Original Article

Cognitive effects of hormone therapy in men with prostate cancer

A Review

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ABSTRACT

BACKGROUND.

Men who receive androgen-deprivation therapy (ADT) for prostate cancer experience several side effects from this treatment. A few recent studies have examined the cognitive implications of ADT and how they impact a patient's treatment decision-making, occupational pursuits, and quality of life. For this report, the authors explored possible mechanisms for this association, reviewed research in animal studies and aging men, and examined the growing literature focused on the relation between ADT and cognitive functioning in patients with prostate cancer.

METHODS.

A systematic literature search was conducted using the PubMed and Information Sciences Institute Web of Knowledge-Web of Science databases to identify relevant studies that investigated the relation between ADT in men with prostate cancer and its cognitive effects.

RESULTS.

Testosterone and its derivatives may have an impact on cognition through several mechanisms in the brain, as supported by studies of animals and in aging men. Studies that researched the impact of ADT on cognition in patients with prostate cancer patients were designed relatively well but suffered from small sample sizes. Between 47% and 69% of men on ADT declined in at least 1 cognitive area, most commonly in visuospatial abilities and executive functioning. Some studies reported contradictory results with increased functioning in verbal memory.

CONCLUSIONS.

There is a strong argument that androgen-ablation therapy is linked to subtle but significant cognitive declines in men with

prostate cancer. The authors believe that clinicians should become aware of this correlation as the use of ADT increases and should inform and monitor patients for this possible side effect of treatment. Cancer 2008. ©2008 American Cancer Society.

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ARTICLE TEXT

Patients with prostate cancer who have early-stage disease can choose between 3 treatment options (ie, surgery, radiation, or watchful waiting), which allow men to select treatments with regard to quality-of-life implications. Men who are diagnosed with metastatic disease do not have the luxury of choice; androgen-ablation therapy is the standard initial treatment. It is well known that androgens drive the growth of prostate cancer cells.[1] The most common way to achieve androgen ablation is through chemical castration with the use of luteinizing hormone-releasing hormone (LHRH) agonists. In the US, leuprolide (Lupron) and goserelin (Zoladex) the 2 most widely used LHRH agonists to significantly decrease the prostate-specific antigen (PSA) levels in men with late-stage prostate cancer and to help manage disease progression. Because LHRH agonists have little or no impact on adrenal sources of androgens (which may account for 5% to 10% of testosterone), nonsteroidal antiandrogens sometimes are combined with LHRH agonists to produce a combined androgen blockage.[2][3] Generally, these medications are effective at controlling the disease for on average 18 to 24 months, after which time PSA levels may start to increase and disease progression may develop.[4] Despite this, men usually stay on the LHRH agonist for the duration of their life, because these medications continue to slow disease progression.[5]

For years, androgen-ablation therapy was indicated solely for patients with late-stage prostate cancer. However, researchers have proven a survival benefit for androgen-deprivation (AD) therapy (ADT) in certain situations for earlier stages of prostate cancer. Several studies have indicated that androgen-ablation therapy in conjunction with primary radiotherapy could lead to improved overall survival compared with radiotherapy alone.[6][7] In addition, researchers are exploring the effectiveness of using ADT in men with rising PSA. Using ADT in this group of men would lead to an increase in the percentage of men with prostate cancer undergoing this form of therapy. In fact, the men in the rising PSA group may use ADT for a longer duration than men with late-stage prostate cancer, such that ADT for men with rising PSA may last for as long as 5 to 10 years or more.[5] A detailed description of the current practices regarding the administration of LHRH agonists is beyond the scope of this report; however, interested readers are referred to the study by Loblaw et al for American Society of Clinical Oncology practice guidelines.[3]

Several side effects and quality-of-life implications accompany ADT, including hot flashes, osteoporosis, anemia, fatigue, sarcopenia, gynecomastia, loss of libido, erectile dysfunction, risk of diabetes, risk of cardiovascular disease and fatal cardiac events, as well as possible emotional distress.[8-12] Recently, review articles discussing the side effects of androgen-ablation therapy have stated that this treatment also impacts cognitive functioning.[8][10] Cognitive deficits can impact a patient's ability to make informed treatment decisions, occupational or intellectual pursuits, and overall quality of life. However, only a few relatively small studies have investigated the impact of this treatment on cognitive functioning, and some of those studies reported contradictory results. In this report, we present the first review of these studies and attempt to summarize the results of this literature to date. In doing so, we discuss the possible mechanisms for the relation between testosterone and cognition, review the literature available from animal studies and studies in aging and/or hypogonadal men, and discuss the existing research on ADT in men with prostate cancer and its effect on cognitive functioning.

