12 months. The associations were significant in basic speed test 10-CRT (errors; \( P < 0.001 \), in word list immediate recall \( P = 0.04 \), in reaction speed of sustained attention (vigilance, milliseconds; \( P = 0.023 \)) and the lower hit rate in this test (vigilance, correct %; \( P < 0.001 \)). Other cognitive domains remained unassociated with SHBG.

**DISCUSSION**

Circulating testosterone levels have behavioral and cognitive effects in humans. Both testosterone concentrations and neuropsychological functioning may decline with ageing in men (2). Because attention and memory are considered vulnerable to changes in sexual hormones (11), we studied cognitive function during ADT, which reduced testosterone to castration level. Significant associations were observed between some cognitive performances and testosterone decline: *i.e.*, slowing in some cognitive domains and an impaired hit rate in the vigilance test but improvement in delayed object recall. The magnitude of change in cognitive performance seemed in the present study to be related to the magnitude of testosterone decline.

We have described previously how PC patients treated with radiotherapy alone maintained their cognitive functioning (9). During a 12-month treatment period with ADT, improvement in some memory tests was found (14).

At group level, the present results again showed preserved cognitive performances improvement in some memory and speed performances. Other investigators have recently published reports with similar (13) and opposed (12) results. Thus, interindividual variability in cognitive response to castration can considerably hamper interpretation of results at group level.

To minimize individual variability and learning effect in the reaction time tasks, there was a practice round preceding the CogniSpeed subtests. Repeated measures of CogniSpeed tests have shown a reliable course over trials in healthy persons and in studies with brain tumor patients (20). Tests of cognitive deterioration, including verbal, visuomotor, and memory tests, are also sensitive to cognitive impairment, even if the same versions are repeated (16, 19). In the present study, improvement in some performances may be because of a learning effect, which can be considered a positive sign of the ability to use experience. Thus, despite the decline in testosterone, the capacity to learn seemed to be generally well preserved. It is also possible that the patients were able to compensate slowing by learning and therefore the associations between hormonal and cognitive changes remained insignificant in most variables.

The magnitude of cognitive changes seemed in the present study to be selectively related to the magnitude of testosterone decline. The statistically significant findings mostly occurred only at 12 months, indicating that a longer duration of castration level is necessary for the impairment to become significant. Baseline testosterone levels differed between subjects, and this may influence the magnitude of changes. However, there may also be a threshold decline in testosterone necessary for at least some cognitive functions such as visuomotor speed.

Recently Cherrier *et al.* (13) with intermittent ADT in PC patients have reported a beneficial effect on verbal memory but impairment on a measure of spatial ability. A weak negative correlation between testosterone and verbal fluency has been reported in elderly men (21), but this was not supported by the present results. Yaffe *et al.* (22) reported no consistent associations between serum testosterone level and cognitive test scores, although men with high bioavailable testosterone achieved better cognitive test scores in the MMSE and some other measures of cognition. In the present study of newly
diagnosed PC patients, cognitive and hormonal changes were found to be linearly associated in some domains during 12-months androgen deprivation. Thus, our results support the earlier findings of Cherrier et al. (13), despite differences in patient populations and methodology. Relatively small sample size and multiple testing add to the limitations of interpretation of present results. However, this study was undertaken with a homogeneous group of newly diagnosed patients with relatively similar baseline characteristics in a longitudinal set-up, which supports the representativeness of the study group.

The present results are in agreement with those of O’Connor (1) and Cherrier (13) in showing that testosterone has differential effects on cognition, as also with those obtained by Perry et al. (23), who suggested that bioavailable testosterone was not as important a determinant of cognitive function as serum testosterone or SHBG. The effect of tes-
Tostosterone is probably accounted for by SHBG, as also suggested by Aleman et al. (4).

The potential mechanisms for the associations between cognition and male sex hormone levels have been elucidated in only a few studies. It is known that androgen receptors colocalize with estrogen receptors in several brain areas (24) and that they are found mainly in the thalamus, hippocampus, and the cerebral cortex, brain areas which are essential for learning and memory (25). Mechanisms by which testosterone affects cognitive performances include modulation of neurotransmitters and stimulation of neuronal connectivity, decreased B-amyloid peptide production and prevention of N-methyl-D-aspartate excitotoxicity (25). Moreover, a CAG repeat polymorphism in the androgen receptor gene has been reported to be associated with cognitive function in older men (26).

The hypothalamus and anterior pituitary area are targets of

Table 2 Statistically significant associations between cognitive function tests and change in testosterone from baseline to 6 months and 12 months (regression analysis, change in testosterone as an explanatory variable)

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>0–6 months regression coefficient (SE)</th>
<th>P</th>
<th>0–12 months regression coefficient (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal tests</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Visuomotor speed</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Digit symbol, correct items</td>
<td>0.38 (0.19)</td>
<td>0.07</td>
<td>0.43 (0.13)</td>
<td>0.006</td>
</tr>
<tr>
<td>Memory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Object recall, delayed, correct items</td>
<td>−0.07 (0.08)</td>
<td>0.35</td>
<td>−0.19 (0.08)</td>
<td>0.03</td>
</tr>
<tr>
<td>Basic speed tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-CRT, errors</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Concentrated attention</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Subtraction time ms</td>
<td>−24.6 (11.2)</td>
<td>0.04</td>
<td>−21.7 (26.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Sustained attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vigilance, correct %</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Recognition speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letters, ms</td>
<td>−0.43 (0.54)</td>
<td>0.45</td>
<td>−1.46 (0.48)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; ms, millisecond; CRT, choice reaction time.