Potential Mechanisms of Action

Researchers only recently have begun to clarify the mechanisms that explain the potential association between testosterone and cognitive functioning.[13] It is important to recognize that 98% of testosterone circulates in the bloodstream bound to protein.[14] In men, approximately 40% of testosterone binds irreversibly to the hepatic protein, sex hormone-binding globulin. The remaining 60% of testosterone binds weakly to albumin and can dissociate easily from protein.[15] Thus, it is this 'free' testosterone that is available for biologic activity. Once secreted, testosterone can undergo several biologic changes peripherally, including conversion to dihydrotestosterone (DHT) by the enzyme 5α-reductase and conversion to estradiol by the enzyme aromatase.[16] In addition, both estradiol and DHT are present throughout the male brain.[17] Aromatase facilitates local conversion from testosterone to estradiol in brain tissue,[18] which is important because both testosterone and estradiol appear to affect cognition in men.[19]

Studies indicate that testosterone, estradiol, and DHT have activity in the brain that may impact cognition in different ways. Testosterone may impact cognition through several mechanisms. For example, activation of calcium channels in the brain occurs through rapid, nongenomic methods of action on G-protein-coupled, agonist sequestrable testosterone membrane receptors that initiate a transcription-independent signal pathway.[17] Testosterone also may impact cognitive performance directly through modulating neurotransmitters and stimulating neuronal connectivity, decreasing β-amyloid peptide

production, and preventing *N*-methyl-D-aspartate excitotoxicity,[20] mechanisms implicated in cognitive disorders such as Alzheimer disease or dementia. Furthermore, some estrogen studies have highlighted several possible mechanisms through which this hormone can impact cognitive functioning.[21] These include increasing cholinergic activity through its action of choline acetyltransferase, maintenance of dendritic spine density on CA1 pyramidal cells of the hippocampus and facilitating induction of long-term potentiation in the hippocampus, increasing serotonergic and cholinergic activity to maintain neural circuitry, altering lipoprotein, and decreasing risk of cerebral ischemia.[22][23] On the basis of estrogen's actions, similar mechanisms may exist for testosterone but require further investigation.

The conversion from testosterone to DHT also is important. Androgen receptors have 4 times greater affinity for DHT than for testosterone, suggesting that DHT is a more powerful androgen.[17] However, its effects on cognition are less clear. In the brain, these androgen and estrogen receptors colocalize in several areas that are important for learning and memory, such as the thalamus, the hippocampus, and the cerebral cortex.[23] In addition, CAG repeat polymorphism in the androgen receptor gene may be associated with cognition.[24]

Effects of Testosterone on Cognition From Animal Studies

Animal studies have demonstrated the effects of testosterone and/or its metabolites on cognitive functioning. The studies discussed below have explored the effects of androgens on the brain structures involved in cognition as well as the relations between testosterone and cognitive performance. These animal studies indicate a strong association between testosterone and hippocampal structures, thereby suggesting that testosterone may affect working memory. In addition, although testosterone and estradiol both impact cognition, they may influence cognitive functioning in different ways. The evidence suggests that, whereas testosterone impacts working memory, estradiol has implications for the rate of learning.

Several animal studies have suggested that testosterone may exert cognitive effects on the hippocampus. Castration decreases hippocampal CA1 synapse density, which can be reversed by the administration of testosterone or DHT.[25][26] Testosterone and DHT appear to help maintain normal spine synapse density by acting primarily on androgen receptors. Androgen-induced changes in hippocampal structure may contribute to the effects of testosterone on hippocampally mediated behaviors.[26] Mechanistically, MacLusky and colleagues observed that testosterone replacement in orchiectomized rats returned CA1 synapse density to levels comparable to those in intact males, indicating a possible physiologic role comparable to that of estrogen in activating synaptogenesis in CA1 spine synapses.[27] Also, Edinger and colleagues observed that 5α-reduced androgens had analgesic, anxiolytic, and cognitive-enhancing effects in the hippocampus.[28][29]

This association between testosterone and hippocampal changes suggests that these hormones may affect tasks such as short-term or working memory. Castration or orchiectomy causes impairment in working memory retention[25] as well as in working memory acquisition of a spatial maze task.[30] Although the effects seem to be inconsistent, the effects of hormone enhancement on cognitive performance in male rats appear to be task-specific. For example, it has been demonstrated that estradiol enhances the rate of learning as opposed to merely improving performance, and testosterone appears to improve working memory in male rats. Similar to observations in female rats, gonadal hormones appear to influence cognitive performance in males.[31]

Initial evidence also suggests that maintaining a balance between serum testosterone and estradiol levels may be critical to performance on memory tasks.[32] The absence of testicular hormones may increase the sensitivity of castrated male rats to the impairing effects of scopolamine (a muscarinic receptor antagonist) and mecamylamine (a nicotinic receptor antagonist) on working memory.[30] In contrast, Johnson and Burk noted that loss of circulating androgens did not make the animals more susceptible to challenges of the cholinergic system. Rather, androgen levels in excess of physiologic norms seemed to impair attentional processing.[33] Testosterone actually may decrease activity of the cholinergic system during nonspatial tasks and, thus, work in concert with the antagonism produced by scopolamine.[34]

Decreasing levels of testosterone, pregnenolone, and dehydroepiandrosterone are associated with aging in mice and may contribute to age-related deficits in learning and memory. Increasing the testosterone levels in aging mice appears to improve cognition.[35] Treating older mice with testosterone or DHT improves working memory and decreases circulating levels of estradiol in aged rats. When applying this animal research to humans, testosterone therapy in aging men may provide positive effects on cognition and on neural regions linked to cognition (eg, hippocampus, entorhinal cortex).[32]

Testosterone Levels and Cognitive Functioning in Older Men

Although they are not entirely consistent, the findings from studies of older men and/or hypogonadal men generally indicate that testosterone and estradiol impact cognitive performance in men.[14] In these studies, testosterone and estradiol seem to impact visuospatial abilities, verbal fluency, memory, and working memory in a task-specific manner.

The production of testosterone in men declines slowly and consistently after the age of 30 years. In a longitudinal study, Harman et al observed that the rates of hypogonadism in men in their 50s, 60s, 70s, and 80s were 9%, 34%, 68%, and 91%, respectively.[36] The implications of this decline on cognitive functioning still is relatively unknown because of the great deal of inconsistency in the studies conducted in this area.[37] Because the decrease in testosterone levels in older men are similar to those observed in hypogonadal men, studies in this area are conducted in both older men and/or

hypogonadal men. This can cause some confusion, and when we indicate 'hypogonadal' men, we do not mean 'aging men'; instead, 'hypogonadal' refers to men who met the criteria to be defined as hypogonadal in the specific study.

Sherwin hypothesized that declining testosterone would decrease visuospatial abilities and that declining estradiol would decrease verbal abilities,[14] because cognitive research comparing men and women has consistently indicated that men score higher on visuospatial tasks and that women excel in verbal abilities.[38] Correlational studies indicating that testosterone and estradiol levels are associated with cognitive functioning in older men partially support this hypothesis; however, the impact appears to encompass more than visuospatial and verbal abilities. A cross-sectional study demonstrated a positive association between free testosterone and working memory, visual scanning, and perceptual organization in elderly men.[23] Testosterone also may correlate with mental control, long-term verbal memory, and spatial abilities.[39] In terms of estradiol, older men demonstrated a positive correlation between higher estradiol levels and spatial span performance.[40] In a longitudinal study, estradiol was correlated with improved scores on working memory in elderly men (Table 1).[41]

Table 1. Correlational Studies Examining the Association Among Testosterone/Estradiol and Cognitive Functioning in Older Men

Study	No. of Participants	Cognitive Functioning Correlated With	Results (Domain)	Results (Task-specific)
Barrett-Connor 1999 [39]	547 Men	Testosterone	↓Long-term memory, ↓long-term storage	↓MMSE, ↓BIMC, ↓'world' backward
Carlson & Sherwin 2000 [41]	31 Men	Estradiol	↓Verbal fluency	↑Forward digit span
Yaffe 2002[23]	310 Men	Testosterone	↓Working memory, ↓visual scanning, ↓perceptual organization	↓11% MMSE, ↓13% digit symbol, ↓20% Trails B
Hogervorst 2004[40]	66 Women 79 men	Estradiol	↓Verbal recall, ↓information processing speed, ↓spatial span performance	

↓ Indicates decrease; MMSE. Mini-Mental State Examination; BIMC, Blessed Information-Memory-Concentration; ↑, increase.