Fig. 3 Scatter plots for changes in six tests of cognition (Y axis) and change in total testosterone levels in patients treated with androgen deprivation therapy for PC (regression line and equation are shown in the figure) at 12 months, except for D, which is at 6 months. A, visuomotor speed (correct items); B, object recall, delayed (correct items); C, 10-CRT, errors (milliseconds); D, subtraction time (milliseconds); E, vigilance hit rate (correct %); F, recognition speed of letters (milliseconds).
therapeutic manipulation with luteinizing hormone-releasing hormone analogs causing androgen deprivation by interrupting hormonal regulation and testicular testosterone production in PC. Although some effects may be because of directly acting testosterone, estradiol may also have a critical role in effects on some cognitive domains, because androgenic steroids are aromatized to estrogens locally in the brain (27, 28). Animal models have indicated that estradiol can increase acetylcholine activity, improve neuronal survival and dendritic sprouting, and protect neurons from ischemia (29). The associations between cognitive performance and decline in testosterone may thus be related to a change in the testosterone/estradiol ratio during ADT (30). Future studies that use the ADT model and/or animal studies are required to assess adequately the individual role of testosterone and estradiol in cognitive functioning in the male population.

In the present study, the cognitive changes found at castration levels of testosterone compared with baseline were parallel but mostly mild and may thus be of no substantial practical consequences to the patients (14). The effects of longer ADT extending over a number of years require additional study. We here studied a newly diagnosed relatively homogeneous group of PC patients. The effects of testosterone decline to castration level may be significantly more severe in patients with basic psychiatric or neurological or other systemic disorders and longer duration of ADT. Significant variation in baseline testosterone levels was observed among PC patients. The influence of baseline testosterone levels on the development of associations between cognition and testosterone decline requires additional studies.

CONCLUSION

Some significant changes were found parallel with decline in testosterone to castration level and impaired cognitive processing efficiency. The results suggest selective associations and interindividual variation between testosterone decline and cognitive performances during 12-month ADT in PC patients. Documentation of cognitive performance in relation to serum testosterone levels has substantial implications for informed patient support in PC.

APPENDIX

Cognitive tests were used to measure verbal, visuomotor, and memory performances, as well as cognitive processing in different attentional domains. The investigations were done in 3-hour sessions, with short breaks if needed, by two experienced psychologists.

Two verbal and two visuomotor subtests (31) were administered: similarities, digit span, digit symbol, and block design. The verbal fluency test comprised generating orally names of animals during 1 minute. In the picture-naming test, the subject had to name 15 line drawings presenting concrete objects.

We investigated episodic memory using four tests: (a) naming time, immediate, and delayed (after 1 hour) recall of 20 common objects; (b) the word list recall consisted of 10 words, which the subject was instructed to read when shown to him one at a time, and there were three trials for immediate and delayed (after 1 hour) recall (32); (c) the visual recognition test consisted of seven designs (form C), shown one at a time for 10 seconds (33). After the study phase, the set was removed, and the subject had to point to the right design among four alternatives; (d) visual memory span comprised tests of tapping squares on a card in a given order. The total score was the sum of a correctly repeated series forward and backward.

The overall cognitive deterioration score consisted of deterioration points in six tasks addressing memory, visuomotor, and verbal domains (similarities, digit span, digit symbol, block design, naming time, and immediate recall of 20 objects). The results on these tests were rescoring based on our earlier results obtained by healthy subjects. The subjects received one deterioration point if their performance in any of the tests was below 1.5 SD compared with the norms, two points if below 2 SD, and three points if below 3 SD. The maximum deterioration score was thus 18 points (15).

To rule out severe cognitive impairment, the MMSE was administered (17); the cutoff was set at 21 points.

The Beck depression inventory was administered to evaluate depressive mood (18). The CogniSpeed software was used to measure the speed and accuracy of automatic and controlled cognitive processing (19). Reaction times were measured in milliseconds in correct responses, and the error scores were recorded. In each CogniSpeed test, a practice session was held before the final test round, and the subject was instructed to respond as quickly as possible. The final test rounds comprised 40 items.

Automatic processing was studied with a task involving recognition thresholds for well-learned targets (4 numbers and 6 letters). A letter “X” shown in the middle of the screen was replaced briefly by the target. The first presentation time of 14 milliseconds was increased stepwise in 14 milliseconds steps, until the target was identified.

Controlled processing addressing different attentional functions was evaluated in series of reaction time tasks, which became more difficult step by step. In the simple reaction time test, the subject had to press the “0” key every time the target “0” appeared on the screen with a random delay ranging from 1 to 4 seconds. In the CRT tests, the stimuli appeared in random order. In the two-choice (2-CRT) test, either “1” or “2” appeared in the middle of the screen, and the subject was instructed to press the corresponding key. In the ten-choice (10-CRT) test, the numbers 0 to 9 appeared in the middle of the screen, and the subject had to press the corresponding number.

The subtraction test, which requires concentrating attention and working memory, was identical to the 10-CRT test, but the instruction given to the subject was different: i.e., the number appearing on the screen had to be subtracted from 9, and the key corresponding to the remainder pressed. The subtraction time was the difference in reaction times between the subtraction test and the 10-CRT test, with similar perceptual and motor requirements. Thus, subtraction time represented conscious working memory components in tasks involving relatively high attentional demands.

The vigilance test of letter cancellation measured sustained attention. This was a monotonous task of 15 minutes, with target events occurring at a relatively slow rate and in random order. There were two target letters (Y, L) appearing with a probability of 20% among all 600 letters; the presentation time
was 500 milliseconds and the interval between letters 1,000 milliseconds. Reaction times to targets, errors, and hit rate of correct responses were recorded.

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