A few studies also have examined the impact of the administration of testosterone to older and/or hypogonadal men (Table 2). In a randomized controlled trial (RCT) that studied the effects of sex steroids on working memory, a group of older, hypogonadal men received intramuscular injections of testosterone enanthate and scored higher on working memory after a month of treatment compared with hypogonadal men who received placebo.[42] The administration of testosterone in older hypogonadal men may improve verbal fluency,[43] although a later cross-sectional study indicated that testosterone injection blocked the practice effect in verbal fluency.[44] Cherrier et al reported that a group of older healthy men who were administered testosterone and estradiol scored higher on spatial memory, spatial abilities, and verbal memory compared with a placebo group.[45] A double-blind RCT conducted by Cherrier et al indicated that healthy older men who were taking testosterone could improve verbal memory but that this improvement depended on aromatization of testosterone to estradiol. Enhanced spatial memory, however, occurred in the absence of an increase in estradiol.[46] In another double-blind RCT, Cherrier et al learned that, in healthy older men, moderate levels of testosterone supplementation improved verbal and spatial memory, whereas low or large increases in circulating testosterone demonstrated no significant changes in cognition.[47]

Table 2. Studies of the Effects of Testosterone Administration in Older and/or Hypogonadal Men

Study	No. of Participants	Type of Therapy	Timing	Results (Domain)
Alexander 1998[43]	33 Hypogonadal men (HRT), 10 eugonadal men (T contraceptive), 19 controls	T	Session 1, before T administration; Session 2, after T administration	↑Verbal fluency
Janowsky 2000[42]	10 Men, 9 controls	T	Baseline, 1 mo	↑Working memory
Wolf 2000 [44]	17 Men, 13 controls	T	Before T injection, 5 d after T injection	↓Verbal fluency
Cherrier 2001[45]	25 Men	T	Baseline, 3 wk, 6 wk	↑Spatial memory, ↑spatial ability, ↑verbal memory
Cherrier 2005[46]	20 Men (T group), 19 men (TA group), 21 controls	T&A	Baseline, 3 wk, 6 wk, after 6 wk of washout	T and T&A, ↑verbal memory; T only, ↑spatial memory
Cherrier 2007[47]	57 Eugonadal men	T	Baseline, 3 wk, 6 wk, after 6 wk of washout	↑↓Verbal memory, ↑↓spatial memory (dependent on T dosage)

HRT indicates hormone-replacement therapy; T, testosterone; ↑ increase; ↓, decrease; T&A, testosterone and aromatase inhibitor.

To summarize, the literature conducted in animals and older men supports the rationale to investigate the impact androgen-ablation therapy in men with prostate cancer may have on cognitive functioning. In addition, early research on the mechanisms that may explain testosterone's impact on cognition has provided the possible explanation for this association. The findings from this research suggest that the depletion of testosterone may impact the areas of working memory, verbal memory, and visual spatial ability.

MATERIALS AND METHODS

We used a systematic literature search by using the PubMed database and the Information Sciences Institute (ISI) Web of Knowledge-Web of Science to identify pertinent studies that examined the relation between hormone therapy in men with prostate cancer and the cognitive effects observed in these patients. Firs, wet used keywords 'androgen deprivation therapy' and 'cognition' to perform the PubMed search. Then, we used ISI Web of Knowledge-Web of Science to cross reference articles that cited the article identified through PubMed. Because there are only a few relevant studies on this subject, all the studies identified are reviewed below.

Cognitive Functioning and Androgen-Ablation Therapy in Men With Prostate Cancer

The following studies are the first in a growing body of literature that has researched the impact of androgen ablation on cognitive functioning. These generally are well designed studies that use a longitudinal design with controls to examine these cognitive implications. These studies, as often is true for initial studies, suffer from small sample sizes and, thus, have reduced power. From these studies, we can draw the conclusion that androgen-ablation therapy appears to have subtle yet significant negative effects on specific domains of cognition as opposed to inducing gross cognitive changes that sweep across all cognitive domains (Table 3). This is evident in the finding that most of these studies examined multiple domains of cognition yet generally reported results in only 1 or 2 of these domains. Animal studies and studies in hypogonadal men suggest that testosterone may correlate with working memory, verbal memory, and visuospatial abilities. Thus, it is reasonable that the cognitive domains that appear to be most susceptible to the impact of androgen ablation in this research are visuospatial abilities (including visuospatial memory), working memory, and executive functioning. It is noteworthy that studies have reported contradictory results in the area of verbal memory, with some studies suggesting an improvement in verbal memory and others reporting a decline in verbal memory.

Table 3. Studies of the Cognitive Effects of Androgen Ablation Therapy in Men With Prostate Cancer

Study	No. of Participants	Timing	Results (Domain)	Results (Task-specific)
Green 2002[48]	39 Men (ADT), 15 controls	Baseline, 6 mo	↑↓Verbal memory	48% Declined in 1 task, 14% declined in 2 tasks
Cherrier 2003[49]	19 Men (ADT), 15 controls	Baseline, 9 mo, 12 mo	↑Verbal memory, ↓visual memory, ↓visuospatial memory	69% declined in 1 task
Almeida 2003[50]	37 Men (ADT)	8 Assessments over 1 y	↑Verbal memory, ↑verbal memory	
Salminen 2004[13]	26 Men (ADT)	Baseline, 6 mo, 12 mo	↓Visuomotor processing, ↓reaction time, ↓working memory, ↓recall of letters, ↑object recall	
Bussiere 2005[52]	14 Men (ADT), 16 controls	Immediately, 2 min, 12 min	↓Memory retention, ↓recognition	
Salminen 2005[51]	23 Men (ADT)	Baseline, 6 mo, 12 mo	↓Verbal fluency, ↓visual recognition, ↓visual memory	
Beer 2006 [53]	18 Men (ADT + estradiol), 18 controls (ADT only), 17 controls (healthy)	Baseline, 4 wk	↓Verbal memory, ↓psychomotor speed/processing speed	
Jenkins 2005[54]	32 Men (ADT), 25 controls	Baseline; T2, 3 mo; T3, 9 mo	↓Spatial memory, ↓spatial ability	47% Declined in 1 task
Joly 2006 [55]	57 Men (ADT), 51 controls		No differences on High-sensitivity Cognitive Screen; no differences on FACT-COG	

ADT indicates androgen deprivation therapy; ↑, increase; ↓, decline; FACT-COG, Functional Assessment of Cancer Therapy-Cognitive.

Green et al were the first to systematically research the impact of androgen-ablation therapy on the cognitive functioning of men with prostate cancer. Sixty-five men (mean age, 73 years) with advanced prostate cancer were assigned randomly to 1 of 4 groups: leuprolide (N = 19), goserelin (N = 20), cyproterone acetate (N = 11), and monitoring without hormone treatment (N = 15). All men participated in a battery of neuropsychological assessments at baseline (ie, 1 week before treatment) and then 6 months later. PSA and testosterone levels decreased significantly from baseline to 6 months for the 3 hormonally treated groups. Conflicting results emerged in the memory domain; men in the goserelin group surprisingly improved on 2 measures of memory (verbal [Wechsler Memory Scale-Revised] and visual [Rey-Osterrieth Complex Figure test]) but declined in another measure of verbal memory (Auditory Verbal Learning Test). The goserelin group also declined in a measure of executive functioning (Trails B). Of the 50 men on active treatments, 24 men showed a reliable decline (ie, >1 standard deviation) on at least 1 cognitive task, and 7 men showed a reliable change on 2 tasks, whereas the monitoring-only group showed no decline on any of the tasks.[48]

Cherrier et al studied the impact of intermittent androgen suppression (IAS) on cognitive functioning in 19 men with increasing PSA after primary therapy for prostate cancer and compared these men with 15 healthy community controls. Cases and controls underwent validated neuropsychological assessments before the onset of IAS, at 9 months (the

conclusion of IAS), and at 12 months (3 months off IAS). The patients ranged in age from 51 years to 76 years. Mean testosterone levels decreased significantly for the IAS group from baseline (3.6 ng/mL) to the 9-month assessment point (0.26 ng/mL), and then significantly increased at the 12-month assessment (3.2 ng/mL). At the 9-month assessment point, 69% of men in the IAS group demonstrated a clinically significant decline in a visuospatial ability task (mental rotation), and, at 12 months, the control group outperformed the IAS group on a measure of visuospatial memory (route test).[49]

In a longitudinal study, Almeida et al followed 37 patients with prostate cancer who started a 36-week course of androgen-ablation therapy.[50] Those researchers assessed cognition with the Cambridge Examination for Mental Disorders of the Elderly-Cognitive Battery (CAMCO-G) and with tests of verbal memory, visual memory, and visuospatial ability. They assessed the patients a total of 8 times over 1 year. At the end of the 36-week course of ablation therapy, they observed an *increase* in performance on a test of verbal memory and visual memory. At the 1-year follow-up assessment (18 weeks off of ablation therapy), there was a significant increase in total CAMCO-G scores and verbal memory. These results suggest that androgen-ablation therapy may have a positive impact on verbal and visual memory and that the removal of the treatment has a similar impact. These results should be reviewed with caution, because the extremely frequent administration of neuropsychological tests leads to practice effects (ie, patients improve over time with practice), and no comparison group was included in the study. It is quite possible that the results of this study were artifacts because of practice effects.

Salminen et al researched the cognitive effects of ADT on 26 men who were diagnosed recently with prostate cancer and who began ADT 2 months before radiotherapy. Assessments occurred at baseline, at 6 months, and at 12 months. The neuropsychological battery consisted of 14 tests that took 3 hours to administer. The average age of the sample was 65years, and all men reached castrate level at 6 months. From baseline to 12 months, tests of visuomotor speed and of reaction time saw significant decreases. The decline in testosterone coincided with a decline in visuomotor processing (digit symbol), reaction time (10-choice reaction time), working memory speed (subtraction), sustained attention (vigilance), and recognition speed (recognition of letters).[13]

Salminen et al also conducted a prospective study of men with newly diagnosed prostate cancer to investigate the association between ADT and estradiol decline and the impact of ADT on cognitive performance. For that study, cognitive testing was conducted on 23 men with prostate cancer (mean age, 65 years) at baseline, at 6 months, and at 12 months of AD. An extensive, standardized, cognitive test battery was given at these time points. The findings indicated a subsequent correlation between the cognitive domains of verbal fluency, visual recognition, and visual memory and a decline in estradiol during AD. Other cognitive domains appeared to be unaffected by estradiol decline during 12 months of AD. These results suggest marginal but selective associations between testosterone decline, estradiol, and cognitive performance.[51]

Bussiere et al[52] studied performance on several memory tasks in a group of 14 men who were receiving ADT (mean age, 67 years; average, 1991 days on androgen-ablation therapy) compared with an age-matched group of 16 healthy men. That study did not examine any other domains of cognitive functioning. Twelve of the men from the study group received leuprolide acetate, and the other 2 men underwent orchiectomy. The memory tasks included 3 parts: encoding, retention interval, and recognition. Retention measurements occurred at 3 intervals: immediate, at 2 minutes, and at 12 minutes. At each interval, the men were presented with sets of words from the encoding phase to determine whether they recognized them. AD did not affect encoding or retrieval significantly, but it did impair retention. There was no significant difference between the study group and the control group at the immediate condition. However, at the 2-minute and 12-minute intervals, the study group could recognize words no better than chance, whereas the control group continued to perform above chance.[52]

In a longitudinal study, Beer et al took a different approach and examined the effects of estradiol administration in men with prostate cancer who previously underwent AD. The study included 18 men with prostate cancer (mean age, 70 years; average, 1954 days on androgen-ablation therapy) and 2 control groups. One group of controls consisted of age-matched men with prostate cancer who were undergoing AD but not receiving the estradiol treatment, and the other control group consisted of age-matched, healthy men. At baseline and then 4 weeks later, the study used the immediate and delayed paragraph tests to test long-term memory, Subject Ordered Pointing), and Trail tests to assess working memory. The baseline results showed that men with prostate cancer (both groups) performed significantly worse than the controls, specifically in their immediate and delayed verbal memory scores. After the estradiol replacement treatment, the study group improved in immediate verbal memory and delayed verbal memory, whereas there was no improvement in the control groups. Further analysis indicated that only immediate verbal memory improved significantly in the study group.[53]

In a pilot study, Jenkins et al assessed 32 men with standard neuropsychological assessments at 3 time intervals: at baseline, 3 months, and 9 months. The average age of these men was 67.5 years, and they used androgen-ablation therapy for 3 to 5 months. Twenty-five healthy men, similar in age, served as the control group. Although there was no overall group effect, a greater percent of men in the ablation group reported a significant cognitive decline in 1 task (47%) compared with the control group (17%; odds ratio, 4.412; $P < .05$) at the 3-month time point. There were no significant differences between the groups at the 9-month time point. On specific domain analysis, the tasks most impacted at the 3 month time point were spatial memory and ability.[54]

Joly et al compared physical and cognitive function in a cross-sectional study of 57 patients who were receiving ADT for nonmetastatic prostate cancer and 51 healthy, age-matched controls. Thirty patients received ADT as adjuvant treatment after prostatectomy or radiotherapy, and 27 patients received ADT for increasing levels of PSA. The median duration on ablation therapy was 1.8 years (range, 0.4-7.4 years). To assess cognitive functioning, the researcher administered the Sensitivity Cognitive Screen and a self-reported assessment on cognitive deficits (the Functional Assessment of Cancer Treatment-Cognitive Scale [FACT-COG]). In contrast to other studies cited above, Joly and colleagues observed that, although men with nonmetastatic prostate cancer who received ADT experienced more treatment-related symptoms, they demonstrated no differences in cognitive function on either the High Sensitivity Cognitive Screen or the FACT-COG. The authors suggested that the High Sensitivity Cognitive Screen may not be sensitive enough to detect the subtle cognitive changes that occur after ADT. In addition, self-report of cognitive function has not been correlated consistently with actual neuropsychological testing.[55]

DISCUSSION

The research outlining possible mechanisms between testosterone and cognition, the data from animal studies, and the results from studies researching cognition in older men support a rationale to investigate the association between ADT and cognitive functioning. The growing literature that has explored this question in men with prostate cancer also generally supports the connection between AD and cognitive decline.

However, there are important points with regard to the results and to issues of methodology that should be emphasized when drawing conclusions from this literature. In terms of the results from the studies, the cognitive changes appear to be subtle and impact specific domains as opposed to gross changes that sweep across multiple aspects of cognitive functioning. For example, a large percentage of men (range, 47%-69%) reported a decline in at least 1 task area; however, Green et al reported that only 14% of men experienced declines in ≥2 areas. Also, it is significant that these studies generally tested multiple domains of cognitive functioning yet observed differences in only 2 or 3 domains. The specific domains that are most likely to be impacted are visuospatial abilities and executive functioning. It is noteworthy that the studies reported contradictory results in verbal memory.

It is also important to highlight issues of methodology within this body of literature. There is significant variability in terms of the types of cognitive tests administered. Most studies used comprehensive neuropsychological batteries; however, the tests that were used to assess specific domains generally varied across studies. Second, only 3 of the 9 studies that we reviewed defined 'cognitive impairment,' and the definition was not consistent across studies. These issues make it difficult to compare results and develop firm conclusions from the literature. In addition, these studies also have not proven a direct connection between androgen ablation and cognition. Although there appear to be specific mechanisms for testosterone to directly impact cognition, it is possible that the side effects of androgen-ablation therapy (eg, hot flashes, fatigue, and anemia) may contribute indirectly to impaired cognition. Finally, all of these studies tend to use relatively small sample sizes (most likely leading to reduced power), and the findings have not been entirely consistent across studies. The most obvious example of this inconsistency occurred in the study by Joly et al, in which no cognitive decline was reported after ablation therapy.

Despite these important considerations, when reviewing this literature as a whole, we conclude from the data that androgen ablation does have implications for cognitive functioning. Therefore, larger longitudinal studies are warranted. Larger studies should explore the moderating/mediating implications of the side effects of ablation therapy (eg, hot flashes, changes in mood, anemia) on cognitive functioning. In addition, future studies should attempt to integrate brain imaging as a component of this research. In studies of the cognitive effects of chemotherapy in women with breast cancer, brain imaging has provided evidence of brain alteration; however, compensatory activation has allowed patients to maintain performance on neuropsychological tasks.[56] It is possible that neuropsychological tests may not be sensitive enough to detect changes in cognitive functioning or may not test the limits of cognitive function.[56] Brain imaging may be useful to determine the extent of the impact of androgen-ablation therapy on cognition. It is also important to consider the clinical implications of these findings. It would be valuable for physicians who use androgen ablation to treat men with prostate cancer to be aware of this relation so they can inform patients and monitor them for possible side effects, as appropriate.

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